Published in final edited form as:

Eur J Med Genet. 2011 ; 54(1): 14–18. doi:10.1016/j.ejmg.2010.09.015.

Psychiatric Adverse Effects of Rimonobant in Adults with Prader-Willi syndrome

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Abstract

Background—Prader Willi syndrome (PWS) without strict environmental modifications can lead to obesity associated with significant morbidity and mortality. In addition to increased appetite, these individuals have decreased energy expenditure with lower insulin like growth factor 1 (IGF-1), which contributes to adiposity. No effective treatment is available for this condition. Endocannabinoid receptor CB1 antagonist, rimonobant, has been effective for treatment of obesity in adult subjects. Rimonobant promotes weight loss by multiple proposed mechanisms, including decreased appetite and lipogenesis, and increased energy expenditure. Therefore, we conducted this pilot study to evaluate the effect of rimonobant on body weight and composition of adults with PWS.

Method—This was a double blind placebo controlled study. Body weight, total fat mass, fasting ghrelin, leptin, IGF1 and insulin like growth factor binding protein (IGFBP3) were collected at baseline, and after 90 and 180 days of treatment with placebo or 20 mg of rimonobant.

Results—Due to psychiatric adverse effects, 50% of subjects in the rimonobant group withdrew, and the study was terminated early (N=10) for safety concerns. There was a trend for weight loss, lower fat mass and higher IGF1 level at the end of study in this group. Leptin followed the fat mass and decreased with rimonobant treatment.

Conclusion—Rimonobant administration may be efficacious for weight loss in adults with PWS; unfortunately it is associated with an unacceptably high risk of psychiatric side effects. Future CB1 antagonists will need a better psychiatric profile before considered in the treatment of obesity in this genetic condition.

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Keywords

Prader Willi syndrome; Obesity; CB1 cannabinoid receptor; Rimonabant

1. INTRODUCTION

Prader Willi Syndrome (PWS) is the most common genetic syndrome associated with obesity. This condition is caused by the absent expression of the paternally active genes in the PWS region on 15q11-q13 [1], and presents with uncontrollable appetite, hyperphagia and excessive weight gain leading to severe obesity. Uncontrolled obesity, is in fact the major cause of death in adults with PWS. [2]

Abnormal central regulation of appetite, due to hypothalamic dysfunction [3] and possibly an imbalance of neurotransmitters such as ghrelin have been proposed to be the cause of overeating and lack of post-feed satiety in PWS. Ghrelin is an orexigenic peptide secreted from oxyntic gastric mucosa that increases food intake and body weight. [4] Several reports have suggested that subjects with PWS may have elevated ghrelin levels that correlate with hunger in PWS. [5–9] Leptin is a hormone secreted from fat tissue and is involved in the regulation of appetite and energy metabolism. [10] In PWS, initial report suggested that leptin has a role in pathogenesis of hyperphagia, while subsequent studies did not observe the same findings. [11–13]

Another feature of PWS that can contribute to obesity is growth hormone deficiency or insufficiency. [14] Low peak Growth Hormone (GH) levels and/or low basal GH secretion with low insulin like growth factor 1 (IGF-1) levels may be responsible for the poor growth and high body fat mass (BFM) frequently encountered in PWS. [14–16]

Interestingly, the endocannabinoid system appears to be critically involved in the regulation of appetite, body weight, and metabolism. Endocannabinoid receptor CB1, is widely expressed in the central nervous system (CNS), autonomic gastric vagus nerve endings of the peripheral nervous system (PNS), and other key cells involved in body energy metabolism, including adipocytes, hepatocytes, and myocytes. [17–19] The CB1 receptor antagonist, rimonabant (SR141716), has been the target of extensive research and is effective for treatment of obesity in adults without PWS. [20] Rimonabant promotes weight loss by multiple proposed mechanisms, including decreased appetite and lipogenesis, and increased energy expenditure. [17,21,22] Also reports have shown that CB1 blockade prevents elevation of ghrelin during both the fasting and post-fed state in rats [23] and Ob/ob mice. Zucker rats with defective leptin signaling have over-activity of the endocannabinoid system. [24] Finally, cannabinoids inhibit GH secretion via direct pituitary and indirect hypothalamic mechanisms. [25] *In vitro* administration of a CB1 agonist, WIN55212-2 directly inhibits growth hormone secretion in cultured acromegaly-associated pituitary adenoma cells, whereas rimonabant reverses this effect. [26]

Currently there is no effective treatment for hyperphagia in PWS. In light of the above information regarding the endocannabinoid system, we initiated this novel pilot study to assess effects of rimonabant on appetite, body weight and composition, and growth hormone secretion in adults with PWS.

