The prevalence of obesity has risen substantially during the past 25 years in the United States and most developed countries, with a related increase in type 2 diabetes mellitus. Almost one third of the adult US population is considered to be obese (body mass index [BMI] ≥30), and 1 in 20 is extremely obese (BMI ≥40). Nearly 17% of children and adolescents are overweight in the United States. Obesity is associated with increased risk for type 2 diabetes mellitus, coronary heart disease (CHD), hypertension, obstructive sleep apnea, and cancer, higher overall mortality rate, and decreased longevity. Extreme obesity can truncate life expectancy in young adults by 5 to 20 years. Accordingly, the expected benefits of weight reduction for obese individuals are profound.

Does Weight Reduction Lead to Other Health Benefits?
Weight loss of 5% to 10% generally lessens many health risks, including cardiovascular risks, although such improvements are most notably demonstrable in studies specifically conducted in high-risk populations, and the benefits are presumed to be greater when healthier weight is maintained for long periods. In overweight and obese individuals, weight loss achieved with most interventions over 1 to 2 years generally leads to improvements in blood pressure (BP), glycemic measures, and triglycerides (TGs). Improvements in total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) have been reported in studies using dietary interventions combined with exercise. When weight loss is achieved primarily via pharmacological interventions, these benefits have not occurred quite so consistently.
Ideal Characteristics Sought in Antiobesity Drugs

Nonsurgical weight-reduction interventions provide minimal long-term weight loss unless the interventions are continued. Thus, we must view weight-reduction interventions as treatments that need to continue for several years, if not forever, similar to management of hypertension and diabetes mellitus. Therefore, an ideal antiobesity drug should have the following characteristics: (1) long-term weight-reduction efficacy and ability to prevent weight regain, (2) simplicity of administration, (3) low adverse-effect burden, (4) low potential for drug interactions, and (5) low cost.

Guidelines for Use of Antiobesity Drugs and Regulatory Issues

According to the recommendations of the National Institutes of Health panel on obesity, pharmacotherapy targeted for weight reduction is indicated for patients with a BMI of $\geq 30$ and also for those with a BMI of $\geq 27$ in the presence of obesity-related illnesses and risk factors, and product labels of prescription antiobesity drugs recommend these selection criteria.\textsuperscript{11} Before 1992, for approval of antiobesity drugs, the policy of the US Food and Drug Administration (FDA) was that these drugs should only be used on a short-term basis (generally understood as 12 to 16 weeks). In sharp contrast, the FDA now seeks demonstration of long-term efficacy with the recognition that patients regain weight quickly after stopping these drugs and that no significant long-term health benefits may be achievable with short-term treatment of obesity. The FDA’s guidance document states that a reasonable primary efficacy criterion for approval of antiobesity drugs is demonstration of a mean placebo-subtracted 1-year weight loss of $\geq 5\%$\textsuperscript{19}. Two-year data provide additional support of efficacy and safety. The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMEA) seeks demonstration of at least 10% weight loss at 1 year and statistical superiority over placebo treatment.\textsuperscript{20} These expectations have not been consistently fulfilled by currently approved antiobesity drugs. At the present time, only 2 drugs, sibutramine and orlistat, are approved for long-term obesity treatment. These are the only antiobesity drugs approved by the FDA in the past 10 years.

Current State of Antiobesity Drug Therapy

Sibutramine

Sibutramine (Meridia/Reductil), a mixed norepinephrine serotonin uptake inhibitor, has been available in the United States since 1997 and in several other countries for a longer period of time. A recent meta-analysis estimated that 1-year treatment with sibutramine yields an average placebo-subtracted weight loss of 4.5 kg.\textsuperscript{21} Some evidence suggests that sibutramine helps patients maintain initial weight reductions. In the Sibutramine Trial of Obesity Reduction and Maintenance (STORM),\textsuperscript{22} after 6 months of open-label treatment, obese patients who had lost at least 5% of their weight were randomly assigned to receive placebo or sibutramine for an additional 18 months. Of the 261 patients completing the trial, 46% treated with sibutramine lost at least 10% of their weight compared with 20% of patients treated with placebo.

Sibutramine is associated with small increases in BP and heart rate in obese patients with and without hypertension.\textsuperscript{21} It is contraindicated for patients with uncontrolled or poorly controlled hypertension, CHD, congestive heart failure, arrhythmias, and stroke and those taking monoamine oxidase inhibitors.\textsuperscript{23} The product label advises caution in using sibutramine for patients receiving the selective serotonin reuptake inhibitor class of antidepressants. In March 2002, sales of sibutramine were temporarily suspended in Italy while adverse events were investigated. After the European Committee for Proprietary Medicinal Products concluded that the risk-benefit profile of sibutramine was positive,\textsuperscript{24} its marketing license was reinstated in Italy. In August 2005, the FDA rejected a petition by the Public Citizen Health Research Group to remove sibutramine from the market, stating that the drug’s risk-benefit profile supports its availability.\textsuperscript{25}

Outcomes of SCOUT (Sibutramine Cardiovascular OUTcomes), a large randomized, controlled trial (RCT) examining the incidence of serious cardiac adverse events in 9000 obese patients at high risk for cardiovascular disease, currently under way in Europe, are eagerly awaited. For now, sibutramine remains available.

