Novel Therapies for Cardiometabolic Risk Reduction and Implications for Clinical Practice

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The growing prevalence of obesity is associated with a dramatic increase in a number of related risk factors for cardiovascular disease and diabetes, including high triglyceride and fasting glucose levels, reduced high-density lipoprotein cholesterol, and increased blood pressure. For many patients, lifestyle interventions (eg, exercise and a reduced-calorie diet) are insufficient for overcoming obesity, and pharmacotherapy becomes necessary. Unfortunately, the currently available agents are associated with side effects such as gastrointestinal distress and increased blood pressure. A new class of drugs targeting the cannabinoid receptors is poised to join the obesity-management armamentarium, with one agent—rimonabant—demonstrating efficacy in 4 recent phase III multinational trials. Patients randomized to rimonabant 20 mg/d showed significant reductions in weight and significant improvements in lipid profiles and other measures of cardiometabolic risk factors.
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Cardiometabolic risk is defined by a constellation of medical conditions that commonly occur together[1] and as a group greatly increase the risk of developing cardiovascular disease and diabetes.[2,3] This collection of risk factors is increasing at a phenomenal rate in our society, largely because of the increasing prevalence of overweight and obese patients.[4] Factors that are included in the definition of cardiometabolic risk include[5]:

- Waist circumference > 40 inches (men) or 35 inches (women)
- Triglyceride levels ≥ 150 mg/dL
- High-density lipoprotein cholesterol (HDL-C) levels < 40 mg/dL (men) or 50 mg/dL (women)
- Blood pressure ≥ 130/85 mm Hg
- Fasting glucose levels > 100 mg/dL

Although lifestyle interventions such as physical activity and weight reduction are generally agreed to be the first line in the management of cardiometabolic risk factors,[6,7] they are often not enough. Drug therapy may be warranted for patients considered to be at very high risk for cardiovascular disease. The traditional approach to drug therapy for managing risk factors involves treatment of the individual components of the syndrome so that overall risk of cardiovascular disease and diabetes is reduced.[6,7] A newer approach attempts to treat the underlying features that unify cardiometabolic risk factors and, by doing so, improve the individual components as well. The underlying cause of cardiometabolic risk is complex, and active investigation continues. Insulin resistance, which is most likely caused by excess visceral fat, is probably a major factor.[8] Visceral fat is adipose tissue that lies deep within the abdomen and encases the visceral organs, as well as fat that lies within these organs.[9] Visceral fat has been associated with insulin resistance, cardiometabolic risk factors, and excess mortality. This review will examine pharmacotherapeutic approaches to managing obesity as a way of controlling cardiometabolic risk, with a focus on the newest options that target visceral fat.

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Current Pharmacotherapy Options for Obesity

The growing worldwide prevalence of obesity has stimulated the search for pharmacologic agents to treat this condition. Various therapeutic strategies have been explored, including:

- Serotonin and norepinephrine reuptake inhibitors (anorectic agents)[10]
- Lipase inhibitors[11]
- Beta-3-adrenoreceptor agonists[12]
- Leptin agonists[13]
- Melanocortin-3 agonists[14]

Phentermine, a sympathomimetic amine, is a commonly prescribed appetite suppressant, but it is recommended only for short-term use (a few weeks). Serotoninergic agents such as fenfluramine and its *D*-isomer dexfenfluramine suppress the appetite, but they were withdrawn from the market because of adverse cardiovascular effects.[15]

Orlistat is a lipase inhibitor that blocks intestinal absorption of dietary fat by about 30%. It is indicated for obesity management when used in conjunction with a reduced-calorie diet. It has a beneficial effect on weight loss and most cardiovascular risk factors.[16-19] Its use, however, is accompanied by considerable gastrointestinal adverse effects such as bloating, flatulence, and oily stools, especially if fat intake remains relatively high. A daily multivitamin supplement is required to counter the malabsorption of fat-soluble vitamins (eg, vitamins A, D, and E).

