

Clinical Study

Efficacy and Tolerability of the Association of Sibutramine and Orlistat for Six Months in Overweight and Obese Patients

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Objective. To assess the efficacy and tolerability of the association sibutramine (10–20 mg/day) and orlistat (120 mg 2-3 times a day) in the treatment of obesity in a six-month open trial. **Methods.** 446 overweight and obese patients who sought treatment for obesity in a private clinic were assessed every 2 weeks during a period of 3 and 6 months. **Results.** After 3 months, the mean weight loss was 10.5 kg (–9.8% of the initial weight, $n = 263$), and after 6 months, the mean weight loss was 13.9 kg (–12.8% of the initial weight, $n = 97$). The tolerability of such association was quite acceptable and coherent with the action mechanism of each component. **Conclusions.** The association of orlistat and sibutramine is quite efficient and it seems to promote a higher rate of weight loss than that reported in clinical studies performed with each drug separately.

1. Introduction

Obesity is a chronic disease with increasing prevalence [1]. Obesity leads to metabolic abnormalities that contribute to the development of diabetes and cardiovascular diseases. Most of these diseases require long-term treatments and are associated with increased risk of morbidity and mortality [2, 3].

Diet, behavioral changes and physical activities often fail to promote weight loss and maintenance [4, 5]. Pharmacological treatment can increase the motivation of the patient and adherence to the treatment. Therefore, it is considered a crucial approach.

Among the anti-obesity drugs, sibutramine and its metabolites affect the central nervous system, inhibiting serotonin and noradrenaline reuptake, increasing the sensation of satiety and thermogenesis [6–8].

Orlistat, on the other hand, is a chemically synthesized hydrogenated derivative of lipstatin that partially inhibits the activity of gastric and pancreatic lipase and carboxyl ester lipase in the gastrointestinal system, reducing the hydrolysis

of triglycerides, and thus preventing the absorption of about 30% of the ingested fat [9, 10].

Since the mechanisms of action of these drugs are completely different, it is possible and reasonable, at least theoretically, to associate sibutramine to orlistat with the purpose of obtaining the benefits of both mechanisms, potentiating the weight loss.

In clinical practice we frequently use such a combination and, in this retrospective open trial, we analyzed the efficacy and tolerability of the association of sibutramine 10 to 20 mg/day and orlistat 120 mg two and three times a day in patients who sought treatment for obesity.

2. Methods

In the present study, 446 patients (208 men and 238 women) sought treatment for obesity at our private clinic from 08/1998 to 11/2006 and received a combination of sibutramine 10 to 20 mg/day and orlistat 120 mg 2-3 times a day associated with a hypocaloric diet and recommendation

TABLE 1: Initial characteristics of the individuals included in the study.

Characteristics	Mean	Variation
N	446	238 F, 208 M
Age (years)	41.3	14–73
	42.2 F, 40.2 M	14–73 F, 14–66 M
Initial weight (kg)	106.6	65.7–183
	95.1 F, 119.7 M	65.7–154.8 F, 77.6–183 M
Initial BMI (kg/m ²)	36.7	25.1–76.0
	35.6 F, 38.2 M	25.1–64.4 F, 25.1–76 M

N = number of individuals included in the study; F = female; M = male.

of regular physical activities since the beginning of the treatment. The patients who took the medication for at least 2 weeks since the beginning of the treatment were included in this study. The patients under 18 years of age (10 patients) who were included in the study had BMI > 32.5 kg/m², which is considered a very severe class of obesity for this age group. These patients also had high blood pressure, dyslipidemia and orthopedic complications. Those individuals who had diabetes and uncontrolled high blood pressure were not included in the study. In addition, we also did not include the patients when sibutramine was contraindicated due to severe hepatic and renal failure, arrhythmia, myocardial infarction, and stroke, or those who were using monoamine oxidase enzyme inhibitors and tricyclic antidepressants. We also did not include in the study the patients with gastrointestinal problems for whom the use of orlistat was contraindicated.