2. SUBJECTS AND METHODS

2.1 Study design

This was a double-blind placebo controlled clinical trial designed to enroll a total of 20 young adults aged 18 to 35 years with Prader Willi Syndrome (PWS). The study was initiated in June 2007 and conducted in the Clinical and Translational Science Center (CTSC) at Weill Cornell Medical College. Then in November 2009, increased risk of depression and suicide with use of rimonabant was reported. These reports led to the removal of rimonabant from the European market. Due to these safety concerns, as well as high frequency of drop out in one blinded arm, we elected to terminate this study before complete enrollment. Approved IRB consent and assent were obtained from 10 patients and their legal guardians prior to early study termination. Subjects were randomized into 2 groups of control and intervention, and were treated with 20 mg per day of rimonabant or placebo for the duration of 6 months. Randomization was done by the research pharmacy at Weill Cornell's CTSC. Participants, investigators and sponsor personnel were blinded to treatment assignment. Patients were seen at the beginning of study, after 3 month and at the end of the 6 months at CTSC of Weill Cornell Medical Center following an overnight fasting. During each visit, body weight, body mass index (BMI) and fasting blood tests were done. Blood tests included liver function tests, leptin, total ghrelin, IGF-1 and insulin like growth factor binding protein (IGFBP3). Presence of side effects, objective assessment of the appetite (satiety after meal, compulsive eating behaviors, and food seeking) and self-abusive behavior were assessed at the beginning of the study, on the 90th day after the initiation of the intervention, and at the end of the study.

For objective assessment of appetite and feeding behavior, we used the Food-Related Problem Questionnaire (FRPQ), which has been validated in this population. This scale evaluates 3 major aspects of feeding behavior in PWS, including pre-occupation with food, impairment of satiety and composite negative behavior. [27] This assessment was done by a single dietitian at CTSC throughout all visits. Depressive or anxiety related symptoms were screened by the Hospital Anxiety and Depression (HAD) scale questionnaire at each visit to CTSC by the research team, and in between formal visits by caregivers at monthly intervals. [28] At the enrollment and end of study, total body fat mass (TFM) was determined using whole body Dual Energy X-ray Absorptiometry (DEXA) scan (GE Lunar, Prodigy scanner with 300 lbs weight limit).

An independent data and safety monitoring board (DSMB) from Weill Cornell University assessed the safety of the participants by reviewing unblinded data every 3 months, and advised as to the continuation, alteration, or cessation of the study.

2.2 Subjects

Subjects were recruited by advertisements placed on the Prader Willi syndrome association's (PWSA-USA) website, and from the Obesity and Metabolic Endocrine Clinics at Weill Cornell Medical Center and Winthrop University Hospital. Subjects were selected if they had a BMI ≥ 30 and diagnosis of PWS confirmed by high-resolution cytogenetics, fluorescent *in situ* hybridization, and/or methylation studies. [14,29,30] Subjects were excluded if they had untreated endocrine disorders, significant behavioral problems or psychiatric illness that interfered with follow up of the protocol, or if they had end stage renal, liver or pulmonary disease. The HAD scoring system was used to assess the presence of anxiety and depression, and to exclude subjects with anxiety or depression. Finally, we excluded subjects on growth hormone, psychotropic medications or any other weight loss medications.

