Efficacy of rimonabant in obese patients with binge eating disorder

Authors
Z. Pataky1, C. Gasteyger1, O. Ziegler2, A. Rissanen1, C. Hanotin1, A. Golay1

Affiliations
1 Department of Community Medicine, Service of Therapeutic Education for Chronic Diseases, World Health Organization Collaborating Centre, University Hospitals of Geneva, Geneva, Switzerland
2 Department of Diabetes, Metabolic and Nutritional Diseases, Jeanne d’Arc Hospital, Nancy University Hospitals, Nancy, France
3 Obesity Research Unit, Helsinki University Central Hospital, Helsinki, Finland

Key words
endocannabinoid system
rimonabant
obesity
binge eating disorder

Abstract
In obesity, a dysregulation of the endocannabinoid system has been shown. The endocannabinoid receptor blockage by rimonabant demonstrated interesting metabolic effects. However, the role of rimonabant in weight loss of patients with binge eating disorder has not been investigated. Thus, our aim was to evaluate the effects of rimonabant on body weight in obese patients with binge eating disorders.

This multicenter, randomized, double-blind, placebo-controlled study included 289 obese subjects (age 18–70 years, body mass index 30–45 kg/m²) with binge eating disorders. Subjects were randomized (1:1) to receive rimonabant 20 mg/day or placebo for 6 months. In total, 289 participants (age: 43.2 ± 10.5 yrs, 91 % of women) were randomized. The completer rate was similar (71 %) in both treatment and placebo groups. Participants treated with rimonabant lost 4.7 ± 5.2 % of their initial body weight, vs. 0.4 ± 4.5 % in the placebo group (difference between both groups: 4.4 ± 0.6 kg, p < 0.0001). The rimonabant group showed a greater reduction on the binge eating scale total score (mean ± SD –40.9 ± 35.2 %) vs. placebo (–29.9 ± 34.6 %, p = 0.02). The incidence of treatment emergent adverse events was comparable in both the rimonabant (82.5 %) and placebo (76.0 %) group. Discontinuations due to treatment emergent adverse events occurred in 13.3 % rimonabant-treated vs. 6.2 % placebo-treated participants.

In conclusion, this is the only randomised, placebo-controlled, double-blind trial having assessed the effect of rimonabant in patients with binge eating disorders. The rimonabant treatment reduced body weight significantly more than placebo in obese subjects with binge eating.

Trial registration number (clinicaltrials.gov): NCT00481975

Introduction
In obesity, the endocannabinoid system shows a general over-activity [1–4] and plays a role in the control of energy balance and metabolism through both central and peripheral mechanisms [5–7]. Rimonabant was the first blocker of G protein-coupled cannabinoid receptors of type 1 (CB1) marketed for the treatment of obesity and was shown to have anorexigenic effects. The efficacy of rimonabant on weight loss and cardiometabolic risk factors has been well demonstrated in several clinical studies [7–10]. Due to the important psychiatric side effects in obese and overweight patients [11], the rimonabant is not available on the market from November 2008. On the other hand, the endocannabinoid system is currently a top contender as a therapeutic target for the treatment of obesity [12].