All patients had a stable weight and were not taking any antiobesity drugs in the previous three months. The subjects received prescription of a hypocaloric diet containing up to 30% of fat and designed by a dietitian, based on an individual interview. During the first visit, the patients received guidance regarding techniques of behavioral change and they were urged to practice physical activities. Patients were assessed every 2 weeks for a period of 3 (263 patients) and 6 (97 patients) months. Weight, heart rate, blood pressure and adverse effects were recorded and the potential relation between adverse effects and treatment was assessed and analyzed by the investigator (AH), who used standardized terms especially designed to describe the expected gastrointestinal events due to the increased release of fat caused by the treatment with orlistat, as well as the side effects potentially caused by sibutramine. The adverse effects were analyzed after 4 weeks of treatment in order to include more individuals.

2.1. Statistical Analysis. The Student paired *T* test was used to compare the data (baseline, 3 and 6 months), using the software SPSS 16.0.

3. Results

3.1. Followup and Weight Loss. The initial characteristics of the individuals are shown in Table 1.

TABLE 2: Weight loss of 446 patients in 3 and 6 months. (LOCF).

N = 446 238 F/208 M	Initial body weight (kg)	Final body weight (kg)	Weight loss (kg)	Weight loss (%)
Baseline	106.6 95.1 F, 119.7 M	—	—	—
3 months	106.6 95.1 F, 119.7 M	98.3 87.9 F, 110.2 M	8.3 7.2 F, 9.5 M	7.8% 7.6% F, 7.9% M
6 months	106.6 95.1 F, 119.7 M	97.4 86.9 F, 109.3 M	9.2 8.2 F, 10.4 M	8.6% 8.6% F, 8.7% M

N = number of individuals included in the study; F = female; M = male.

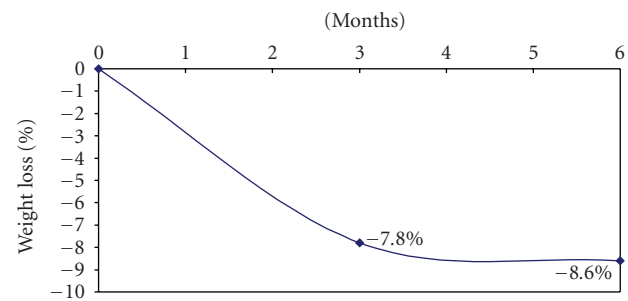


FIGURE 1: Weight loss of 446 patients in 3 and 6 months (LOCF).

One hundred eighty-three out of 446 initial patients quit treatment during the first 3 months and 166 dropped out treatment between the visits in the 3rd and 6th months. The basic known reasons for quitting treatment were lack of weight-loss efficacy (10.9%) and lack of adherence to medication (7.7%). For the remaining patients, the reason for quitting the treatment was not known or could not be established because they just interrupted the scheduled visits. We used the method of last observation carried forward (LOCF). The results regarding weight loss for all patients are shown in Table 2 and in Figure 1.

Results shown in Figure 2 take into consideration only the individuals that completed the study at 3 and 6 months.

The weight loss in 3 and 6 months for female patients who completed the study was -9.9% and -13.4%, respectively. For male patients who completed the study, the weight loss in 3 and 6 months was -8.7% and -12.3%, respectively.

There was a statistically significant difference between initial weight and after 3 months (106.6 ± 22.9 kg versus 98.3 ± 21.4 kg, *P* < .001) as well as between initial BMI and after 3 months (36.7 ± 6.7 kg/m² versus 34.0 ± 6.3 kg/m², *P* < .001).

Statistically significant differences were also observed between initial weight and after 6 months (106.6 ± 22.9 kg versus 97.4 ± 21.2 kg, *P* < .001) as well as between initial BMI and after 6 months (36.7 ± 6.7 kg/m² versus 33.6 ± 6.2 kg/m², *P* < .001).

