The Challenge of Treating Obesity: The Endocannabinoid System as a Potential Target

KATHY KEENAN ISOLDI, MS, RD; LOUIS J. ARONNE, MD

ABSTRACT

Obesity and cardiometabolic risk, or the metabolic syndrome, continue to be major public health concerns. To date, treatment with lifestyle and pharmacotherapy interventions has resulted in limited efficacy in reversing the upward trend in this present-day health crisis. Research reveals that a modest 5% to 10% weight loss results in substantial improvement in health. While obtaining modest weight loss is often achievable, maintaining lost weight is challenging. Research has recently improved our understanding of several endogenous pathways that influence body weight regulation and disease risk. The endocannabinoid system has been found to regulate appetite and energy expenditure, as well as lipid and glucose metabolism. Interest in blocking stimulation of this pathway to aid weight loss and reduce cardiometabolic risk factor development is an area of interest and research. This article reviews the mechanisms by which the endocannabinoid system is believed to influence body weight regulation and cardiometabolic risk factors, as well as the results of clinical trials investigating the safety and efficacy of a selective cannabinoid-1 receptor antagonist (rimonabant). Clinical trials investigating rimonabant treatment resulted in substantial reductions in body weight and markers for cardiometabolic risk in study participants. However, increases in adverse events were reported in the drug-treated group. Data regarding long-term benefit and adverse events from rimonabant treatment are being collected in several ongoing clinical trials. Rimonabant is currently available in 42 countries, but has not received United States Food and Drug Administration approval. Food and nutrition professionals play a pivotal role in tackling the current obesity crisis; it is essential that they understand the many physiological mechanisms regulating body weight. Emerging research data reveals pathways that influence appetite and energy metabolism, and this knowledge may form the foundation for new clinical treatment options for obese individuals. J Am Diet Assoc. 2008;108:823-831.

Obesity is not a new health problem. Archeological finds in Egypt dating back to between 2,000 and 2,500 BC reveal that some individuals in the upper social classes were obese (1). The current obesity epidemic, however, presents as a major public health concern for all socioeconomic groups, with higher prevalence rates noted in minority and economically impoverished groups (2). Prevalence of overweight and obesity, defined as a body mass index (BMI; calculated as kg/m²) ≥ 25 and ≥ 30, respectively, continues an upward trend in developed as well as in developing countries (3). Two thirds of all adults in the United States are overweight, with close to one third meeting the criteria for obesity (4), increasing the risk for developing cardiovascular disease, type 2 diabetes mellitus (T2DM), cancer, gallstones, osteoarthritis, nonalcoholic fatty liver disease, sleep apnea, and asthma (5,6). The direct cost of overweight and obesity in the United States, expressed in 2002 dollars is estimated at $92 billion (7).

Overweight and obese individuals also experience psychosocial burdens as a consequence of excess fat mass. Increased stigmatization, being a target of discrimination, and scoring lower on health-related quality-of-life surveys have been associated with overweight and obesity (5,6,8). The multiple benefits of weight loss appear obvious, yet the ability to lose and maintain lost weight remains extremely difficult (9,10). It is essential that food and nutrition professionals guiding those seeking lasting weight loss understand the physiological obstacles faced in accomplishing this goal. New therapeutic pathways have been discovered offering hope to obese individuals fighting to regain their health. One pathway recently

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identified is the endocannabinoid system, stimulation of which is associated with fat mass deposition and disease development. Factors influencing disease promotion in overweight and obese individuals, as well as current treatment options, are briefly presented, followed by a review of the endocannabinoid system and results from clinical trials with a compound that blocks the endocannabinoid system.

**EXCESS FAT MASS AND DISEASE INITIATION**

There is a strong association between fat mass and disease promotion. Fat cells, also known as adipocytes, secrete proteins, referred to as adipokines, which influence body weight regulation, vascular integrity, inflammation, and disease initiation (11,12). Leptin is secreted from fat cells and crosses the blood-brain barrier to bind to its receptor in the hypothalamus. Depending on the amount of leptin available, it will activate or deactivate signals that inhibit or increase food intake and regulate energy expenditure (11). Leptin is known to affect the gene expression and pathway of both appetite-suppressing and appetite-stimulating substances (13).

