

## Sibutramine as an Adjuvant Therapy in Adolescents Suffering from Morbid Obesity

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**Key words:** sibutramine, obesity, adolescents

### Abstract

**Background:** The prevalence of morbid obesity is increasing rapidly. Weight reduction is very difficult using diet restriction and physical activity alone. Sibutramine has been shown to be effective and safe as an adjuvant therapy to diet restrictions.

**Objectives:** To describe our experience using sibutramine in weight reduction treatment of adolescents suffering from morbid obesity.

**Methods:** The study group comprised 20 young persons (13 females, mean age 15 years 4 months, range 13–18 years) with morbid obesity (body mass index above the 95th percentile for age and/or  $\geq 30$  kg/m<sup>2</sup>) who were treated with sibutramine 10 mg once a day for 1 year.

**Results:** Mean BMI was  $40 \pm 5.6$  kg/m<sup>2</sup> (range 30.1–49.5 kg/m<sup>2</sup>) at the beginning of treatment. Most patients showed an early weight reduction to mean BMI  $39.3 \pm 4.9$  and  $35.9 \pm 5.7$  at 3 and 6 months respectively, but stopped losing weight over the next 6 months. During the follow-up period 17 patients discontinued the treatment. The main reason for dropout was the slow rate of weight reduction after 6 months. Patients suffering from concomitant disorders (severe asthma, hypertension, sleep obstructive apnea) showed improvement after weight reduction. Adverse reactions from the treatment were transient, mild and well tolerated.

**Conclusions:** Sibutramine may help in achieving weight reduction for a short period and in improving concomitant health problems, however its long-term effect is limited.

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Morbid obesity is one of the significant treatable health hazards [1] whose prevalence is growing rapidly in the western world [2]. Overweight can be the cause of cardiovascular and respiratory illnesses, type 2 diabetes, and social and psychiatric problems such as eating disorders [3,4]. Weight reduction is very difficult with diet restriction and physical activity alone [5]. Several medications were therefore administered as an adjuvant therapy, but with various rate of success. Sibutramine is a non-amphetamine appetite suppressant that may also have antidepressant properties. It acts by blocking neuronal reuptake of norepinephrine, and to a lesser extent, serotonin and dopamine (Prod Info Meridia®, 1999). Sibutramine, along with diet restrictions, is indicated for obese patients with an initial body mass index  $\geq 30$  kg/m<sup>2</sup>, and for overweight patients with a BMI  $\geq 27$  kg/m<sup>2</sup> in the presence of other obesity-related risk factors such

as diabetes, dyslipidemia, respiratory disorders or hypertension. Sibutramine was previously shown to be effective and safe for adults [6,7], and recently was found to be effective in combination with behavioral therapy in adolescents [8,9]. However, difficulties in reaching and maintaining normal weight were noted [7]. In the present study we describe our experience with weight reduction treatment using sibutramine in adolescents suffering from morbid obesity.

### Patients and Methods

Between November 2000 and November 2001, 20 young persons (15 females) with morbid obesity (BMI above the 95th percentile for age and/or  $\geq 30$  kg/m<sup>2</sup>) were treated at the nutrition clinic of Assaf Harofeh Medical Center, Israel. Excluded were patients with specific organic disorders that affect metabolism like hypothyroidism, diabetes mellitus or Cushing syndrome, severe hyperlipidemia, known significant hypertension or other cardiovascular disease, psychiatric conditions or specific eating disorders, and participation in other weight control programs within 3 months prior to this intervention.

All patients had an initial evaluation that included history, physical examination, blood work (complete blood count, electrolytes, urea, creatinine, lipid profile, liver transaminase, thyroid-stimulating hormone, free thyroxine and blood cortisol at 8 a.m.) and psychiatric assessment by a psychiatrist.

The intervention included a personally tailored, moderate and balanced calorie-restricted diet of conventional food planned by a pediatric dietitian, taking into account age, gender, personal preferences and growth potential. The diets of younger adolescents were less restrictive and closer to the recommended daily allowance of calories in order not to impair growth. The adolescents were instructed to consume 1200–1700 calories: 30% from fat, 15% from protein and the remainder from carbohydrates. Multivitamins and calcium supplements were added as needed. Physical activity, such as an hour of brisk walking, cycling or a ballgame daily was encouraged.