Furthermore, statistically significant differences were observed between weight after 3 months and weight after 6 months (98.3 ± 21.4 kg versus 97.4 ± 21.2 kg, *P* < .001) as

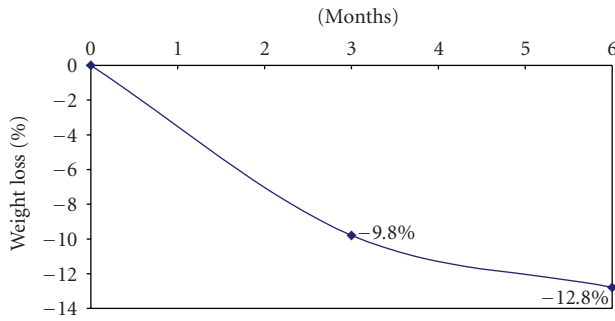


FIGURE 2: Evolution of weight loss in 3 and 6 months for patients who completed the study.

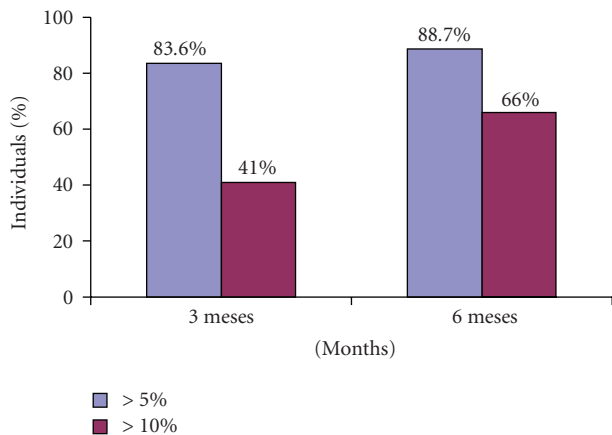


FIGURE 3: Categorical analysis of weight loss (>5% and >10%) in 3 and 6 months.

well as BMI after 3 and 6 months ($34.0 \pm 6.3 \text{ kg/m}^2$ versus $33.6 \pm 6.2 \text{ kg/m}^2$, $P < .001$).

In the categorical analysis, the percentage of individuals who lost more than 5% and more than 10% in 3 months was 83.6% (220 patients—123 F/97 M) and 41% (108 patients—58 F/50 M), respectively, and in 6 months was 88.7% (86 patients—47 F/39 M) and 66% (64 patients—35 F/29 M) (Figure 3). In the same analysis, the percentage of female patients who lost more than 5% and more than 10% in 3 months was 89.9% and 36.5%, respectively, and in 6 months was 92.2% and 68.6%. The percentage of male patients who lost more than 5% and more than 10% in 3 months was 77% and 39.7%, respectively, and in 6 months was 84.8% and 63%.

One-fifth of the patients were postmenopausal women ($n = 19$, 19.6%) at the end of the follow-up. The weight loss was not statistically different when compared to the women in the premenopausal state.

3.2. Adverse Effects. In order to include a significant number of adverse effects, we studied the same effects after 4 weeks of treatment (446 patients).

One hundred nineteen (26.7%) out of 446 patients reported at least one adverse effect. Table 3 shows the adverse effects reported by more than 5% of the individuals.

TABLE 3: Adverse effects seen in more than 5% of the cases in the first month of treatment.

	N	%
Fatty stool	55	47.1
Increased defecation	22	18.5
Dry mouth	13	10.9
Diarrhea	13	10.9
Oily drops	12	10.1
Flatus with discharge	11	9.2
Increased appetite	10	8.4
Constipation	8	6.7
Fecal urgency	7	5.9

N = Number of individuals who reported adverse effects.

TABLE 4: Studies carried out with sibutramine in non-diabetic patients.