Orlistat

Orlistat (Xenical), a lipase inhibitor that reduces fat absorption in the gut, has been available in the United States since 1999. Orlistat is the only drug approved in the United States for weight reduction in obese adolescents (aged $\geq 12$ years). A recent meta-analysis estimated that orlistat treatment led to an average placebo-subtracted weight loss of 2.7 kg at 1 year.\textsuperscript{26} Overall, the magnitude of weight loss achievable with orlistat appears to be less than that with sibutramine after 1 to 2 years. However, orlistat is the only antiobesity drug with a published 4-year RCT. In a Swedish study of 3305 obese, nondiabetic patients (21% had impaired glucose tolerance), orlistat treatment was associated with a 3.6-kg weight loss compared with 1.4 kg for placebo at 4 years (intention-to-treat [ITT] analysis).\textsuperscript{27} The cumulative incidence of diabetes mellitus was 6.2% with orlistat therapy and 9.0% with placebo; a difference in diabetes incidence was detectable only in the subgroup of patients with impaired glucose tolerance at baseline.

No major safety concerns have been identified with orlistat therapy. Approximately 15% to 30% of those taking orlistat experience oily stool, fecal urgency, or oily spotting, and 7% report fecal incontinence, particularly at the initiation of treatment.\textsuperscript{26}

Phentermine

Although sibutramine and orlistat are the only drugs approved by the FDA for long-term treatment of obesity, phentermine remains the most prescribed antiobesity drug in the United States, where prescriptions for the drug, which was approved in 1959, outnumber combined prescriptions for sibutramine and orlistat.\textsuperscript{17} Whereas phentermine is approved for short-term use (generally taken as 12 to 16 weeks), physicians commonly prescribe it for longer periods.\textsuperscript{17} Its
long-term efficacy (for at least 1 year) has never been tested in an RCT.

Investigational Drugs
With this state of the field of obesity pharmacotherapy, there exists a considerable need for safe and effective drugs to assist obese patients in losing weight. Although some of the drugs indicated for other conditions—bupropion, topiramate, and zonisamide, to name a few—have been studied for the treatment of obesity with positive results, these findings have limitations, because most of these trials have not examined large samples for long durations. Topiramate has consistently been shown to be effective for weight reduction, with notable improvements in BP and hemoglobin A1C (HbA1C), but neuropsychiatric adverse events, which occur at high frequency, limit its usefulness as an antiobesity drug. Numerous drug candidates for obesity treatment have fizzled in the past few years because of safety concerns or lack of efficacy in phase II or III trials. More than 100 drugs are currently being investigated as potential candidates for treatment of obesity; most are in the early stages of development, and the few that have reached clinical phases of development have yielded unimpressive results. Rimonabant is an exception.

Rimonabant
Pharmacology
Rimonabant is a selective cannabinoid CB1 receptor antagonist that has undergone extensive testing in the treatment of obesity, as well as for treating nicotine dependence in humans. The story of rimonabant begins with the understanding that endocannabinoids, cannabis-like substances in the central nervous system, play a significant role in stimulating obesity, as well as for treating nicotine dependence in humans. The story of rimonabant begins with the understanding that endocannabinoids, cannabis-like substances in the central nervous system, play a significant role in stimulating the drive for food ingestion. The endocannabinoid system interacts with several neuropeptides that modulate hunger and satiety signals, with the net result being stimulation of appetite. In 1990, Matsuda et al37 reported that a specific cannabinoid receptor, CB1, was found extensively in the brain. CB1 receptors appear to regulate the activity of mesolimbic dopamine neurons, thereby possibly modulating hedonistic or reward behaviors mediated by dopamine, and to interact with neuropeptides such as the melanocortins and gut peptides such as ghrelin in regulating food intake. This knowledge sparked the development of numerous CB1 antagonists, of which rimonabant has by far had the most success in human applications.

In animal studies, considerable evidence indicates that rimonabant suppresses eating and reduces the preference for sweet foods. In addition to its modulatory effect on food intake, the endocannabinoid system has been implicated as having effects on various other neuronal systems that regulate addictive behaviors. For example, the endocannabinoid system and the endogenous opioid systems may have synergetic effects; thus, cannabinoid antagonists bolster the effects of opioid antagonists such as naltrexone and nalmeprine. In rodents trained to self-administer morphine, heroin, Δ⁴-tetrahydrocannabinol, and alcohol, rimonabant suppresses such behavior and preference for these drugs. Moreover, rimonabant decreases nicotine self-administration and the dopamine-releasing effects of nicotine in animals. Taken together, the findings from animal studies suggested a potential broad-spectrum efficacy for rimonabant in controlling food intake and dependence on alcohol, nicotine, and various drugs of abuse.