Sibutramine (Reductil®, Teva, Israel) 10 mg once daily was initiated at the second visit to the clinic after the medical and psychiatric assessments were completed. Patients were evaluated weekly at the nutrition clinic. The study was approved by the Helsinki Committee of Assaf Harofeh Medical Center.

BMI = body mass index

## Statistics

The results are presented as means and standard deviations. Paired *t*-tests were performed to assess the significance of the weight reduction at different time points. The Pearson correlation test was used to calculate correlations between weight reduction and age.

## Results

The study group included 20 patients of mean age 15 years and 4 months (range 13–18 years). The initial mean BMI of the group was  $40 \pm 5.6$  kg/m<sup>2</sup> (range 30.1–49.5 kg/m<sup>2</sup>). Most patients showed an early weight reduction to mean BMI  $39.3 \pm 4.9$  and  $35.9 \pm 5.7$  kg/m<sup>2</sup> at 3 and 6 months respectively. During the follow-up period most of the patients dropped out of the program: seven rejected the intervention after a few visits in the first 3 months, six more in the next 3 months, and after a year only three patients continued the treatment. One patient underwent the surgical procedure, laparoscopic gastric banding. After 1 year of the treatment, only three patients were left. Their weight loss since admission was 8–19 kg ( $4.2$ – $7.5$  kg/m<sup>2</sup>), but they were still overweight.

Analysis of the changes in the 13 patients remaining in the program after 3 months revealed a statistically significant reduction in weight ( $\Delta = 6.2 \pm 4.3$  kg,  $P < 0.001$ ) and in BMI ( $\Delta = 2.4 \pm 1.7$  kg/m<sup>2</sup>,  $P < 0.001$ ) [Figure 1]. In the seven patients remaining after 6 months, a further statistically significant reduction was detected in weight ( $\Delta = 10.8 \pm 3.7$  kg,  $P < 0.001$ ) and in BMI ( $\Delta = 4.4 \pm 1.7$  kg/m<sup>2</sup>,  $P < 0.001$ ) from baseline [Figure 1]. A statistically significant reduction in weight ( $\Delta = 4.1 \pm 3.7$  kg,  $P < 0.05$ ) and in BMI ( $\Delta = 1.8 \pm 1.3$  kg/m<sup>2</sup>,  $P < 0.01$ ) was also found in these seven patients from 3 months to 6 months [Figure 1]. In the three patients who lasted the treatment for the whole year, a significant reduction in weight ( $\Delta = 13.5 \pm 5.5$  kg,  $P = 0.051$ ) and in BMI ( $\Delta = 6.1 \pm 1.7$  kg/m<sup>2</sup>,  $P < 0.05$ ) was found at 12 months [Figure 1]. All weight changes over the second 6 months had no statistical significance. No correlation was found between weight reduction and age.

The main reason for dropout was the slow rate of weight reduction after 6 months. However, a few of the patients stopped the treatment earlier because they feared being disappointed again, having attempted weight reduction programs in the past. In two patients this slow rate of weight reduction improved by raising the dose of sibutramine to 15 mg/day, and in one patient the medication was discontinued for 2 months following 8 months of treatment and then restarted with regained effect. Patients were motivated to stay longer in the treatment by aiming at secondary gains, such as academic or army service qualification, peer acceptance and resolution of obesity-related medical problems.

Two patients with severe asthma demonstrated marked amelioration of clinical complaints; they reported decreased use of bronchodilator therapy, and no hospitalizations were recorded as compared to frequent admissions prior to the sibutramine treatment. Lung function tests revealed a 10–15% improvement in expected forced expiratory volume during 1 second, from 65%

to 75–80% after weight reduction. Three patients with blood pressures above the 90th percentile for age, gender and height showed a reduction in the mean arterial pressure from 105, 90 and 100, to 93, 80 and 93 mmHg, respectively, which are within the normal limits for their age, gender and height. One patient with Down's syndrome who suffered from obstructive sleep apnea that was managed with a BiPAP device was able to sleep freely without deoxygenation episodes and an otolaryngologic surgical procedure was avoided.

Adverse reactions were mild, transient, well tolerated and were not the reason for dropout. Two patients complained of constipation and two described headaches.