Sibutramine is a potent inhibitor of serotonin and norepinephrine reuptake (in vivo) that acts primarily via its amine metabolites. Used in conjunction with a reduced-calorie diet, it is indicated for obesity management and has fewer gastrointestinal adverse effects than orlistat.[20,21] It can cause a dose-related sustained increase in blood pressure in some patients and should not be used in patients with a history of high blood pressure, coronary heart disease, heart failure, arrhythmia, or stroke.

A new class of weight-loss agents may soon be available.[22] The first member of this class, rimonabant, targets the endocannabinoid system and cannabinoid type 1 (CB1) receptors (Figure 1). The endocannabinoid system is a physiologic neuromodulatory signaling system that plays a role in a number of physiologic responses, including food intake.[22] Activation of the CB1 receptors by endogenous cannabinoids, such as anandamide, increases appetite, and increased endocannabinoid activity is associated with excessive food intake. Rimonabant is a selective CB1 receptor antagonist for the treatment of obesity.[23] It works by blocking endogenous cannabinoid binding to neuronal CB1 receptors, thus blocking this activation and reducing appetite. Rimonabant is the first endocannabinoid receptor antagonist developed and thus offers a unique therapeutic approach to appetite control and weight reduction. The efficacy of rimonabant on weight reduction has been confirmed in a series of clinical studies—the Rimonabant in Obesity (RIO) program—including pivotal phase III trials involving over 6600 obese subjects worldwide.

The RIO program enrolled obese patients worldwide in 4 clinical trials designed to explore the role of rimonabant in obesity management (weight loss and weight maintenance), prevention of weight regain after weight loss, and improvement of obesity-related cardiometabolic risk