2.3 Laboratory assays

Blood samples were collected after overnight fasting and prior to breakfast for leptin, ghrelin, IGF-1 and IGFBP-3 levels. Serum total ghrelin and leptin were assessed with radioimmunoassay kits (Millipore, Missouri, inter and intra assay variability of 3.5% and 13.3%, and 5.2% and 7.8%, respectively). IGF-1 and IGFBP-3 were assessed by enzyme-linked immunosorbent assay kit (Beckman Coulter, California) following the manufacturer's instruction (inter and intra assay variability of 6.4% and 6.8%, and 5.7% and 11.4%, respectively). All laboratory assays were performed by the CTSC core lab at Weill Cornell Medical College (NIH Grant UL1-RR024996). Rimonabant and placebo was purchased from Rockwell Compounding Associates, Inc. Rye, NY under IND No. 77336.

2.4 Statistical methods

Due to the early termination of the trial, numbers at each time point were small, and statistical significance was not expected. Descriptive statistics, such as median and range, were used to describe active and placebo patients at specific time points due to the small sample size. We compared the distribution of the values between placebo and active patients at day 0 and at day 90, separately (i.e., between group comparisons at select time points). We also compared time points within each group of active and placebo patients (i.e., within group comparisons). Because of small sample size, the nonparametric Wilcoxon rank-sum test (analogous to the two-independent samples t-test) was performed for between group comparisons at select time points (i.e., active vs. placebo) and the nonparametric Wilcoxon signed-rank test (analogous to the paired t-test) was performed for comparison of time points within each group of active and placebo patients. All p-values are two-sided and statistical significance was assessed at the 0.05 alpha levels. No adjustment for multiple comparisons was performed given the small number of patients contributing to each of the analyses. All analyses were performed in SPSS Version 17.0 (SPSS Inc., Chicago, IL).

3. RESULTS

We studied a total of 10 adult subjects with Prader Willi Syndrome aged 19.5 to 36.3 year old (mean/SD of 23.73 ± 5.14). All subjects were obese with mean/SD weight of 99.58 ± 16.46 kg and BMI of 42.89 ± 8.90 kg/m². The research pharmacy at CTSC of Weill Cornell Medical College randomly assigned subjects to either placebo (n=4) or rimonabant (n=6).

The entire placebo group completed the course of study, while 3 out of 6 subjects dropped out in the rimonabant group. Two subjects dropped out after the baseline visit (at 2 and 4 weeks) and one after the first follow up visit at 4 months. Two of the three subjects reported mild dysthymia. Another subject initially developed sleep problems and anxiety, and subsequently after 2 weeks of rimonabant administration presented with paranoid ideation and psychotic reaction. This subject was instructed to discontinue study drug and referred to psychiatry for evaluation and management. Despite discontinuation of drug, she continued to have sleep problems and paranoid ideation requiring psychotropic medications to alleviate symptoms. The psychiatric team involved in the care of this subject could not determine if clinical presentation was directly due the effect of rimonabant, or if an underlying psychiatric problem had been triggered by rimonabant. No other adverse reactions were reported on subjects who completed the study. One subject that dropped out at 4 months had pre-diabetes treated with metformin. None of the other 9 study subjects had any other endocrine disorders.

For comparison of the median values from day 0 to day 90 and day 180, we eliminated the 2 subjects who dropped out after the baseline visit. None of the parameters of interest showed a statistically significant difference between the two groups by the end of 6 months.

However, we observed interesting positive trends in the rimonabant treated group compared to the placebo. Results are shown in Table 1 and 2. Overall, with rimonabant treatment there was a trend towards lower body weight, BMI and TFM. (Table 1) Figure 1 displays normalized trends over time for BMI (right panel) and TFM (left panel).

With respect to hormonal profiles, fasting ghrelin levels increased after 6 months in the placebo (58%) and rimonabant (50%) group. Leptin levels followed the changes in body fat mass in each group. (Table 2) Despite a trend for weight loss, the IGF1 levels increased in rimonabant group at the end of study. (Table 2)

With respect to appetite and feeding behavior, the total FRPQ score and individual questions assessing preoccupation with food, impairment of satiety and composite negative behaviors, varied throughout study and did not show any particular trends in various aspects of feeding behaviors.