Other adipokines secreted from fat cells include tumor necrosis factor-α, interleukin-6, and plasminogen activation inhibitor-1, all of which promote a pro-inflammatory and prothrombotic state. Interleukin-6 levels have been found to be 10-fold higher in obese than lean individuals (14). It has been proposed that excess fat mass overstimulates the innate immune system, creating a state of chronic, low-level inflammation, ultimately propagating disease (15).

**OBESITY AND THE METABOLIC SYNDROME**

Risk for developing the metabolic syndrome is greater in overweight and obese individuals, particularly those with abdominal adiposity (16,17). The metabolic syndrome consists of a “constellation” of cardiometabolic risk factors that increases disease risk. The syndrome is characterized by increased serum levels of triglycerides and glucose, reduced serum levels of high-density lipoprotein (HDL) cholesterol, increased blood pressure, and central adiposity (18,19). Development of the metabolic syndrome can lead to development of T2DM and cardiovascular disease (19). Age-adjusted prevalence rate for the metabolic syndrome in the United States adult population is estimated at 27%, with the greatest rise noted in women (16).

**TREATING OBESITY**

Prevention measures are of paramount importance in halting the exponential rise in the prevalence of overweight and obesity; however, the need for effective treatment options to manage obesity is an urgent matter. Obesity treatment modalities include diet, exercise, pharmacotherapy, and surgery (20,21). The National Heart, Lung, and Blood Institute of the National Institutes of Health recommends lifestyle modification targeted at decreasing caloric intake and increasing physical activity as the first line of action in the treatment of overweight and obesity (20). If no substantial weight loss has occurred after 6 months of treatment, those with a BMI of ≥30 or a BMI of ≥27 with the presence of comorbidities, may require the addition of pharmacology to their treatment plan (20). Surgical intervention to treat severe obesity is reserved for those with a BMI ≥40, or with a BMI ≥35 with comorbid illness (20). The American Dietetic Association endorses ongoing lifestyle management as an integral component of obesity care. However, if optimal control cannot be reached with medical nutrition therapy (MNT) alone, and concurrent pharmacotherapy is required, the American Dietetic Association proposes a team approach, with active collaboration among food and nutrition professionals and other members of the health care team (22).

**REASONABLE GOAL SETTING**

A reduction of 5% to 10% of body weight will improve the lipid profile, insulin sensitivity, and endothelial function, as well as reduce thrombosis and inflammatory markers (20,23). Encouraging patients to lose a modest amount of weight can be a challenge, as data collected during weight-loss trials report that many dieters desire to lose >30% of their body weight (24-26). Results from the Diabetes Prevention Program highlight the powerful effect a small reduction in body weight can have on derailing disease incidence. This trial had a mean follow-up of 2.8 years, and participants who lost an average of 5.9% of baseline body weight (5.6 kg) decreased their incidence of developing T2DM by 58%, compared to the control group (27).

Lifestyle modification has been effective in promoting short-term weight-loss success with many individuals achieving a 9% to 10% reduction in body weight in the first 6 months of treatment (10). However, long-term treatment success through lifestyle interventions is less encouraging, with weight regain a common occurrence (9,10). Researchers report that weight loss typically peaks after 6 months of treatment; however, by the 1-year mark, one third of lost weight is usually regained, and often all lost weight is regained within 5 years (9,10). Weight regain was noted as a common outcome in a review of several lifestyle modification weight-loss interventions. In a meta-analysis, six randomized clinical trials treating overweight or obese adult study participants with either diet alone or with diet and exercise were reviewed (28). Although diet combined with exercise resulted in greater weight loss than diet alone (13 vs 9.9 kg; $P=0.063$), almost half of lost weight was regained after 1 year in both groups (28).