Interestingly, one of the early clinical applications of rimonabant was to treat schizophrenia and schizoaffective disorder, perhaps with the assumption that the effects of CB1 receptor blockade on dopamine activity in the mesolimbic system might alleviate psychotic symptoms. Rimonabant was not superior to placebo on any outcome measure in this trial.55

Rimonabant in Obesity
In a phase II 16-week trial in obese patients, average weight losses for placebo and 5-, 10-, and 20-mg/d doses of rimonabant were 1.1, 3.5, 3.9, and 4.4 kg, respectively. Thus, it was logical to carry the 5- and 20-mg doses to the next level of testing.

The Rimonabant in Obesity (RIO) program consisted of 4 phase III RCTs: (1) RIO-Europe, (2) RIO-Lipids, (3) RIO-North America, and (4) RIO-Diabetes. All 4 trials compared rimonabant 5 and 20 mg/d with placebo. Consistent with most pharmacological trials for weight reduction, all subjects received diet and lifestyle therapy in addition to drug or placebo. RIO-Europe and RIO-North America were 2-year trials, whereas RIO-Lipids and RIO-Diabetes examined 1-year treatment. Detailed reports of RIO-Lipids and RIO-North America and the first-year results of RIO-Europe have been published in peer-reviewed journals. Summary results of RIO-Diabetes have been presented at scientific meetings; a full peer-reviewed journal report had not been published at the time this review was written.

RIO-Europe
RIO-Europe was conducted primarily in Europe, with a few patients enrolled in the United States. Important exclusion criteria were diabetes mellitus; significant cardiovascular, pulmonary, hepatic, and renal disorders; and substantial neurological or psychiatric illness. Patients were excluded if they had 2 or more episodes of depression, a history of hospitalization for depression, or suicide attempt; concomitant use of antidepressants was not permitted. After a 4-week placebo run-in during which 158 patients were excluded, 1507 patients with BMI ≥30 or BMI ≥27 with comorbid dyslipidemia and/or hypertension were assigned to receive placebo (n = 305), rimonabant 5 mg/d (n = 603), or rimonabant 20 mg/d (n = 599) in addition to a hypocaloric (600-kcal deficit) diet. Patients were mostly white (94%) and female (80%), with an average age of 45 years and an average weight of 101 kg. At baseline, 41% had hypertension, 61% had dyslipidemia, and 41% met the criteria for metabolic syndrome. Patients were seen twice in the first month and monthly thereafter. A total of 920 patients (61%) completed the 1-year follow-up.

In the ITT analysis with the last observation carried forward (LOCF), the rimonabant 20-mg group lost an average of 6.6 kg, whereas the 5-mg and placebo groups had weight losses of 3.4 and 1.8 kg, respectively. The proportions of patients losing at least 5% of their weight in the rimonabant...
20-mg, rimonabant 5-mg, and placebo groups were 51%, 33%, and 19%, respectively; for 10% weight loss, the corresponding proportions were 27%, 10%, and 7%, respectively. Greater improvements (21% versus 12%) in HDL-C and TGs (−14% versus 1%) were observed in the rimonabant 20-mg group than with placebo, but total cholesterol and LDL-C did not improve with any of the treatments. Statistically significant but clinically minor reductions in fasting plasma glucose and insulin were noted with rimonabant 20 mg. The 3 treatments did not differ with regard to the proportion of patients who had impaired glucose tolerance at baseline who subsequently showed improvement on this measure. Systolic and diastolic BP measures showed no significant decrease with any of the study treatments after 1 year. One would have liked to have known whether BP decreased for the 41% of patients who had hypertension at baseline, but this information was not reported.

With regard to adverse events, the incidence of nausea was higher with rimonabant 20 mg (13%) than with 5 mg (5%) or with placebo (4%). In the rimonabant 20-mg group, 87 patients (15%) withdrew owing to adverse events; corresponding figures for the rimonabant 5-mg and placebo groups were 50 (8%) and 28 (9%), respectively. Of note, almost half (42 of 87) of the adverse event–related dropouts in the rimonabant 20 mg group were attributed to psychiatric events, including mood alterations.

Mood was assessed with the Hospital Anxiety and Depression Scale (HADS) at baseline and every 3 months. HADS contains 7 items to assess depressive symptoms and 7 items to assess anxiety symptoms, with scores ranging from 0 to 3 for each item. Depressive and anxiety symptoms are separately totaled. Scores of 0 to 7 are considered normal, 8 to 10 represent borderline symptoms, and ≥11 are considered significant enough to warrant further assessment of the patient. Questions probing suicidal thoughts are absent in HADS. Thus, HADS is generally not used as the primary outcome measure in clinical trials of depression but is considered an acceptable tool to screen for depression and anxiety in primarily nonpsychiatric patients. In RIO trials, when HADS scores reached ≥11 during the treatment period, patients were required to be seen by a psychiatrist for further assessment. However, none of the published papers reported the number of subjects who were removed from RIO trials after psychiatric consultations. Whereas the RIO-Europe report stated that there were no significant changes in HADS scores for depression or anxiety, given the above-described methodology of removing patients with mild depressive symptoms, one would wonder if the LOCF imputation method might have underestimated mood changes over time.