New findings on the endocannabinoid system are of interest. Surprisingly, even after rimonabant withdrawal from the market, they are recent studies evaluating the effects of rimonabant in humans, particularly from the metabolic point of view [13,14]. We consider that assessing the effects of rimonabant on binge eating disorders (BED) could also be of interest because it could add to the scientific understanding of the potential role of endocannabinoids in eating disorders. BED is defined as an eating disorder referenced in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition [15]. This disorder is characterized by the consumption of large amounts of food in a short period of time accompanied by a subjective sense of loss of control, but without compensatory behaviour for limiting weight gain, such as vomiting or laxative abuse, as occurs in bulimia nervosa.
Increased plasma levels of arachidonoylthanolamide (AEA) has been shown in patients with BED [16]. Knowing that the AEA exerts a stimulatory action on food intake [17, 18], the endocannabinoid system could potentiate the drive to eat and thus, the blockade of CB1 receptor might be beneficial in obese patients with BED. CB1 inactivation by blockade is a strategy used to suppress eating by decreasing hedonic aspects of food intake, which could suggest the importance of tonic endocannabinoid signaling for normal feeding [19]. Very recently, Parylak et al. have shown in animal model a reduction of binge-like intake after pre-treatment with a CB1 antagonist [20]. BED is often associated with obesity and correlates with adiposity [21, 22]. The prevalence of obese individuals with binge episodes varies from 10% to 30% of obese populations engaged in weight-loss programs [23,24]. Treating patients with BED with the aim of attaining weight loss has been shown as being particularly challenging: only modest decreases in body weight could be observed by using pharmacotherapy, cognitive or behavioural treatments or a combination of these options [25].

Up to date, results on the effects of rimonabant on body weight in obese patients with BED have not been published. Therefore, the primary objective of this study was to assess the effect of rimonabant compared to placebo on body weight over a period of 6 months when prescribed together with a hypocaloric diet in subjects with obesity and BED. Secondary objectives were to assess the effect of rimonabant on the number of binge episodes per week in the study population, to assess the effect of rimonabant on eating behaviour, and to evaluate the safety and tolerability of rimonabant over a period of 6 months.

Materials and Methods

Study design
This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose regimen, 6 month, phase 3b study (trial registration number NCT00481975, www.clinicaltrials.gov). The study was conducted between August 2004 and August 2005 in 29 active centres in 7 countries (Finland, France, the Netherlands, Portugal, Sweden, Switzerland and the United States). Patients in all centres were recruited in Internal medicine settings and General practitioners, among subjects seeking help for weight loss. Following a 15-day screening period, participants were randomly allocated to placebo or 20mg/day of rimonabant using a randomization ratio of 1:1. Randomization was performed by an investigator with no clinical involvement in the trial and by using SAS statistical software, version 8.2. The rimonabant and placebo were in capsule form and identical in appearance. They were prepacked in bottles and consecutively numbered for each patient according to the randomization schedule. Each patient was assigned an order number and received the capsules in the corresponding prepacked bottle. The study flow chart is shown in ▶ Fig. 1.

The study protocol was approved by independent ethics committees. The protocol complied with recommendations of the 18th World Health Congress (Helsinki, 1964) and all applicable amendments. In compliance with the Declaration of Helsinki, written informed consent was to be obtained from each participant before enrolment in the study.

Study population
Inclusion criteria were as follows: men or women aged ≥18 years and ≤70 years, body mass index (BMI) ≥30 to ≤45 kg/m² and diagnosis of eating disorder based on DSM-IV criteria using the Questionnaire on Eating and Weight Patterns (QEWP-R) [26]. The QEWP-R is a 27-item, self-report measure that explores weight and dieting history, binge eating, behaviour, and purging behaviour. Previous studies indicate that the QEWP-R identifies individuals with clinically meaningful BED [27] and is a useful screening measure for the disorder [28].

Main exclusion criteria were as follows: history of surgical procedures for weight loss; marijuana or hashish users; presence or recent history (within 6 months prior to screening visit) of DSM-IV substance abuse or dependence; administration of anti-obesity drugs (e.g sibutramine, orlistat) or administration of other drugs for weight reduction (phentermines, amphetamines); presence of any clinically significant endocrine disease; presence of treated or untreated type 1 or type 2 diabetes; thyroid preparations or thyroxine treatment; presence of any other disease deemed as being clinically significant, or any other medical condition that might interfere with the evaluation of study medication; presence or history of DSM-IV bulimia or anorexia nervosa; the initiation of anti-depressive treatment within the last 3 months with fluoxetine hydrochloride (Prozac®, Seraphem®, Symbax®) or other drugs known to lower the binge eating frequency.