Endogenous mechanisms can help to explain the great difficulty experienced in weight-loss maintenance. Body weight regulation is controlled, in part, by multiple physiological mechanisms, such as the endocannabinoid system, which act on overlapping separate pathways to ultimately defend body fat and impede weight-loss efforts as a survival strategy (11). Furthermore, experts point to a plethora of obstacles in our “obesogenic” environment that create difficulty in maintaining lost weight (9). The expanding portion size of foods served, increased accessibility to high-fat fast food, increased soda consumption, and fewer opportunities for daily calorie usage though leisure time and nonleisure time physical activities are cited as a few of the many culprits that lay in the path of a healthy lifestyle (9,29). The impact of the many physical and environmental obstacles present has prompted inter-
est in more aggressive treatment options to aid those struggling to achieve lasting weight loss (30,31).

CURRENT PHARMACOLOGICAL TREATMENT OF OBESITY

Pharmacological treatment of obesity dates back to the 1950s, when phentermine received US Food and Drug Administration (FDA) approval for short-term management of obesity (30). Phentermine remains available today (30). In 1997 and 1999, approval was received from the FDA for sibutramine and orlistat, respectively, for long-term treatment of obesity (32). A review of mechanisms of action, side effects, and placebo-corrected weight-loss outcomes for FDA-approved medications is provided in Table 1. Although these medications produce considerably more weight loss than placebo, total weight loss has been only modest.

Combining both behavioral guidance and weight-loss medication may hold the promise of additive or synergistic results. Wadden and colleagues (33) studied 224 men and women and reported substantial improvement in weight-loss success in the group of dieters who received medication may hold the promise of additive or synergism and degradation (36). Interest in the endocannabinoid system began with the observation that marijuana use transiently reduces endocannabinoid system activity, as well as in various peripheral tissues, such as adipocytes, hepatocytes, skeletal muscles, endothelial cells, and the gastrointestinal tract. Cannabinoid receptors-2 are found in the spleen, thymus, and tonsils, and are not believed to be involved in regulation of food intake and energy homeostasis (38).

Cannabinoid Receptors: CB1 and CB2

High-affinity cannabinoid-binding sites were discovered in rodent brain cells (42), and two cannabinoid receptors were subsequently cloned in humans. Cannabinoid receptor-1 (CB1), which primarily modulates food intake and energy expenditure, was cloned in 1991 (43). Cannabinoid receptor-2 (CB2), which appears to influence immune function, was cloned in 1993 (44). cannabinoid receptors-1 are located throughout the central nervous system, as well as in various peripheral tissues, such as adipocytes, hepatocytes, skeletal muscles, endothelial cells, and the gastrointestinal tract. Cannabinoid receptors-2 are found in the spleen, thymus, and tonsils, and are not believed to be involved in regulation of food intake and energy homeostasis (38).

Endocannabinoid Ligands

The search for compounds that couple to cannabinoid receptors led to the discovery of N-arachidonoyl-ethanolamine (AEA or anandamide) (45), and 2- arachidonoyl-glycerol (2-AG) (46), endogenous cannabinoid ligands (38), which are potent mediators of energy homeostasis (41). They primarily activate CB1 and/or CB2 receptors (38,47,48). Engeli and colleagues (41) measured circulating levels of endogenous endocannabinoids in 20 lean and 20 obese postmenopausal women to investigate the association between fat mass and endocannabinoid levels. Levels of AEA and 2-AG were 35% and 52% higher, respectively, in obese vs lean subjects. In addition, a strong negative correlation was found between expression of fatty acid amide hydrolase, the enzyme that degrades AEA, and circulating endocannabinoid levels. This suggests that obese individuals may have higher circulating endocannabinoids because of reduced degradation enzymes available (41). External factors have also been implicated in increasing serum endocannabinoid levels. The amount of n-6 polyunsaturated fatty acids in the diet may directly influence endocannabinoid levels by increasing availability of phospholipid precursors (49). Conversely, n-3 polyunsaturated fatty acids are believed to suppress endogenous ligand production, thus potentially reducing endocannabinoid system stimulation (50,51).