N	Reference	Duration(weeks)	Dose (mg/day)	Weight loss
112	12	12	10	-4.5 kg
59	13	12	10	-5.1 kg
62	13	12	15	-4.9 kg
107	14	24	10	-6.1%
99	14	24	15	-7.4%
98	14	24	20	-8.8%

N = Number of individuals treated with sibutramine.

Eleven patients quit treatment due to adverse effects (headache, restlessness, and tachycardia).

Since this is an open trial and the laboratory tests were not performed in the same center, we did not consider the results of the lipid profile at the beginning and at the end of the treatment. On the other hand, we did not find clear changes in blood pressure and pulse rate.

4. Discussion

Obesity is a complex and multifactorial disease that similarly to high blood pressure and diabetes frequently requires pharmacological treatment.

Since the body weight regulation involves several modulating pathways and redundant systems in terms of physiological action and these mechanisms “protect” the individual who is undergoing diet and physical activity against “starvation”, it is probable that the ideal treatment for obesity might involve the association of two or more medications in the future [11].

The great majority of the studies on anti-obesity medications include only one drug. There are very few publications in the literature showing the effects of the pharmacological treatment for obesity with association of medications. In an attempt to compare these studies with our results, we designed Tables 4 and 5 to show the results of weight loss with sibutramine and with orlistat in 3 and 6 months.

Most adverse effects reported in the present study are similar to those published in the other previous studies. Regarding orlistat, we found increased evacuation, oily feces

TABLE 5: Studies carried out with orlistat in nondiabetic patients.

N	Reference	Duration (weeks)	Weight loss
47	15	12	-4.8 kg
136	16	24	-9.8%
147	17	24	-6.8%

N = number of patients treated with orlistat.

and fecal urgency. Regarding sibutramine, the adverse effects reported were dry mouth and intestinal constipation. Other adverse effects found in other studies with sibutramine, such as headache and insomnia, were not reported by more than 5% of the patients at the end of the first 4 weeks of treatment. Such effects are consistent with the pharmacology of orlistat and sibutramine.

Only few studies previously assessed the association of sibutramine and orlistat. A 3-month study carried out with 86 patients compared four types of treatment: sibutramine, orlistat, association of sibutramine and orlistat, and only diet. We found that patients treated with medication had better results, but there was not a significant difference regarding weight loss between the groups treated only with sibutramine and the sibutramine and orlistat group [12]. Another study that also assessed the waist circumference with the same groups of treatment as the previous study found reduced BMI and waist circumference. These rates were higher in the treatment group that combined sibutramine and orlistat. However, after correlating the increased rates of BMI and waist circumference, the authors found that the best result was obtained in the group treated only with orlistat followed by the group that used the combined treatment. The worst result was obtained by the group treated only with sibutramine [13]. Nevertheless a study carried out with 34 obese women showed that after one year of treatment with sibutramine the addition of orlistat revealed little benefit in patients who had lost previously 11.6% of initial weight. However, the authors emphasize that the results must be interpreted with caution because of the small sample size [14].

In the present study, weight loss was evident, being comparable with (or higher than) that obtained with sibutramine or orlistat separately in 3- and 6-month studies [15–20].

In the above mentioned studies, weight loss with sibutramine ranged from 6.1% to 8.8%, and with orlistat it ranged from 4.8% to 9.8%.

Sibutramine and orlistat are new drugs with different mechanisms of action; therefore, their association is very reasonable.

5. Conclusions

In conclusion, our data suggest that the association between orlistat and sibutramine is quite efficient and it seems to promote a higher rate of weight loss than that reported in clinical studies performed with each drug separately. The tolerability of such association is quite acceptable; therefore, it is a valid option for the treatment of obesity. Further

long-term studies to evaluate the association of orlistat and sibutramine in the treatment of obesity are needed.

Conflicts of Interest

Dr. Halpern is member of the Advisory Board of Roche and speaker for Abbott, Medley and GlenMark. Dr. Mancini is speaker for Roche, Abbott, Medley and GlenMark.

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