Drug used
The treatments consisted of capsules containing 20mg of rimonabant or placebo administered once per day, before breakfast. Treatment compliance was defined as the percent of actual investigational product taken compared to the total scheduled amount.

Diet
During the 6-month treatment period, a mild hypocaloric diet was prescribed to all participants. The energy requirement was calculated by the dietician based on the estimated basal metabolic rate and the physical activity of each participant at baseline (day -1) and at month 3 (day 90). Basal metabolic rate was calculated according to Harris-Benedict formula for women: 655.1 + (9.96 × weight in kilos) + (1.850 × height in cm) – (6.775 × age in years) – (4.676 × age in years) and for men: 66.5 + (13.75 × weight in kilos) + (5.003 × height in cm) – (6.775 × age in years). From this amount of energy, 600 kcal/day was subtracted to obtain the recommended diet. The daily diet should not have been less than 1200 kcal/day and contained approximately 50% carbohydrates, 30% lipids, and 20% proteins; alcohol consumption should have been ≤20g/day or ≤140g/week.

Assessments
The participants were seen every 2 weeks up to month 1 (day 30), and then monthly until month 6 (day 180). The primary efficacy assessment was the change in body weight from baseline to month 6. Body weight was measured with the participant wearing undergarments or very light clothing and no shoes, and with an empty bladder. Waist circumference was measured according to established methods [29].

Participants were instructed to report in the 14-day period preceding each visit, the daily number of binge episodes with indication of dates on a 14-day questionnaire. This questionnaire
helped in calculating the number of binge episodes per week during the screening period and the treatment period, respectively.

The binge eating score is a self-assessment questionnaire (16 items) developed to assess binge-eating problems among obese persons; it was shown to be useful in quantifying the level of binge-eating severity.

Participants assessed eating behaviour by using the TFEQ [30]. The TFEQ is a self-assessment questionnaire (51 items) developed to measure cognitive and behavioural components of eating in 3 separate subscales: cognitive restraint (21 items) designed to measure dietary restraint, i.e., control over food intake in order to influence bodyweight and body shape; disinhibition (16 items) designed to measure episodes of loss of control over eating; hunger (14 items) concerns subjective feelings of hunger and food craving.

Statistics
Sample size calculations were performed based on the primary endpoint in the Intention-to-Treat (ITT) population. The nominal type I error rate was 0.05. Results observed in the phase 2B trial (DRI3388) of rimonabant in obese participants were used to power the study. The observed standard deviation of change in weight from baseline was approximately 4 kg in DRI3388 (after 4 months of treatment). It was assumed, based on published data that it may increase to 6 kg after 6 months of treatment. A total sample size of 200 (100 per treatment group) provided 94% power to detect a 3 kg difference between rimonabant and placebo after 6 months of treatment assuming a standard deviation of 6 kg.

All statistical tests were two-sided tests at the 5% significance level. Continuous data was summarized for each treatment group using the number of observations available (n), means and standard deviations; categorical data was summarized for each treatment group using counts and percentages.

For quantitative/continuous efficacy variables, for parameters not associated with any baseline measurement, a one-way analysis of variance (ANOVA) with treatment as fixed effect was used. Otherwise analysis of covariance (ANCOVA) using the baseline value as covariate and with treatment as fixed effect was used. The model included the interaction term of the covariate and

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**Fig. 1** Study flow chart.
treatment. This interaction term was to be removed from the model if non-significant at the 5% level. The adjusted means (and their standard error, SE) was computed and the comparisons were performed using a student’s t-test.

Categorical data was analysed using Pearson’s Chi-square test. For efficacy analyses, the primary population was the ITT population. We used the ITT-LOCF analysis. For each individual, missing values were replaced by the last observed value of that variable. The ITT population corresponded to participants randomized and exposed to double-blind study drug having at least 1 post-baseline evaluation for a given parameter. For the safety analyses, the population consisted of all randomized participants who had at least 1 dose of double-blind study drug and was used as the reference population in the overall clinical (adverse events) safety analyses. All analyses were performed using SAS, version 8.2.