## Discussion

In the present study we demonstrated a beneficial short-term effect of a weight reduction program using sibutramine as an adjuvant therapy, with only mild and transient adverse reactions. However, there was a very high rate of therapy cessation.

Treating morbid obesity is a challenge for the physician. Results of different treatment modalities are discouraging, especially in adolescents [10–12]. Sibutramine is a non-stimulating medication for assisting weight reduction in morbidly obese individuals. Our experience in treating adolescents suffering from obesity is similar to other studies [13,14] and demonstrates the limitations of weight loss programs in general and of adjuvant drug therapy in particular. The only other non-stimulating commonly used medication is a lipase inhibitor, orlistat, which has many uncomfortable intestinal reactions [10].

Sibutramine was proven to facilitate weight control in adults [6,7,14]. To our knowledge, however, only two studies have demonstrated its beneficial effect in adolescents [8,9]. In the first one, Berkowitz et al. [8] showed the favorable effect of sibutramine in conjunction with behavior therapy in a randomized double-blind placebo-controlled study. These investigators compared a comprehensive behavior therapy plan that included group and individual treatments with and without sibutramine for 6 months, which was then switched to an open label study in which all participants received the adjuvant treatment of the

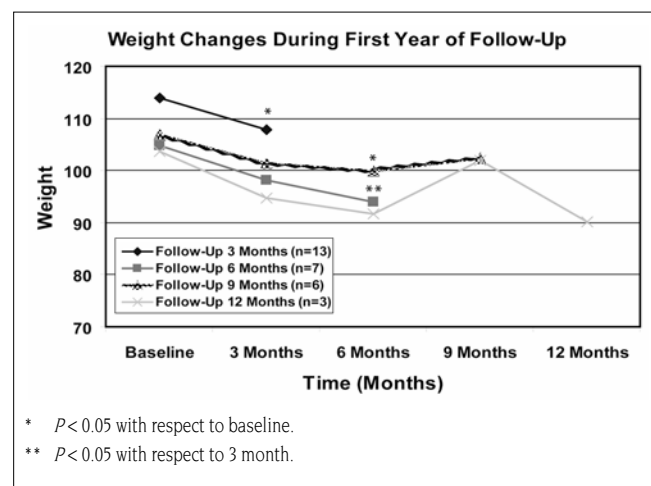


Figure 1. Weight changes during first year of follow-up

drug for another 6 months. As in our study, Berkowitz and co-workers showed a significant weight reduction only within the first 6 months of therapy with no further improvement over the next 6 months. Godoy and associates [9] presented their results that also showed the benefits of sibutramine compared to placebo, but their study lasted only 6 months. In contrast to our study and the STORM trial [15] that had dropout rates of 85% and 50% respectively, Berkowitz et al. [8] and Godoy et al. [9] demonstrated a relatively low dropout rate of 24% and 17% respectively. This can be attributed to the very protective and supportive research environment in which they conducted their studies. Unfortunately these support systems are unrealistic in the common primary care weight control clinics.

The main reason for dropout was the slow rate of weight reduction. However, manipulation with the drug dosage can override the wearing-off effect after 6 months of treatment. A few patients who stopped the treatment early in the program feared experiencing further disappointment, having participated in unsuccessful weight reduction methods in the past. Patients who were more diligent in the treatment were those who had experienced an amelioration of obesity-related medical problems. External factors such as ambition for army service qualification or higher education also counted as reasons for persevering in the program.

In the present study, weight reduction made a dramatic improvement in patients suffering from concomitant disorders such as severe asthma, hypertension and obstructive sleep apnea. Therefore, when rapid weight reduction is warranted for concomitant health hazards, sibutramine may be a reasonable choice.

The study demonstrates our experience in using sibutramine as part of an outpatient treatment of adolescents suffering from morbid obesity, and was not intended to assess the efficacy of the medication by a randomized controlled study. Another limitation is the very high dropout rate, which we regard as an important finding illustrating the difficulties in treating these patients.

## Conclusions

Although sibutramine may help in achieving weight reduction and improving concomitant health problems, its long-term effect is limited. This emphasizes the need for alternative strategies to convince patients to change their lifestyle in order to achieve a long-term healthy weight rather than merely participating in weight reduction programs.

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*Distrust all in whom the impulse to punish is powerful*

Friedrich W. Nietzsche (1844-1900), German philosopher