One would have liked to have known the proportions of patients by treatment with scores reaching ≥11 or those with HADS scores that increased by ≥25% relative to baseline.

The main efficacy finding of RIO-Europe was that treatment with rimonabant 20 mg (plus diet) led to approximately 4.7-kg (10.3-lb) greater weight loss than with placebo treatment (plus diet) at 1 year.

**RIO-Lipids**

RIO-Lipids was conducted at 67 sites in 8 countries. Eligibility criteria were similar to those of RIO-Europe, with a few exceptions. Because this study was aimed at demonstrating improvements in lipids in addition to weight loss, patients included in this study were required to have fasting TGs of 1.7 to 7.9 mmol/L (150 to 700 mg/dL), a total cholesterol to HDL-C ratio of >5 for men and >4.5 for women, or both. Patients who received pharmacological treatment for dyslipidemia within 6 weeks of screening were excluded. Other notable exclusions were diabetes mellitus (type 1 or 2) and history of depression requiring hospitalization or history of suicide attempts. After a 4-week placebo run-in period, during which 135 patients were excluded, >1000 patients with BMIs ranging from 27 to 40 were randomly assigned to receive placebo (n = 342), rimonabant 5 mg/d (n = 345), or rimonabant 20 mg/d (n = 346) in addition to a hypocaloric (600-kcal deficit) diet. Race distribution of the patients was not reported. Mean age was ~48 years, and ~40% were men. Average weight was ~96 kg, and the average BMI of ~34 was lower than in the RIO-Europe trial. Just more than half of the patients met the criteria for metabolic syndrome. Although the report did not state whether patients with hypertension were excluded, we gathered via correspondence with the lead author that patients were excluded if they had systolic BP >165 mm Hg and/or diastolic BP >105 mm Hg on 2 consecutive visits from screening to baseline. Approximately 40% of the patients in each group did not complete the trial.

In the ITT-LOCF analysis, the rimonabant 20-mg group lost 6.9 kg, whereas the rimonabant 5-mg and placebo groups lost 3.1 and 1.5 kg, respectively. The proportions of patients who lost at least 10% of their weight in the rimonabant 20-mg and placebo groups were 33% and 7%, respectively. A modest increase (19% versus 11% for placebo) in HDL-C and a modest reduction (13% versus no significant change for placebo) in TGs were noted in the rimonabant 20-mg group, whereas total cholesterol increased slightly with all treatments. LDL-C increased by ~7% in all treatment groups, not finding one would wish to see. There was no significant reduction in fasting plasma glucose with any treatment. Systolic and diastolic BP measures showed statistically significant but clinically less significant decreases in the rimonabant 20-mg group.

With regard to the incidence of specific adverse effects, nausea (13% versus 3% for placebo) and anxiety (9% versus 4% for placebo) were notable with rimonabant 20 mg. More patients dropped out owing to adverse events with rimonabant 20 mg (15%) than with the other 2 treatments (8% and 7%). As was the case in RIO-Europe, psychiatric adverse events in RIO-Lipids accounted for half (26 of 52) of the adverse event–related dropouts in the rimonabant 20-mg group compared with one third (8 of 24) of the withdrawals in the placebo group. The authors of this article presented mood changes separately as “depression,” “major depression,” and “depressed mood,” when all these could have been combined as “depression”; if so combined, 14 patients in the rimonabant 20-mg group had treatment-emergent depression versus 2 in the placebo group. According to the lead author (personal communication, January 2006), patients with HADS scores ≥11 were not excluded from participation in the study, but when the HADS score reached 11 or higher...
during the study, the patient was referred to a psychiatrist, and the study drug was discontinued for patients needing treatment with antidepressants. It is unclear how patients with HADS scores ≥11 were allowed to participate in the study when this score was considered high enough to require the patient to be seen by a psychiatrist during the course of the study.

The main efficacy finding of RIO-Lipids was that treatment with rimonabant 20 mg/d (plus diet) led to ~5.4-kg (11.9-lb) greater weight loss than with placebo (plus diet) at 1 year.