Results

A total of 289 participants were randomized, 205 (70.9%) completed treatment. The number of participants reaching ≥80% compliance was 95.9% in the rimonabant group and 99.2% in the placebo group.

Baseline characteristics

Baseline characteristics of the study population are presented in Table 1. These characteristics were similar across treatment groups. The overall mean (SD) age was 43.2 (10.5) years, and the mean BMI was 36.8 (4.1) kg/m². A large percentage of participants had morbid obesity (BMI ≥40 kg/m²) (24.2%). At screening, both treatment groups had a similar history of binge eating disorder. A greater percentage of participants in the rimonabant group (18.2%) were smokers at screening compared to the placebo group (12.3%).

Effect on anthropometric characteristics

Table 2 shows changes in anthropometric characteristics according to treatment group in the ITT population. A significantly greater body weight loss from baseline to 6 months was seen in participants treated with rimonabant when compared with placebo: participants in the rimonabant group lost a mean (SD) of 4.7% (5.2) of their initial body weight, while participants in the placebo group lost only 0.4% (4.5). The mean (SE) difference in weight loss between both groups was 4.4 (0.6) kg. Consistent with the results for body weight, a significantly greater decrease in waist circumference was observed in participants treated with rimonabant when compared with placebo at 6 months. The mean (SE) difference between both groups was 3.4 cm (0.7).

In the rimonabant group, 42.0% of participants lost 5% of their initial body weight, vs. 13.2% in the placebo group (p < 0.0001): a 10% body weight loss was observed in 14.0% vs. 3.5% of participants (p = 0.0016), respectively.

Effect on eating behaviour

A greater number of participants treated with rimonabant (78.7%) met the response definition (≥50% reduction in binge per week frequency) when compared with placebo (69.1%), with no significant difference (p = 0.07). With respect to reduction in number of binge episodes/week, a mean (SD) change of −64.9% (78.1) in the rimonabant group was observed, while in the placebo group, this change was −59.4% (71.7): this difference was not statistically significant (Table 3).

At 6 months, participants treated with rimonabant showed a significantly greater reduction in binge eating scale from baseline when compared with participants treated with placebo: the mean (SD) observed changes were of −49.9% (35.2) vs. −29.9% (34.6), respectively. No significant difference between both groups was observed for changes in dietary restraint, changes in disinhibition and changes in hunger (Table 3).

Safety evaluation

The safety population consisted of participants randomized and exposed to at least 1 dose of investigational product. The mean (SD) treatment duration was comparable for each treatment group (151 (54) days in the placebo group and 149 (54) days in the rimonabant group).

The incidence of treatment emergent adverse events (TEAE) was comparable in both the rimonabant (82.5%; 118/143) and placebo (76.0%; 111/146) treatment groups. 19 (13.3%) participants in the rimonabant group discontinued due to TEAEs when compared with 9 (6.2%) participants in the placebo group. Serious adverse events (SAE) were reported in similar frequencies in both treatment groups (2 participants with any SAE in each treatment group). There were no deaths reported during the study.