4. DISCUSSION

The endocannabinoid system is an important regulator of appetite, and inhibition of CB1 receptor can improve satiety and suppress feeding. In addition, reported data have suggested that CB1 antagonism with rimonabant improves overall metabolism, independent of food intake. [17,18,22] Obesity in Prader Willi Syndrome is a debilitating problem that is caused by an absent sense of satiety leading to obsession with food and overfeeding. Without treatment, obesity can lead to cardiovascular disease, diabetes, cor pulmonale and sleep apnea. Currently, there is no effective therapy to target satiety in PWS. Therefore, we conducted this novel double blind randomized clinical trial of 6 months duration to provide the first insight into the possible role of the endocannabinoid system on regulation of satiety, body weight and growth hormone secretion in adults with PWS.

The primary objective of this study was to determine if there would be a significant difference between rimonabant-treated patients and controls with respect to body weight and fat mass at the end of six months. Unfortunately, we had to terminate the study early following recruitment of only 10 subjects, which limits interpretation of our data due to small sample size. Early termination was due to the unacceptably high occurrence of psychiatric side effects (anxiety, dysthymia and paranoia) in the rimonabant treated patients that led to 50% withdrawal in this group. Based on a recent report by FDA, rimonabant administration was associated with 9% incidence of depression and suicide (versus 5% incidence in placebo) in overweight adults without PWS which led to withdrawal of rimonabant from the commercial market. [31] Although we specifically screened and excluded potential subjects for any degree of psychiatric issues, we observed an even higher incidence of psychiatric side effects than previously reported. Our much higher incidence of psychiatric symptoms with rimonabant may be due to the fact that adults with PWS are particularly vulnerable to psychiatric disorders. [32,33]

Despite the small sample size, we observed a trend towards weight loss and lower body fat mass in the rimonabant group compared to the placebo group. The rimonabant group experienced an approximately 30% decrease in body weight versus a 1 % increase in the placebo group. (Figure 1) These findings are in agreement with multi-center large clinical trials conducted on non-PWS adults with obesity that demonstrated that rimonabant promotes significant weight loss. [20,34] Our results suggest that future CB-1 antagonists with improved psychiatric profile may be efficacious for promoting weight loss in PWS. This may become clinically important due to a paucity of treatment options for these patients.

Our secondary objectives were to explore potential mechanisms for weight loss after treatment with rimonabant. After 6 months of treatment, leptin levels followed the changes in body fat mass in each group. The placebo group had slight increase in body fat content and leptin levels, whereas the rimonabant group had decreases in both body fat mass and in leptin levels (Table 2). This may suggest that rimonabant did not have any additional effects on leptin, beyond the weight loss. Fasting ghrelin increased in both groups by the end of study (Table 2). However, a less pronounced increase in ghrelin level was noted in the rimonabant group despite a trend for weight loss. Another characteristic of PWS is subnormal growth hormone production and responsiveness [15,16] that leads to excess of body fat mass. Endocannabinoids are also involved in regulation of growth hormone. Both marijuana consumption and CB-1 stimulation decreases plasma levels of growth hormone in normal humans [25,35], and CB-1 antagonism would be expected to increase growth hormone levels. One interesting trend was that fasting IGF1 levels increased in the rimonabant group, despite the overall weight loss. In contrast, IGF1 levels in the placebo group had decreased by the end of study (Table 2). This was unusual, as it is known that excess of body fat is associated with blunted growth hormone response and is positively correlated with IGF1 levels. [36,37] Therefore, it is possible that in the rimonabant group either growth hormone levels increased or responsiveness to endogenous growth was relatively enhanced by treatment with CB1 antagonist. This important finding should be further explored and validated in future studies.

We also explored if changes in feeding behaviors may explain our trend of weight loss with rimonabant. However, there were no observed changes in feeding behavior, as total FRPQ score was lower in both groups at the end of 6 months. This observation could be explained by the either the placebo effect, or lack of sensitivity of this questionnaire to detect any changes for such a small sample size.