ENDOCANNABINOID SIGNALING SYSTEM AND WEIGHT REGULATION

Research on animal models revealed a strong association between the endocannabinoid system and body weight regulation (52). Exogenous administration of 2-AG directly into the nucleus accumbens of rats caused an acute increase in food consumption (53). Alternately, CB1 receptor antagonists decreased food intake and body weight.
<table>
<thead>
<tr>
<th>Compound</th>
<th>FDA-approval (yes/no), year of approval</th>
<th>Organ target</th>
<th>Mechanism of action</th>
<th>Usual dosage</th>
<th>Placebo-corrected weight loss (kg) (95% CI)</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phentermine</td>
<td>Yes, 1959</td>
<td>CNS&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Sympathomimetic amine</td>
<td>15-30 mg daily</td>
<td>−3.6&lt;sup&gt;d&lt;/sup&gt; (−6.0 to −0.6)</td>
<td>Palpitations, tachycardia, elevated blood pressure, gastrointestinal effects</td>
</tr>
<tr>
<td>Sibutramine</td>
<td>Yes, 1997</td>
<td>CNS</td>
<td>Combined norepinephrine and serotonin reuptake inhibitor</td>
<td>10 or 15 mg once daily</td>
<td>−4.45&lt;sup&gt;d&lt;/sup&gt; (−5.29 to −3.62)</td>
<td>Increased blood pressure, increased pulse, dry mouth, insomnia, constipation</td>
</tr>
<tr>
<td>Orlistat</td>
<td>Yes, 1999</td>
<td>Gut</td>
<td>Gastric and pancreatic lipase inhibitor</td>
<td>120 mg three times daily</td>
<td>−2.75&lt;sup&gt;d&lt;/sup&gt; (−3.3 to −2.20)</td>
<td>Diarrhea, flatulence, bloating</td>
</tr>
<tr>
<td>Rimonabant</td>
<td>No</td>
<td>CNS/peripheral organs</td>
<td>Cannabinoid-1 receptor antagonist</td>
<td>20 mg once daily</td>
<td>−4.6&lt;sup&gt;d&lt;/sup&gt; (−4.3 to 5.0)</td>
<td>Depression, anxiety, dizziness, nausea</td>
</tr>
<tr>
<td>Rimonabant in Obesity trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>North America&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>−4.7 (−4.1 to −5.4)</td>
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<tr>
<td>Europe&lt;sup&gt;e&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td></td>
<td>−4.8 (−3.9 to −5.7)</td>
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<tr>
<td>Lipid&lt;sup&gt;e&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td></td>
<td>−5.4 (−4.6 to −6.3)</td>
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<td>Diabetes&lt;sup&gt;e&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td></td>
<td>−3.9 (−3.2 to −4.6)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>FDA—US Food and Drug Administration.
<sup>b</sup>CI—confidence interval.
<sup>c</sup>CNS—central nervous system.
<sup>d</sup>Results from pooled data.
<sup>e</sup>Data based on intention-to-treat analysis (last observation carried forward).
Researchers found that even while taking in the same number of calories, mice without CB1 receptors were resistant to diet-induced obesity when compared to mice with intact receptors, suggesting a metabolic as well as appetite effect associated with the endocannabinoid system. Administration of a CB1 receptor blocker (rimonabant) in genetically obese and leptin-deficient mice protected the rodents from developing characteristic hyperphagia and weight gain.

