0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(11):4101–4106

doi: 10.1210/jc.2007-0826

Impact Sibutramine Therapy in Children with Hypothalamic Obesity or Obesity with Aggravating Syndromes

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Objective: Behavioral treatment of children suffering from hypothalamic obesity or uncomplicated obesity in combination with syndromes that aggravate this condition has proven to be ineffective. The combination of comorbidities and severe obesity lower the quality of these children's lives drastically. The present goal was to determine whether treatment with sibutramine has a beneficial effect on such children.

Design and Subjects: A double-blind, placebo-controlled, cross-over study (20 + 20 wk), followed by a 6-month open phase, was performed. The primary indicator of efficacy was the body mass index (BMI) SD score (SDS) value, which was analyzed using an ANOVA repeated-measures design [intention to treat (ITT)]. The 50 children (7–20 yr of age) involved included 22 with hypothalamic obesity and 28 with uncomplicated obesity plus aggravating syndromes. Forty-five patients completed the first phase, and 42 participated in the entire study.

Results: The group that initially received the placebo demonstrated an insignificant decrease (−0.06) in BMI SDS during this treatment but a significant decrease (−0.68; $P < 0.001$) when treated with sibutramine. The other group demonstrated a reduction in their BMI SDS of −0.72 during administration of sibutramine and a rebound of +0.43 when placed on the placebo ($P < 0.001$ in both cases). The response of children with hypothalamic obesity was also significant but was less pronounced than that of children with nonhypothalamic obesity. During the open phase, a continuous reduction in weight was observed. The treatment was tolerated well.

Conclusion: The clinically and statistically significant weight reduction caused by sibutramine in this short-term study indicates that treatment of hypothalamic and syndromal obesity with this drug may be beneficial. **(*J Clin Endocrinol Metab* 92: 4101–4106, 2007)**

OBESITY AMONG CHILDREN is of increasing concern to public health officials in many countries. The pronounced prevalence of obesity at a young age (1), in combination with increasing awareness of the associated risk for morbidity later in life (2), has motivated both medical societies and health authorities to devote more effort to the development of effective strategies for prevention and treatment of this disorder.

However, in certain subgroups of children, obesity is definitely not primarily the result of a sedentary lifestyle or inappropriate diet. For example, a dominant feature of the Prader Willi (PWS) and Laurence Moon Bardet Biedle (LMBB) syndromes is severe obesity (3). Individuals afflicted by these syndromes appear to have hypothalamic disturbances that result in an abnormally large appetite (4). Furthermore, children who suffer hypothalamic damage as a consequence of tumors, irradiation, or surgery involving the central nervous system (CNS) may also develop extremely severe obesity. One typical example of this phenomenon is children who have been operated on for craniopharyngiomas, 30–50% of whom develop a pattern of compulsory eating and severe obesity after surgery (5–7). Specific, genetically defined syndromes associated with the development of obesity have also been identified (8). The term hypothalamic obesity has been coined to describe these types of conditions (9). In addition, children with attention deficiency syndromes [attention deficiency hyperactivity disorder (ADHD)], autism, or mental retardation who also become obese may have difficulties in complying with antiobesity programs that focus on behavioral changes. These various groups of children are almost invariably resistant to the types of antiobesity treatment offered children today. Not infrequently, their severe obesity is combined with other physical and/or mental problems and thus their quality of life very poor (10, 11). Despite that, these children are often ignored in reviews on treatment of obesity (12, 13).

Development of effective pharmacological treatment of subjects with these conditions is highly urgent. However, because such patients constitute a small group that is difficult to treat, virtually no reports have studied the effects of pharmacological treatment of either children or adults with hypothalamic obesity or obesity in combination with other syndromes. The findings from studies on individuals with uncomplicated or simple obesity cannot be extrapolated to these other groups of patients because hypothalamic damage and poor self-control may diminish or abolish the efficacy of the drug.

Sibutramine is an unspecific inhibitor of the presynaptic reuptake of neurotransmitters that is somewhat selective for serotonin and norepinephrine (14). Under the names of Re-

First Published Online August 28, 2007

Abbreviations: ADHD, Attention deficiency hyperactivity disorder; ASD, autism spectrum disorder; BMI, body mass index; CNS, central nervous system; LMBB, Laurence Moon Bardet Biedle syndrome; PWS, Prader Willi syndrome; SDS, SD score; SSRI, selective serotonin reuptake inhibitor.