**RIO-North America**

RIO-North America, the largest of the rimonabant trials in obesity, enrolled 3500 obese patients at 72 centers in the United States and Canada. As was the case with the RIO-Europe and RIO-Lipids trials, patients with type 1 or type 2 diabetes mellitus were excluded from participation. During a 4-week run-in period, 455 subjects were excluded, which left 3045 subjects randomized to receive rimonabant 20 mg (n=1222), rimonabant 5 mg (n=1216), or placebo (n=607) in addition to a 600-kcal/d deficit diet. The study participants were predominantly white (84%) and female (81%) and weighed ~105 kg, with an average BMI of just under 38. Almost half of the patients failed to complete the full 1-year study duration, although the dropout rate was somewhat lower with rimonabant 20 mg (45%) than with the other 2 treatments (49%). At 1-year follow-up, in the ITT-LOCF analysis, patients assigned to rimonabant 20 mg had a mean weight loss of 6.3 kg, whereas patients assigned to rimonabant 5 mg and placebo lost 2.9 and 1.6 kg, respectively. Thus, treatment with rimonabant 20 mg for 1 year led to 4.7-kg greater weight loss than achieved with placebo, a finding consistent with the observations made in the RIO-Lipids and RIO-Europe trials. More patients achieved 10% weight loss with rimonabant 20 mg than with placebo (25% versus 9%). Relative to placebo, treatment with rimonabant 20 mg was associated with a 7% increase in HDL-C. TGs decreased by 5% with rimonabant 20 mg compared with an increase of 8% with placebo, thus showing a 13% difference relative to placebo. As seen in other RIO trials, more patients withdrew owing to adverse events with rimonabant 20-mg treatment relative to placebo over 1 year (13% versus 7%), and more patients dropped out owing to psychiatric adverse events with rimonabant 20-mg treatment (6.2% versus 2.3%).

At the end of 1 year, patients who received rimonabant were re-randomized to either the same dose of rimonabant or placebo and followed up for an additional year, whereas the placebo patients remained on the same treatment. Approximately three fourths of the re-randomized subjects completed the second year. At 2-year follow-up, patients who had received rimonabant 20 mg for the entire 2-year duration (n=328) had a mean weight loss of 7.4 kg. In contrast, patients who received rimonabant 20 mg in the first year and placebo in the second year (n=323) achieved an average weight loss of 3.2 kg, and those who received placebo for 2 years (n=292) managed to lose an average of 2.3 kg. These findings suggest that 2-year treatment with rimonabant 20 mg helps obese patients maintain the weight loss achieved in the first year, whereas those who discontinue the treatment regain more than half of the lost weight in the following year. Thus, it appears that patients who have lost significant weight with rimonabant after 1 year are better off continuing the treatment for at least another year, or perhaps longer.

**RIO-Diabetes**

The RIO-Diabetes trial was conducted at 151 centers in 11 countries. In this study, 1045 patients with type 2 diabetes mellitus were randomized to treatment with placebo (n=348), rimonabant 5 mg/d (n=358), or rimonabant 20 mg/d (n=339) for 1 year. The study participants were overweight or obese, with BMI 27 to 40 and an average weight of ~98 kg. Approximately half of the patients were women. To be eligible, patients must have been taking metformin or a sulfonylurea monotherapy for at least 6 months, with fasting plasma glucose between 100 and 271 mg/dL (5.55 to 15.0 mmol/L) and HbA1c between 6.5% and 10%. Approximately two thirds of the sample received concomitant metformin, and one third received a sulfonylurea. In the ITT analysis, treatment with rimonabant 20 mg was associated with 5.3-kg weight loss at 1 year compared with 2.3-kg and 1.4-kg losses with rimonabant 5 mg/d and placebo, respectively. Absolute change in HbA1c was −0.6% with rimonabant 20 mg/d, whereas placebo treatment led to a 0.1% increase; thus, placebo-subtracted change was −0.7%. Similar to the other RIO trials, greater improvements in HDL-C and TGs were observed with rimonabant 20 mg/d relative to placebo. Nausea, dizziness, anxiety, and hypoglycemia occurred more frequently with rimonabant 20 mg than with placebo. Further details of this study are not available, because a peer-reviewed full report had not been published at the time this report was prepared.

**Does Rimonabant Produce Greater Weight Loss Than Currently Marketed Antiobesity Drugs?**

As presented in Table 1, treatment with rimonabant 20 mg and diet is associated with 3.9- to 5.4-kg (8.6- to 11.9-lb) greater weight loss than could be achieved with placebo and diet after 1 year; this finding is similar to the efficacy noted with sibutramine treatment in 1-year RCTs (Figure). The 7.4-kg (16.3-lb) weight loss observed with continuous 2-year treatment with rimonabant 20 mg/d in the RIO-North America study is an impressive finding because there was further weight loss and not weight regain during the second year. Although the STORM trial showed significant weight reduction with sibutramine treatment for 2 years, only those patients who had achieved at least 5% weight loss in the first 6 months continued further in the study; thus, the net weight loss reported at 2-year follow-up was for the initial responders to sibutramine, and the 2-year sibutramine results could not be compared with RIO-North America study findings. In 4 separate 2-year RCTs, patients treated with orlistat regained some degree of the weight during the second year of continuous treatment. At this time, RIO-North America is the only 2-year RCT with rimonabant; studies of longer duration (5 years) will provide more valuable information about efficacy, safety, and cost-benefit analysis of rimonabant therapy.
Weight loss achieved with rimonabant in all RIO trials, with placebo-subtracted increases ranging from 12% to 16% (Table 2). Furthermore, HDL-C showed consistent reduction in TGs has been observed with rimonabant. In the RIO-Diabetes trial, which enrolled overweight/obese patients with type 2 diabetes mellitus, rimonabant treatment led to a negligible 0.7% absolute reduction in HbA1C among overweight adults with type 2 diabetes mellitus in studies of 12 to 26 weeks’ duration. In a 1-year trial of sibutramine in metformin-treated overweight diabetic subjects (not included in the meta-analysis), treatment with 2 doses of sibutramine has not led to reductions in total cholesterol or LDL-C. It is notable that sibutramine-promoted weight loss also led to improvements in TGs and HDL-C but not in total cholesterol or LDL-C in most studies. In contrast, long-term treatment with orlistat is often associated with greater improvements in total cholesterol and LDL-C relative to placebo and less so to improvements in TG and HDL-C.