The communication between the satiety-stimulating hormone leptin, the hunger-inducing peptide ghrelin, and endocannabinoid production illuminates the power of the endocannabinoid system on appetite. Leptin has been found to suppress production of endocannabinoids in the hypothalamus. Genetically obese mice with defects in the leptin-signaling pathway exhibit elevated levels of both AEA and 2-AG in the hypothalamus. Conversely, ghrelin appears to upregulate hypothalamic endocannabinoid levels. Blockade of CB1 receptors with rimonabant was found to strongly reduce the appetite-stimulating action of ghrelin when injected into the hypothalamus of mice.

In addition, endocannabinoids and CB1 receptors are found in the neurons of the gastrointestinal mesentery and the mucosa of the fundus and appear to influence gastric emptying, gastric motility, and release of ghrelin into the circulation. Hence, leptin downregulates endocannabinoid levels, whereas ghrelin upregulates production.

Cannabinoid receptor-1 antagonists may influence weight by increasing energy expenditure. Obese rats treated with rimonabant reduced their body weight by 20% after 4 days of reduced food intake, and continued to lose weight throughout the 2-week treatment period, even when food intake became comparable with that of lean rats. Researchers measured oxygen consumption in genetically obese mice treated with a CB1 antagonist (rimonabant). They found that a 7-day treatment with a CB1 receptor antagonist caused a 37% increase in basal oxygen consumption, thus supporting the theory that the endocannabinoid system influences energy expenditure.

Endocannabinoid Signaling System and Lipid and Glucose Regulation

A growing body of evidence suggests that the endocannabinoid system is involved in the physiological regulation of glucose and lipid metabolism in peripheral tissues. For example, in animals, the intake of a high-fat diet activates the hepatic endocannabinoid system, which leads to increased lipogenesis and the subsequent development of hepatic steatosis (fatty liver). Thus, blocking the endocannabinoid system to reduce cardiometabolic risk proved appealing. The many favorable results from animal trials led researchers to develop a CB1 receptor antagonist to treat obesity in humans.

Human Trials with CB1 Receptor Antagonist Rimonabant

Results from human clinical trials investigating the safety and efficacy of a selective CB1 antagonist (rimonabant), in the treatment of obesity report favorable outcome measurements. The Rimonabant in Obesity trials, which constitute four separate trials, collected data from >6,600 participants. The Rimonabant in Obesity trials were conducted using a randomized, double-blind, placebo-controlled study design in multiple sites throughout North America, South America, and Europe. Rimonabant in Obesity North America and Europe trials included adult men and women with a BMI ≥30 or a BMI of ≥27 with obesity-induced disease. The Rimonabant in Obesity Lipids trial enrolled drug naive, hyperlipidemic overweight and obese men and women. The Rimonabant in Obesity Diabetes trial included overweight and obese men and women on monotherapy for treatment of T2DM. Mean age range for study participants was 18-55 years.
participants in the Rimonabant in Obesity trials was 45 to 56 years, mean weight range was 93 to 105 kg, and mean BMI was 34 to 38 (66). Study participants were randomized into placebo, 5 mg rimonabant, or 20 mg rimonabant treatment groups and were followed for 1 year. The Rimonabant in Obesity North America study captured data for 2 years. During the second year of the trial, subjects in the placebo group continued to receive placebo, and the treatment group was re-randomized to receive either the same dose of rimonabant as year 1, or to receive placebo (62). In the four Rimonabant in Obesity trials, all study participants were guided individually by health care professionals to follow a 600-calorie deficit diet, and on ways to increase daily physical activity (62-65).

At the 1-year mark, statistically significant reductions in weight in the 20 mg rimonabant groups were reported in the Rimonabant in Obesity North America, Europe, Lipids, and Diabetes trials (–6.3, –6.6, –6.9, and –5.3 kg, respectively), compared to the placebo groups (–1.6, –1.8, –1.5 and –1.4 kg, respectively) (62-65). In a recent Cochrane review, pooled weight loss results with rimonabant treatment from the Rimonabant in Obesity trials were reported as slightly greater than the pooled weight loss results from trials with sibutramine, and greater than the weight loss results observed with orlistat (67). A review of placebo-corrected weight-loss outcome measurements from the Rimonabant in Obesity trials is reported in Table 1.