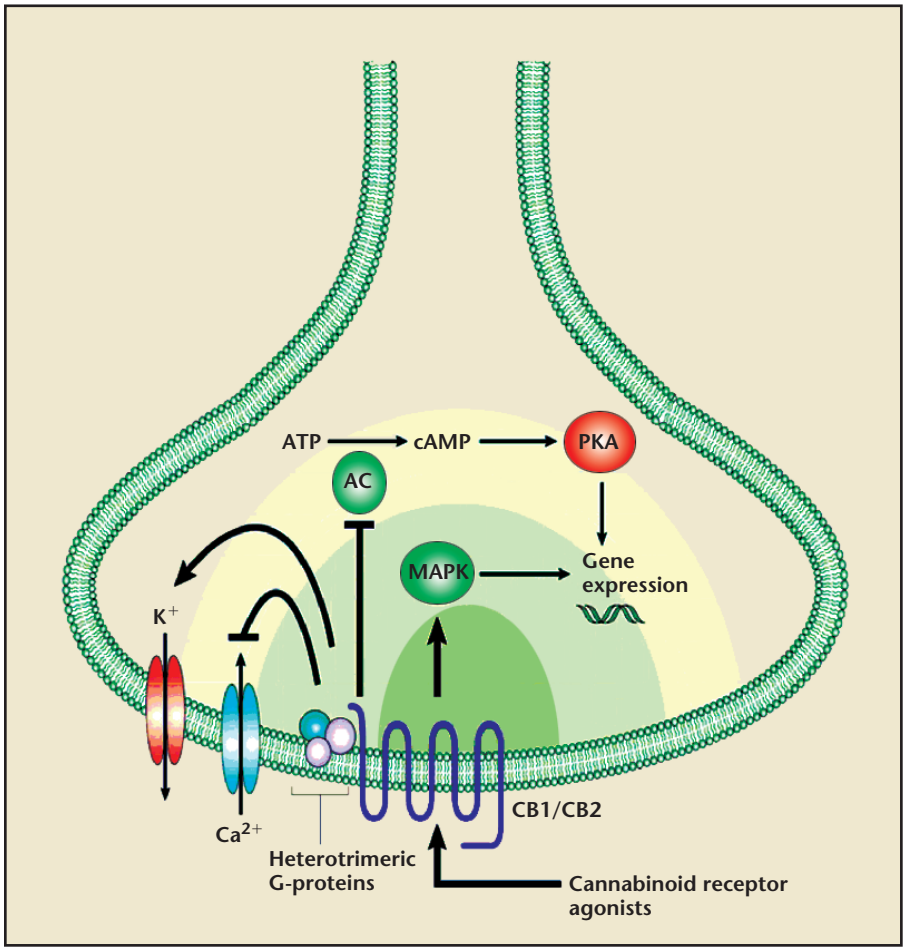

Figure 1. *A schematic representation of the endocannabinoid receptor. This receptor is a member of the family of 7 transmembrane receptors. It is a G-protein–coupled receptor. CB type 1 receptor is highly expressed in the central nervous system. CB type 2 is highly expressed in peripheral tissues. The composition of the cannabinoid binding site is highly hydrophobic. ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; AC, adenylate cyclase; MAPK, mitogen-activated protein kinase; G-proteins, guanine nucleotide-binding proteins; CB, cannabinoid.*

factors. The 4 trials were RIO-North America, RIO-Europe, RIO-Lipids, and RIO-Diabetes.

RIO-North America

This multicenter, double-blind, placebo-controlled trial enrolled 3040 overweight or obese patients (80% women) from 72 medical centers in the United States and Canada.[24] Patients were randomized to receive rimonabant 5 mg/d, rimonabant 20 mg/d, or daily placebo for 1 year. After the first year, patients on either dose of rimonabant were re-randomized to receive either the same dose of rimonabant or a placebo for a second year. Throughout the study, average daily calorie intake was reduced by 600 calories.

The primary objective of the trial was to assess weight loss over 1 year and then determine the ability of rimonabant to prevent weight regain during a second year of treatment. Secondary objectives included assessment of changes in cardiometabolic risk factors associated with abdominal obesity, such as dyslipidemia, glucose intolerance, and metabolic syndrome.

Result

Of the patients treated for a full 2 years with rimonabant 20 mg/d, 62.5% lost more than 5% of their body weight, compared with 36.7% of those receiving rimonabant 5 mg/d and 33.2% in the control group. Moreover, 32.8% of patients treated for the full 2 years with rimonabant 20 mg/d lost more than 10% of their body weight, compared with 20% of patients taking rimonabant 5 mg/d and 16.4% of patients in the control group. The study also showed that patients treated for 2 years with rimonabant 20 mg/d reduced their waist circumference by an average of 3.1 inches, versus 1.9 inches and 1.5 inches for the rimonabant 5 mg/d and control groups, respectively.

Patients treated with rimonabant 20 mg/d increased their HDL-C by 24.5% compared with 15.6% for those on rimonabant 5 mg/d and 13.8% for those in the control group. At the same time, patients treated with rimonabant 20 mg/d for 2 years lowered their triglycerides by 9.9%, compared with 5.6% for patients on rimonabant 5 mg/d and 1.6% for those in the control group. The investigators reported that the effect of rimonabant on HDL-C, triglycerides, fasting insulin, and insulin sensitivity appeared to be twice that which would be expected from the degree of weight loss achieved. Rimonabant was generally well tolerated; the most common drug-related adverse event was nausea (11.2% in the rimonabant 20 mg/d group vs 5.8% in the placebo group).

RIO-Europe

This multicenter, double-blind, placebo-controlled study enrolled 1507 overweight or obese patients

from 60 medical centers in Europe and (because of recruitment difficulties) 20 centers in the United States.[25] The dosing regimens and primary and secondary objectives were the same as in RIO-North America. Patients were again randomized to receive rimonabant 5 mg/d, rimonabant 20 mg/d, or placebo for 1 year, then re-randomized either to the same dose for an additional year or to placebo for the second year.