In the RIO-Diabetes trial that enrolled overweight or obese patients with type 2 diabetes mellitus who were given metformin or a sulfonylurea, treatment with rimonabant for 1 year reduced HbA1C by 0.7% relative to placebo. Changes in glycemic indices were less remarkable with rimonabant treatment. There were no significant changes in diastolic BP, total cholesterol, HDL-C, or LDL-C with rimonabant. In the RIO-Diabets trial, which enrolled overweight/obese patients with type 2 diabetes mellitus, rimonabant treatment led to a 0.7% reduction in HbA1C relative to placebo.

**What About Reduction in Cardiovascular and Metabolic Risk Factors?**

In the 4 RIO trials, rimonabant treatment led to a negligible reduction in systolic BP that ranged from 0.2 to 2.3 mm Hg relative to placebo and no reduction in diastolic BP. A consistent reduction in TGs has been observed with rimonabant in all RIO trials, with placebo-subtracted decreases ranging from 12% to 16% (Table 2). Furthermore, HDL-C showed consistent improvement with rimonabant treatment in all RIO trials, with placebo-subtracted increases ranging from 7% to 9%. However, weight loss achieved with rimonabant

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Data are from ITT analysis. Changes presented are relative to placebo treatment. There were no significant changes in diastolic BP, total cholesterol, or LDL-C with rimonabant.
led to 0.1% to 0.3% greater reduction in HbA1c relative to placebo.26

The efficacy of orlistat in improving glycemic measures or preventing progression to type 2 diabetes mellitus in overweight diabetic or prediabetic patients has been examined in several long-term trials, including a 4-year RCT. In 1 recently published trial, orlistat treatment was associated with a 0.9% greater absolute reduction in HbA1c relative to placebo.28 The above-cited meta-analysis,81 which did not include this recent study, estimated that orlistat treatment was associated with an average 0.4% absolute reduction in HbA1c relative to placebo.

In summary, the most notable changes in lipids with rimonabant treatment in RIO trials were a 12% to 16% reduction in TGs and a 7% to 9% increase in HDL-C.

The National Cholesterol Education Program guidelines emphasize that lowering LDL-C is of primary importance in reducing cardiovascular morbidity and mortality.82 Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) decrease LDL-C by 18% to 55% and TG by 7% to 30% and increase HDL-C by 5% to 15%; they have also been shown to reduce CHD risk significantly, and even regress atherosclerosis.82,83 The FDA requires demonstration of at least a 15% reduction in LDL-C for approval of absorbable antiobesity drugs.84 It is rather disappointing that weight loss achieved primarily with the help of centrally acting antiobesity drugs does not lead to reduction in LDL-C in most studies, and rimonabant is yet another example of this. In contrast, plant-based and high-fiber diets have been shown to reduce LDL-C significantly and as much as the statins in some studies of short duration.85,86 Although the National Cholesterol Education Program has not placed primary emphasis on HDL-C and TG improvements for CHD risk reduction, the guidelines state that high TG (≥150 mg/dL) and low HDL-C (<40 mg/dL in men and <50 mg/dL in women) confer increased risk for CHD. Thus, one might logically assume that improvements in TG and HDL-C, along with weight and waist-size reduction, would eventually decrease CHD risk in obese patients, although one could not arrive at this conclusion without data from long-term studies using primary cardiac end points. Rimonabant has demonstrated somewhat meaningful improvements in TG and HDL-C, but other highly effective interventions are available for this purpose.83 Nicotinic acid and fibric acids reduce TGs by 20% to 50% and raise HDL-C by 10% to 35%. Thus, the value of rimonabant for obese patients with dyslipidemia and/or type 2 diabetes mellitus as monotherapy remains open to question.

Rimonabant to Assist Smoking Cessation

Three STRATUS (Studies with Rimonabant and Tobacco use) studies examined the efficacy of rimonabant for treating nicotine dependence. Key findings of 2 of these studies have been presented in the form of abstracts, posters, or oral presentations at scientific meetings.87,88 Abstinence rates in these RCTs were not highly impressive, although rimonabant appeared to partially attenuate weight gain associated with smoking cessation. The FDA has issued a nonapprovable letter for rimonabant for the smoking cessation indication.89