Glycemic control was measured in the Rimonabant in Obesity Diabetes Trial, and twice as many participants receiving 20 mg rimonabant (43%) achieved the target endpoint of glycosylated hemoglobin A1c <6.5% compared with placebo (21%) (65). More than 50% of the improvement in glycosylated hemoglobin A1c levels reported were independent of the weight loss achieved (65).

At the end of the 2-year mark in Rimonabant in Obesity North America, subjects who were randomized from 20 mg rimonabant to placebo experienced weight regain, whereas those who remained on the drug maintained their favorable outcome. Researchers concluded that 20 mg per day of rimonabant plus lifestyle changes for 2 years promoted sustained reductions in weight, waist circumference, and favorable changes in cardiometabolic risk factors, including reductions in serum triglycerides and fasting glucose, and an increase in serum HDL cholesterol levels (62).

At the 1-year mark, substantial improvements in food-behavior parameters, assessed by a visual analog scale, were found in participants in the 20 mg rimonabant group vs the placebo-treated group. Participants in the 20 mg rimonabant group reported lower appetite (P<0.0001), increased ease in following the diet (P<0.0001), less desire for high-fat foods (P=0.0003), and less desire for sweets (P=0.04), when compared with the placebo-treated group (65).

A higher incidence of adverse events was reported in the 20-mg rimonabant group as compared to those in the placebo or 5-mg rimonabant group. Dizziness, headache, anxiety, depressed mood, and nausea were the most common side effects reported as reasons for study discontinuation in the 20-mg rimonabant group (62-65). A review of adverse events reported in the Rimonabant in Obesity trials is presented in Table 2. Rimonabant is currently available in 42 countries; however, it is not available in the United States (71).

The emergence of psychiatric conditions with the use of a cannabinoid receptor antagonist is biologically plausible, therefore, reports of psychiatric adverse events in the Rimonabant in Obesity trials have been documented and are being evaluated. Pooled data from the four Rimonabant in Obesity trials reveal that 26% of participants in the 20-mg rimonabant group reported psychiatric symptoms (depressive events, anxiety, psychomotor agitation, or sleep disorder) vs 14% in the placebo group. Symptoms of depression were reported in 9% of participants in the 20-mg rimonabant group, vs 5% of participants in the placebo group (depressed mood, depression, depressive symptoms, or major depression) (72). Depressive episodes were most often mild or moderate in severity with recovery after discontinuation of drug, or corrective treatment (73). Rimonabant was approved in Europe in 2006 and the European Medicines Agency recommended contraindicating use of rimonabant in patients with ongoing major depression, or in those being treated with antidepressants because of risk of exacerbation of existing conditions. The agency also recommended discontinuation of rimonabant if depression develops (74).

Participants of the Rimonabant in Obesity trials were predominately white females. Therefore, study results cannot be generalized to minority populations, and this presents as a study limitation. The high attrition rate,
approximately 50% reported in the Rimonabant in Obesity trials, is another limitation that may influence outcome measurement reporting. High attrition rates have been documented as a common problem in weight-loss medication trials (75). In addition, questions regarding duration of treatment with rimonabant beyond the 2-year point, as well as long-term side effects, remain unanswered. To address these questions several studies are currently underway, continuing the investigation of treatment with rimonabant on abdominal adiposity, lipid profile measures, diabetes outcome, and cardiovascular disease risk factors (76). The Comprehensive Rimonabant Evaluation Study of Cardiovascular Endpoints and Outcomes trial is currently investigating the effect of rimonabant on myocardial infarction, stroke, and cardiovascular death in 17,000 obese study participants spanning 4 to 5 years (76,77). There is still much to learn about the endocannabinoid system; however, what has been uncovered during the past decade suggests that this pathway may lead to a new treatment option for obese individuals.