Table 4 presents individual TEAE reported in ≥5% of rimonabant participants and more frequently (≥1% difference) than in the placebo group. These TEAE included nausea, nasopharyngitis, diarrhoea, insomnia, anxiety, depression and vomiting. The incidence of depression was slightly higher in the rimonabant group than in the placebo group (6.3% vs. 4.1%) but the difference did not reach statistical significance.
pressant medications, such as for example randomised placebo-controlled trials have investigated antidepressants and antiepileptic medications classes varied considerably, from modest effects (mean change: \(-1.7 \) kg) for selective-serotonin reuptake inhibitors to larger effects for antiepileptic (\(-4.6 \) kg) and antiobesity (\(-3.6 \) kg) medications. The additional weight reduction by medication compared to placebo was of \(3.4 \) kg in 8 of the 14 trials that provided usable data (1236 patients). Thus, the mean difference in weight change between the rimonabant group and the placebo group we observed in our study was superior to the mean value reported in this meta-analysis, as well as superior to the mean value observed with selective-serotonin reuptake inhibitors. The dropout rate (29.1% overall) in this trial was comparable to drop-out rates observed by Brownley et al. [49] who reviewed randomized controlled trials assessing different treatment modalities in binge eating disorder (16–57%), as well as to the mean dropout rate observed by Reas and Grilo (30.4% in patients treated with medication) [25]. It should however also be noted that twice as many participants in the active treatment group dropped out due to adverse effects. With respect to secondary endpoints, the fact that the number of self-reported binge episodes/week decreased in a comparable manner across both treatment groups is probably due to the participation in the study itself. We observed a statistically significantly greater decrease in the scores obtained on the binge eating scale in the rimonabant group vs. the placebo group. However, this change was probably clinically not significant. In fact, neither the change in the number of binge episodes per week, nor changes in dietary restraint, disinhibition and hunger did differ significantly between both groups. It is difficult to compare our results to those of other studies, as definitions of the effect on binge-eating vary among studies. Generally, data from the literature, as highlighted by Reas and Grilo [25], suggest that pharmacotherapy with or without psychotherapy is unlikely to enhance binge-eating outcomes.

Discussion and Conclusions

This is the only randomised, placebo-controlled, double-blind trial having assessed the effect of rimonabant in subjects with BED. Our results show that rimonabant exerts a significantly greater effect than placebo on weight loss in patients with obesity and BED. This weight loss can be considered as being clinically significant, as it has been shown that even modest weight loss (approximately 5–10% of body weight) improves obesity-related cardiovascular and metabolic abnormalities [31, 32].

Table 2: Modifications of anthropometric characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Rimonabant</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>LOCF</td>
<td>Baseline</td>
</tr>
<tr>
<td>body weight – kg</td>
<td>100.6 ± 14.6</td>
<td>100.2 ± 15.3</td>
<td>101.5 ± 15.8</td>
</tr>
<tr>
<td>waist circumference – cm</td>
<td>109.4 ± 11.3</td>
<td>107.4 ± 12.1</td>
<td>108.7 ± 12.6</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SD; LOCF = Last observation carried forward; CI = 95% Confidence Interval; Difference = Difference in changes between the 2 groups.

Table 3: Modifications of eating behavior.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Rimonabant</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>LOCF</td>
<td>Baseline</td>
</tr>
<tr>
<td>number of binge episodes/week</td>
<td>4.9 ± 5.1</td>
<td>1.8 ± 2.8</td>
<td>5.7 ± 5.1</td>
</tr>
<tr>
<td>binge eating scale</td>
<td>25.1 ± 8.4</td>
<td>17.3 ± 9.6</td>
<td>26.4 ± 7.2</td>
</tr>
<tr>
<td>dietary restraint (TFEQ)</td>
<td>8.3 ± 4.0</td>
<td>10.7 ± 5.0</td>
<td>8.1 ± 4.0</td>
</tr>
<tr>
<td>disinhibition (TFEQ)</td>
<td>12.4 ± 2.3</td>
<td>10.1 ± 3.7</td>
<td>12.8 ± 2.4</td>
</tr>
<tr>
<td>hunger (TFEQ)</td>
<td>9.3 ± 3.5</td>
<td>7.2 ± 3.9</td>
<td>10.1 ± 3.0</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SD. LOCF = Last observation carried forward. TFEQ = Three factor eating questionnaire.

Table 4: Individual treatment emergent adverse events reported in ≥5% of rimonabant patients and more frequently (≥1% difference) than in the placebo group.