Pharmacokinetic Profile of Rimonabant

Rimonabant is absorbed rapidly after oral doses and exhibits linear pharmacokinetics in doses up to 20 mg/d.90 Gender does not appear to have a significant influence on the pharmacokinetic profile of rimonabant. Maximum plasma concentration is attained in ~2 hours after an oral dose of 20 mg. Terminal half-life is lengthy in healthy, nonobese individuals (mean 6 to 9 days) and even longer in obese subjects (mean 16 days). Hence, the time it takes to reach a steady state is longer in obese (median 25 days) than in nonobese (median 13 days) individuals. Orlistat has no significant effect on the pharmacokinetic profile of rimonabant. In small studies, rimonabant did not influence the pharmacokinetic profile of digoxin, warfarin, or midazolam, which suggests a lack of significant effects on substrates of P-glycoprotein and CYP2C9 and CYP3A isoenzymes. Furthermore, rimonabant does not appear to significantly alter the pharmacokinetic profile of oral contraceptives (ethinylestradiol and levonorgestrel combination was tested). Rimonabant is metabolized via both hepatic CYP3A and amidohydrolase pathways in vitro. Hence, coadministration of CYP3A4 inhibitors (eg, ketoconazole, itraconazole, ritonavir, and clarithromycin) could result in a significant increase in plasma concentration of rimonabant. Similarly, one might expect CYP3A4 inducers (eg, rifampin, phenytoin, phenobarbital, carbamazepine, and St John’s wort) to reduce plasma concentration of rimonabant.

Adverse Effects of Rimonabant

Nausea has been the most frequent adverse effect of rimonabant in weight-loss trials, particularly with the effective 20-mg dose; however, very few discontinuations were attributed to this adverse event in RIO trials. Among the adverse events that led to early withdrawal of patients, psychiatric events, mood changes in particular, accounted for about half of such dropouts. This was the case in the RIO-Europe, RIO-North America, and RIO-Lipids trials, for which detailed peer-reviewed reports are available (Table 3).

Given the knowledge that cannabinoid CB1 receptors are located in the limbic system and other areas of the brain that mediate stress responses (eg, hypothalamus), it is conceivable that these receptors play a role in modulating emotional responses.91-93 Using laboratory paradigms such as the light/dark test and the chronic unpredictable mild stress model, Martin et al94 have demonstrated that CB1 knockout mice exhibit increased anxiety-like responses and enhanced sensitivity in developing an anhedonic or depressive state. In a review of this topic, Hill and Gorzalka95 have argued that pharmacological and genetic blockade of the CB1 receptor

<table>
<thead>
<tr>
<th>Study</th>
<th>Rimonabant 20 mg</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>RIO-Europe</td>
<td>7.0%</td>
<td>5.2%</td>
</tr>
<tr>
<td>RIO-Lipids</td>
<td>7.5%</td>
<td>2.3%</td>
</tr>
<tr>
<td>RIO-North America</td>
<td>6.2%</td>
<td>2.3%</td>
</tr>
<tr>
<td>RIO-Diabetes*</td>
<td>Data unavailable</td>
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</tbody>
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*Reasons for early withdrawals were not listed in the RIO-Diabetes results summary available to the authors in the form of a poster handout.
induces a state that is similar to melancholic depression. However, a mice study conducted by the manufacturer of rimonabant suggested that the drug might actually have antidepressant-like effects. Endocannabinoids have significant effects on mesolimbic dopamine neurons. In animal studies, chronic cannabinoid treatment upregulates serotonin 5-HT2A receptor activity while downregulating 5-HT1A receptors, and there might be opposite effects on these serotonin receptors with chronic blockade of endocannabinoid activity. Furthermore, it has been reported that CB1 receptor density is upregulated in the prefrontal cortex of suicide victims who suffered from depression and alcoholism. On the basis of the findings from animal experiments and human postmortem studies, one would be hard-pressed to draw any definitive conclusions about the potential mood-altering effects of acute and chronic CB1 blockade in humans. Nevertheless, these findings suggest that the endocannabinoid system has significant modulatory effects on mood and emotional responses to stress. With this understanding, it would not be an extremely unlikely finding if one were to observe mood changes associated with pharmacological manipulation of CB1 receptors in vulnerable individuals.

Summary

Nonsurgical interventions—pharmacological or lifestyle modifications—do not appear to provide more than 10% weight loss for most obese patients after treatment for 1 to 2 years. Because antiobesity drugs are almost always tested in combination with lifestyle therapies, in the absence of these ancillary interventions and the structure of a clinical trial, one would suspect that these drugs might be even less effective in real-life clinical practice settings than in clinical trials. Multimodal therapies such as combining pharmacotherapy with intensive lifestyle modification therapy might provide better results, but only if such interventions are continued for several years. Lack of access, lapses in patient motivation, inadequate health insurance reimbursement, and cost issues limit the practical usefulness of such multimodal therapies to obese patients at large. At present, very few effective pharmacological treatment options are available to assist obese patients in losing weight. Rimonabant is a new antiobesity drug currently under FDA review.