In summary, after 6 months of rimonabant treatment we observed a general trend towards weight loss, decreased fat mass and higher IGF1 level. Although, the CB1 antagonists may prove to be promising for treatment of subjects with PWS, our study was limited to a small sample size and results need to be reproduced by other studies. Most importantly, we found a high rate of adverse psychiatric symptoms with exposure to rimonabant. As this particular population is inherently prone to psychiatric disorders, rimonabant, the current CB1 antagonist does not seem to have a favorable profile. Future CB1 antagonists with less psychiatric adverse effects may be desirable for reevaluation in PWS and provide a hope for treatment of this debilitating condition.

Acknowledgments

This work was supported by a grant from Prader Willi Syndrome Association (USA), and CTSC of Weill Cornell Medical College (M01 RR00047 and UL1-RR024996). We would like to thank Dr. Loius J Aronne, Dr. James B. Bussel for their guidance on the design of this study, and Dr. Spencer S. Liu, Dr. Saroj Nimkarn and Dr. Charles Sklar for their critical review of this manuscript.

Abbreviations

PWS	Prader Willi syndrome
BMI	Body mass index
BFM	Total body fat mass
IGF1	Insulin like growth factor-1
IGFBP3	Insulin like growth factor binding protein-3

GH Growth Hormone

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Fig 1.

The median values were normalized to the Median value at the beginning of study at day 0 to show the change in TFM (left figure) and BMI (right figure).

Table I

Comparison of anthropometric characteristics at variable time points between groups
(n) number of subjects, (BMI) body mass index, (TFM) total fat mass

	Day 0	Day 90	Day 180
Variables	Median (range) (n)	Median (range) (n)	Median (range) (n)
Weight (kg)			
Rimonabant	95.5 (71.7–115.7) (4)	95.47 (68.95–117.0)(4)	77.11(73.02–112.80)(3)
Placebo	98.64(84.37–114.30)(4)	99.39 (83.2–116.12)(4)	99.56(81.19–118.73)(4)
BMI (kg/m²)			
Rimonabant	40.7 (31.9–58.7)(4)	40.26(30.68–60.56)(4)	32.51(32.50–47.56)(3)
Placebo	37.66(36.6–50.82)(4)	38.26(36.49–51.6)(4)	38.81(35.6–51.31)(4)
TFM (g/cm²)			
Rimonabant	49115.5(31415.0–66527.0)(4)		37259.0(33081.0–63869.0)(3)
Placebo	54951.5(39487.0–59116.0)(4)		56401.0(42976.0–64852)(4)

Table II

Comparison of hormone profile at variable time points between the 2 groups
(n) number of subjects, (IGFBP-3) insulin like growth factor binding protein-3, (IGF-1) insulin like growth factor-1

	Day 0	Day 90	Day 180
Variables	Median (range) (n)	Median (range) (n)	Median (range) (n)
IGF-1(ng/ml)			
Rimonabant	101.6 (45.7–114.4)(4)	84.35 (42.2–134.9) (4)	104.37 (95.9–113.0) (3)
Placebo	167.5(110.6–228.2) (4)	164.6 (93.3–220.0) (4)	146.4 (63.7–170.0) (4)
IGFBP-3(ng/ml)			
Rimonabant	39.5 (31.3–47.2) (4)	40.99 (28.21–54.28) (4)	46.6 (30.7–47.3) (3)
Placebo	61.7(38.6–83.6) (4)	81.24(38.2–101.9) (4)	68.14(32.8–88.3) (4)
Ghrelin (pg/ml)			
Rimonabant	1161.7 (1036.4–1306.2) (4)	1577.5(796.7–2129.0) (4)	1744.3(1253.0–3976.3) (3)
Placebo	1640.7(1215.0–3499.3) (4)	2319.7(1426.0–4444.0) (4)	2588.2(992.8–4017.0) (4)
Leptin(ng/ml)			
Rimonabant	56.2 (28.1–104.4) (4)	59.35 (28.3–105.4) (4)	34.2(32.5–82.0) (3)
Placebo	50.2 (25.2– 79.9) (4)	50.9 (22.7–104.1) (4)	58.65 (17.6–86.9) (4)