Table 1
Changes in Weight and Waist Circumference at 1 Year

	Placebo	Rimonabant 5 mg	*P* Value*	Rimonabant 20 mg	*P* Value*
Weight (kg)	−1.8	−3.4	.002	−6.6	< .001
Waist circumference (cm)	−2.4	−3.9	.002	−6.5	< .001

*Versus placebo.
Data extracted from Van Gaal LF et al.[25]

Results

As in RIO-North America, patients on the higher dose of rimonabant were far more successful in losing weight than patients on the lower dose or in the placebo control group (Table 1). Nearly 70% of patients treated for 1 year with rimonabant 20 mg/d lost more than 5% of their body weight, compared with 44.2% of those on rimonabant 5 mg/d and 30.5% of patients in the control group. Moreover, 39% of patients treated for 1 year with rimonabant 20 mg/d lost more than 10% of their body weight, compared with 15.3% of patients on rimonabant 5 mg/d and 12.4% of patients in the control group. Weight and waist circumference were significantly improved in the rimonabant 20 mg group. This study also showed that patients treated for 2 years with the higher dose of rimonabant reduced their waist circumference by an average of 3.1 inches compared with 1.9 inches for those on the low dose of rimonabant and 1.5 inches for patients in the control group.

After 1 year, lipid levels significantly improved among patients in the 20 mg rimonabant group (Table 2). After 2 years, patients treated with rimonabant 20 mg/d increased their HDL-C by 22.3%, compared with 16.2% for those treated with rimonabant 5 mg/d and 13.4% for those in the control group. At the same time, patients treated with rimonabant 20 mg/d for 2 years lowered their triglycerides by 6.8% compared with a 5.7% increase for patients taking rimonabant 5 mg/d and an 8.3% increase for patients taking placebo. For those patients who met criteria for the metabolic syndrome at the outset of the study, more than half of those taking rimonabant 20 mg/d no longer met these criteria after 1 year (Table 3). Side effects were mainly mild and transient and most frequently involved nausea, diarrhea, and dizziness.

Table 2
Changes in Lipids at 1 Year

	Placebo	Rimonabant 5 mg	*P* Value*	Rimonabant 20 mg	*P* Value*
HDL cholesterol (%)	13.4	16.2	.048	22.3	< .001
Triglycerides (%)	8.3	5.7	NS	−6.8	< .0001

*Versus placebo.
HDL, high-density lipoprotein. Data extracted from Van Gaal LF et al.[25]

RIO-Lipids

This multinational, multicenter, double-blind, placebo-controlled trial enrolled 1036 overweight or obese patients with dyslipidemia (high triglycerides and/or a high total cholesterol/HDL-C ratio) and a body mass index (BMI) between 27 and 40.[26] Patients were randomized to receive 1 year of treatment with either rimonabant 5 mg/d, rimonabant 20 mg/d, or placebo, along with a reduced-calorie diet.

Results

As in the first 2 RIO studies, patients treated with the higher dose of rimonabant were far more successful in losing weight than were patients on the lower dose or in the placebo control group. Nearly 75% of patients treated for 1 year with rimonabant 20 mg/d lost more than 5% of their body weight compared with 41.8% of those on rimonabant 5 mg/d and 27.6% of patients in the control group. A total of 44.3% of patients treated for 1 year with rimonabant 20 mg/d lost more than 10% of their body weight compared with 16.3%

Table 3
Change in Metabolic Syndrome Status at 1 Year

	Placebo	Rimonabant 5 mg	*P* Value*	Rimonabant 20 mg	*P* Value*
Baseline (%)	39.9	41.2	NS	42.2	NS
1 year (%)	31.4	28.6	NS	19.6	< .001

*Versus placebo.
NS, not significant. Data extracted from Van Gaal LF et al.[25]

of patients on rimonabant 5 mg/d and 10.3% of patients in the control group. The patients treated for a year with rimonabant 20 mg/d also reduced their waist circumference by an average of 3.5 inches.

Side effects were generally transient and self-limiting, and most commonly included nausea, dizziness, influenza, anxiety, diarrhea, and insomnia. The most frequent side effects leading to discontinuation of placebo, rimonabant 5 mg, and rimonabant 20 mg included depression (0.6% vs 1.7% and 2.9%), anxiety (0.6% vs 0.3% and 1.7%), and nausea (0% vs 0.6% and 1.2%).