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 146) N (%)</th>
<th>Rimonabant (n = 143) N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>nausea</td>
<td>6 (4.1)</td>
<td>43 (30.1)</td>
</tr>
<tr>
<td>nasopharyngitis</td>
<td>24 (16.4)</td>
<td>29 (20.3)</td>
</tr>
<tr>
<td>diarrhoea</td>
<td>10 (6.8)</td>
<td>13 (9.1)</td>
</tr>
<tr>
<td>insomnia</td>
<td>4 (2.7)</td>
<td>11 (7.7)</td>
</tr>
<tr>
<td>anxiety</td>
<td>4 (2.7)</td>
<td>9 (6.3)</td>
</tr>
<tr>
<td>depression</td>
<td>6 (4.1)</td>
<td>9 (6.3)</td>
</tr>
<tr>
<td>vomiting</td>
<td>2 (1.4)</td>
<td>8 (5.6)</td>
</tr>
</tbody>
</table>

This is a copy of the author's personal reprint.
It has to be highlighted that the mean binge eating scale score of the participants in our study was <27. A score of 27 or above is classically considered as being consistent with the presence of a BED [50]. Thus, a significant proportion of our participants might have had subjective binge eating episodes, rather than a true BED: this has also been called subthreshold BED. However, it has been suggested that a differentiation between obese people with subthreshold BED and BED might not be of practical utility because they do not differ in general and eating-related psychopathology and seem to show an equivalent response to multimodal treatment interventions [51].

The finding that rimonabant induced a weight loss whereas placebo did not seems to be in contradiction with the lack of significant effect on the scores reflecting eating behaviour. This may be explained by the difficulty of accurately assessing BED through self-administered questionnaires. The presence of a significant weight loss reflects a change in dietary intake and, consequently, eating behaviour. In that sense, weight loss should certainly be considered as a much better marker of drug efficacy. The tolerability profile of rimonabant during this study can be considered as good, notably when taking into account the fact that participants with binge eating very often present psychiatric co-morbidities [52]. In this study, anxiety and depression were the 2 only psychiatric symptoms reported as occurring more often in participants treated with rimonabant than in those receiving placebo. We must mention that among contraindications to rimonabant use were patients with an uncontrolled psychiatric condition as well as patients who were clinically depressed or who were taking any antidepressant. One could speculate that if these contraindications would have been taken into account and respected in all patients in whom the rimonabant was prescribed, the destiny of this class of medication would have been different! Internist and general practitioners should be able to diagnose severe depression. In our study, in purpose we included patients with moderate BED, mostly seen in internal clinical settings.

Our study has several strengths and weaknesses. Among the strengths, it should be mentioned that the present study included a large amount of participants, which was sufficient to ensure a sufficient power for the study to demonstrate its primary endpoint. Also, the duration of the treatment period was longer than the mean treatment duration of similar trials. Finally, the randomised, placebo-controlled design ensured a proper evaluation of the effect of rimonabant on weight loss. The first weakness of our study is that a self-administered questionnaire without a concomitant clinical interview was used in order to detect the presence of binge eating. Still, the binge eating scale has been shown to perform satisfactorily as an initial screening tool for the diagnosis of BED; it is however less accurate in identifying non-BED individuals and the frequency of binge eating [28]. Secondly, the fact that we did not define remission in binge eating as zero binges for past 28 days – which is probably the most conservative definition – may be criticized. However, even the use of our less conservative definition did not show clinically significant changes: thus, a posteriori, one might conclude that the more strict definition would have had no added value. Finally, the study did not include any follow-up of the participants after the treatment period, which is unfortunately the case of most trials in this area: additional research is needed in order to evaluate the outcome of these participants when they exit the treatment period.

In conclusion, our results show that rimonabant, when compared to placebo, exerts a clinically significant effect on weight loss in obese participants with binge eating disorder. This effect is equivalent, if not greater, to other medications which have been studied in this indication. Our data did not show a clinically significant effect of rimonabant on eating behaviour. This may not be considered as extremely surprising, taking into account that treating these patients is very challenging and usually requires a combination of behavioural, dietary and pharmacological therapy to attain successes which most often can be considered as modest and transient at the best.

**Conflict of interest:** Corinne Hanotin was an employee of sanofi-aventis at the time of the study.

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