CONCLUSIONS AND PRACTICAL APPLICATION
Research data collected during the past decade has greatly improved our understanding of the development of obesity and cardiometabolic risk factors. However, recent obesity prevalence rates confirm that our improved knowledge has not resulted in a reduction in incidence rates (4). Achieving a body weight loss of 5% to 10% has been shown to improve health and decrease disease incidence. However, we are reminded by data collected during weight-loss trials that many obese individuals desire to lose much greater amounts of weight. Data also supports that MNT is the hallmark of effective, long-term weight-loss success. Food and nutrition professionals counseling overweight and obese patients are in a unique position to educate patients on the many physical benefits of modest weight loss, as well as the endogenous factors that oppose loss of large amounts of body weight. To substantially reduce disease risk, maintenance of lost weight is essential and, therefore, continuation of MNT is of paramount importance.

The American Dietetic Association, in a position paper on weight management, proposes that to improve health requires a “lifelong commitment” to a healthful lifestyle (78). The need to manage obesity as a chronic illness is apparent, and patients need to learn that there is no quick fix to maintaining a healthy weight. Lifestyle modification techniques that are realistic and sustainable

Table 2. Adverse events reported in the Rimonabant in Obesity trials (≥5% in any group)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>North America</th>
<th>Europe</th>
<th>Lipids</th>
<th>Diabetes</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=498)</td>
<td>20 mg Rimonabant (n=1,042)</td>
<td>Placebo (n=305)</td>
<td>20 mg Rimonabant (n=599)</td>
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<tr>
<td>Nasopharyngitis</td>
<td>14</td>
<td>17</td>
<td>15.7</td>
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<tr>
<td>Upper respiratory infection</td>
<td>15.2</td>
<td>18.5</td>
<td>7.5</td>
<td>5.5</td>
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<tr>
<td>Influenza</td>
<td>7.7</td>
<td>8.8</td>
<td>10.5</td>
<td>9.0</td>
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<tr>
<td>Gastroenteritis</td>
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<td>7.9</td>
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<tr>
<td>Vomiting</td>
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<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>5.1</td>
<td>4.3</td>
<td>5.2</td>
<td>5.7</td>
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<tr>
<td>Nausea</td>
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<td>11.2</td>
<td>4.3</td>
<td>12.9</td>
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<tr>
<td>Diarrhea</td>
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<td>5.3</td>
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<td>7.2</td>
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<tr>
<td>Depressed mood</td>
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<td>5.2</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Dizziness</td>
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<td>Arthralgia</td>
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<td>6.9</td>
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<td>Fatigue</td>
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<td>Hypoglycemia</td>
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<td>Serious adverse event</td>
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<tr>
<td>Adverse events that led to study discontinuation</td>
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<td>4.5</td>
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<tr>
<td>Placebo (n=348)</td>
<td>20 mg Rimonabant (n=339)</td>
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\textsuperscript{a}Data from references 62-65.
should be instituted in a team-approach setting to facilitate the best possible outcomes.

Pharmacological obesity treatment options are limited. However, several pathways have recently emerged as potential targets to modify endogenous appetite and energy mechanisms. The endocannabinoid system presents as an intriguing target to modulate obesity, as well as cardiometabolic health. Research efforts continue with several large-scale trials investigating the efficacy and safety of rimonabant currently underway (77).

Food and nutrition professionals play a pivotal role in tackling the difficult mission of preventing and treating obesity. To work in concert with physicians, combining lifestyle modifications along with medication use requires that food and nutrition professionals remain current with advances in pharmacology for obesity treatment (79). Understanding the physiological mechanisms that defend fat mass will help practitioners educate and effectively guide obese patients toward an improved understanding of obesity, and a realistic treatment plan. In addition, educating the public about the physiological factors underlying fat mass deposition will help to oppose the negative biases aimed at obese individuals. Staying current with obesity treatment options, and participating as a team member along with physicians, will aid those working with this population in dispensing the best quality of care, ultimately leading to the best hope for improved health outcomes for obese patients.

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