RIO-Diabetes

Results of the RIO-Diabetes study were presented at the American Diabetes Association 65th Annual Sessions in 2005.[27] RIO-Diabetes was a phase III multinational, multicenter, randomized, double-blind, placebo-controlled trial carried out at 151 centers in 11 countries. The 1045 participants enrolled in the trial had type 2 diabetes, with a mean BMI of 34 and mean hemoglobin A_{1c} of 7.5%. Two thirds of the patients were taking metformin as therapy for diabetes, and the rest were taking a sulfonylurea. Patients were randomized to receive 1 year of treatment with either rimonabant 5 mg/d, rimonabant 20 mg/d, or placebo, along with a reduced-calorie diet.

Results

As in all of the RIO studies, patients taking rimonabant 20 mg/d were far more successful in losing weight than were patients on the lower dose (5 mg/d) or in the placebo control group. In fact, the differences between the lower dose of rimonabant and placebo were not considered significant by the investigators; thus their reporting of the results centered on the differences between the rimonabant 20 mg/d and placebo groups.

Patients taking rimonabant 20 mg/d lost an average of 11.7 pounds compared with 3 pounds for patients in the placebo group. In addition, patients treated with rimonabant 20 mg/d had a reduction in waist circumference of 2 inches versus 0.7 inches for those taking the placebo.

Patients treated with rimonabant 20 mg/d achieved an A_{1c} reduction of 0.6% from a baseline value of 7.3% compared with an increase of 0.1% for those taking placebo—a difference of 0.7%. Among patients taking rimonabant 20 mg/d, 43% achieved an A_{1c} level below 6.5% compared with only 21% in the placebo group. HDL-C and triglycerides were also significantly improved in patients treated with rimonabant 20 mg/d throughout the 1-year period. Furthermore, there was a small decrease of 0.8 mm Hg in systolic blood pressure in the rimonabant 20 mg/d group compared with a 1.6 mm Hg increase in the placebo group. The difference in diastolic blood pressure between the 2 groups was not statistically significant.

According to the investigators, side effects in the rimonabant 20 mg group were mainly mild and transient and most frequently included

Main Points

- The metabolic syndrome, a collection of risk factors that includes abdominal obesity, dyslipidemia, and glucose intolerance, and that puts a patient at increased risk for developing heart disease and type 2 diabetes, is becoming increasingly prevalent, most likely because of the dramatic growth in the incidence of obesity.
- Activation of cannabinoid type 1 receptors by endogenous cannabinoids, such as anandamide, increases appetite, and increased endocannabinoid activity is associated with excessive food intake.
- In the 4 Rimonabant in Obesity studies, patients taking rimonabant 20 mg/d were far more successful in losing weight than were patients on the lower dose (5 mg/d) or in the placebo control group.
- Rimonabant use was associated with decreases in systolic blood pressure and fasting glucose and triglyceride levels and increases in high-density lipoprotein cholesterol.

nausea (12.1%), dizziness (9.1%), diarrhea (7.4%), vomiting (5.9%), hypoglycemia (5.3%), fatigue (5.3%), and anxiety (5%). These side effects, which mostly occurred within the first few weeks, led to a drop-out rate of 3.3% among those treated with rimonabant 20 mg/d and 0.9% in the placebo group.

Conclusion

Cardiometabolic risk is a significant problem that increases the possibility of both type 2 diabetes and cardiovascular disease. Weight management is the foundation of reducing cardiometabolic risk and its associated diseases. Data from the phase III multicenter RIO trials demonstrated significant reductions in body weight and waist circumference, improved lipids, and improved glycemic control in overweight and obese patients taking rimonabant 20 mg/d. Rimonabant also had a significant impact on cardiometabolic risk factors which, according to the investigators, was greater than that expected by weight loss alone. Effective weight management will likely require life-long attention with a combination of lifestyle modifications and pharmacologic management. New therapeutic strategies and approaches such as this one are desperately needed in order to reduce cardiometabolic risk factors and lead to improved health outcomes. ■

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