The strengths of rimonabant are as follows: (1) In 4 well-designed studies with >6600 overweight and obese patients, rimonabant has demonstrated consistent efficacy with regard to weight reduction. (2) Rimonabant offers a novel mechanism of action, which may make it well suited as an alternative for people who do not respond well to other agents and for combination treatment with other antiobesity agents. (3) Weight loss achieved with rimonabant also appears to improve some features of metabolic syndrome. (4) Its pharmacokinetic profile appears to be favorable in general. (5) Most side effects appear to be mild and transient. (6) No evidence of any significant cardiovascular adverse effects exists.

The limitations of rimonabant are the following: (1) Weight-reduction efficacy is not superior to the modest effects observed with currently approved antiobesity drugs. (2) Although some features of metabolic syndrome have been shown to improve modestly, no reduction in LDL-C occurs, although this appears to be the case with all centrally acting antiobesity drugs. (3) Whereas rimonabant has been shown to be superior to placebo in helping smokers quit in short-duration trials, its overall efficacy is not particularly impressive, and it has been judged to be not approvable for this indication at this time. (4) Although rimonabant appeared to be reasonably well tolerated in general, psychiatric symptoms were the most common adverse effects that led to early withdrawal of patients in RIO trials. (5) Given the exclusion of patients with a past history of significant depression and current presence of even mild depressive symptoms (as reflected by normal mean HADS scores at baseline) and the removal of patients from the RIO trials after a slight increase in depressive symptoms, it is unclear whether this drug is suitable for obese patients with coexisting depression. (6) The sample of subjects enrolled in the RIO trials had limited racial diversity.

Future Directions

In April 2006, the FDA issued an “approvable” letter for rimonabant for a weight-management indication. Rimonabant (Acomplia/Zimulti) has recently received approval from the EMEA and is currently marketed in some European countries with the precautions that it should not be used in patients with serious psychiatric illness such as major depression until the psychiatric condition is controlled, and that it is not recommended for patients receiving antidepressants. If encouraging results are obtained in ongoing studies with rimonabant in alcoholism and other addictive disorders, there will be increased enthusiasm for this drug, with a view toward broader applications. Because one of the major reasons that clinicians advise obese patients to lose weight is to better manage hypertension, studies should be conducted with rimonabant in overweight/obese patients with hypertension, who are taking antihypertensive drugs, to examine potential benefits such as reduction in the number of BP medications and/or doses required. Because the prevalence of depression is quite high in obese patients seeking treatment for this problem in clinical settings, studies examining the efficacy and safety of rimonabant in this population will provide much needed practical knowledge about this drug to clinicians. Studies enrolling greater proportions of blacks and Hispanics will likely enhance the generalizability of the findings of RIO trials. Studies examining outcomes over longer periods (at least 5 years) will provide more meaningful data with regard to risk reduction and prevention. Results of the STRADIVARIUS study (Strategy To Reduce Atherosclerosis Development InvOlving Administration of Rimonabant: the Intravascular Ultrasound Study), a large international trial assessing the effect of rimonabant treatment on the progression of atherosclerosis, may not available for a few years.

Note Added in Proof

After submission of this article, Dr Gaddde and Dr Pt-Sunyer, lead author of the RIO-North America report, exchanged correspondence related to psychiatric events observed in the RIO trials.
Disclosures
Dr. Gadde has received research support from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), GlaxoSmithKline, Eli Lilly & Co., and Vivus, Inc. He has served as a consultant for and owns stock in Orexigen Therapeutics, Inc. Dr. Gadde has also served as a consultant for GlaxoSmithKline and Vivus. Dr. Allison has received research support from NIDDK, Eli Lilly & Co., Ortho-McNeil, and Pfizer. He has also received other support (educational grants) from Jansen-Cilag, Eli Lilly & Co., Merck, Ortho-McNeil, and Pfizer. He has served as a consultant for Amgen, Bristol Myers Squibb, Fertin Pharma, GlaxoSmithKline, and Jansen-Cilag.

References


Key Words: obesity □ drugs □ pharmacology
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Kishore M. Gadde and David B. Allison

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/content/115/19/e465.full.pdf

Data Supplement (unedited) at:
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The article, “Cannabinoid-1 Receptor Antagonist, Rimonabant, for Management of Obesity and Related Risks” by Gadde and Allison that appeared in the August 29, 2006 issue (Circulation. 2006;114:974–984) contained the following errors:

On pages 976–977, while discussing the results of RIO-Europe, it was stated that the proportions of patients losing at least 5% of their weight in the rimonabant 20-mg, rimonabant 5-mg, and placebo groups were 67%, 44%, and 31%, respectively. The corrected statement should read that the proportions of patients losing at least 5% of their weight in the rimonabant 20-mg, rimonabant 5-mg, and placebo groups were 51%, 33%, and 19%, respectively.

Table 1 (page 979) incorrectly noted that the mean placebo-subtracted 1-year weight loss for sibutramine in the study by Apfelbaum et al was 4.7 kg. The correct mean placebo-subtracted (simple subtraction, not based on the estimates obtained from the analysis of variance model) 1-year weight loss for sibutramine in the study by Apfelbaum et al was 5.7 kg.

This correction has been made to the current online version of the article, available at http://circ.ahajournals.org/cgi/content/full/114/9/974. The authors regret the error.

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