TABLE 1. Characteristics of the subjects included in the present study

Diagnosis	n	Age (yr)	BMI SDS (range)	Gender (male/female)	SSRI (n)
CNS damage	10	9–19.6	3.0–6.9	3/7	2
LMBB	6	7.4–20.2	3.6–9.7	3/3	0
PWS	4	13.2–17.5	3.9–4.5	2/2	2
Mb Down	3	11.6–17.6	4.0–6.6	0/3	0
mMC4R	2	14.5–19.4	2.9–6.9	1/1	0
MMC	4	7.6–18.2	4.0–8.9	1/3	0
MR/ADHD/ASD	21	7.0–17.0	3.8–10.0	14/7	1
Total	50	7–20	2.9–10.0	24/26	5

The data are presented as medians and ranges. The group of patients with CNS damage consisted of individuals who had undergone surgery for craniopharyngeoma (n = 4), astrocytoma (n = 3), opticus glioma (n = 1), or prolactinoma (n = 1) as well as one patient with histiocytosis X. mMC4R, Mutation in the melanocortin receptor 4; MMC, myelomeningocele; MR, mental retardation.

ductil or Meridia, this drug has been approved for the treatment of obesity in adults in most countries. A number of investigations with treatment periods of 6–12 months have revealed beneficial effects of sibutramine in combination with behavioral changes on adolescents with uncomplicated obesity (15–19), whereas one short-term study did not observe any difference, compared with placebo (20). The aim of the present study was to determine whether children suffering from hypothalamic obesity or simple obesity together with syndromes that aggravate this condition can benefit from treatment with sibutramine.

Subjects and Methods

Subjects

Fifty children and adolescents suffering from defined syndromes were recruited, and their characteristics are documented in Table 1. The criteria for inclusion were obesity defined as a body mass index (BMI) SD score (SDS) greater than 3, as calculated according to Rolland-Cachera *et al.* (21); an age of 5–20 yr; and, in addition, a diagnosis of having a defined syndrome for which obesity is a definitive criterion or a disease that makes behavioral treatment impossible or damage to the CNS that causes obesity (Table 1). A subgroup (n = 21) consisted of subjects with mental retardation and/or ADHD and/or autism spectrum disorder (ASD). Among them, three had mental retardation as their primary diagnosis, 15 ADHD, and three ASD. Thirteen attended special schools/classes for mentally handicapped children

The criteria for exclusion were the use of high doses of psychoactive drugs that might render treatment with sibutramine hazardous or the presence of severe psychological and/or medical problems that would create difficulties for the patient to comply with the study protocol.

Many of the subjects included were being treated for their specific diseases, *e.g.* glucocorticoids or hormonal replacement for panhypopituitarism. Five subjects were using selective serotonin reuptake inhibitor (SSRI) drugs concomitantly. Alterations in the nature or doses of drugs administered were avoided during the study period.

Study design

This study was conducted in two phases (Fig. 1). The initial phase consisted of a double-blind, placebo-controlled, cross-over study, in which the primary variable monitored was the BMI z-score (BMI SDS) (21). Interpretation of long-term changes in BMI or weight in growing subjects is difficult and was therefore avoided (22). The other variables examined in this first phase were fasting levels of blood glucose and insulin, nonfasting serum levels of cholesterol and triglycerides, and body composition as determined by dual-energy x-ray absorptiometry (Lunar Corp., Madison, WI).

In this first phase, the patients within each subgroup were divided randomly into pairs consecutively when they entered the study. APL (Stockholm, Sweden) performed this randomization using coded envelopes as well as the labeling and packaging of sibutramine in capsules that could not be identified by the patients or the medical staff. One patient in each pair was initially treated daily with 10 mg sibutramine and the other with placebo. If a weight reduction of at least 4 kg was not obtained within 8 wk, the daily dose of sibutramine or placebo was increased to 15 mg. After 20 wk the patients receiving sibutramine were placed on the placebo for an additional 20 wk, and vice versa, with no washout period in between.

In an attempt to determine whether children with hypothalamic obesity are resistant to sibutramine treatment, the subjects were also divided into two groups on the basis of whether their obesity was hypothalamic or nonhypothalamic. The former group included children suffering from CNS damage, craniopharyngioma, LMBB, melanocortin-4 receptor mutation, and PWS (n = 22 in total). All other diagnoses were considered to reflect uncomplicated obesity accompanied by aggravating syndromes (Table 1).

The second phase of this study was an open 28-wk trial. Patients receiving 15 mg sibutramine or placebo daily during both periods of phase 1 were administered this same dose during the second phase; otherwise 10 mg was used.

All patients visited the clinic at times indicated in Fig. 1. In connection with each visit, the patients and their parents were encouraged to make all possible changes in lifestyle that might alleviate the child's obesity. The parameters measured at the clinic included height (Ulmer stadiometer, Ulm, Germany), weight (Vetek TI-1200; Väddö, Sweden), and blood pressure (at the wrist while sitting; EW3000; Matsushita Co., Kyoto, Japan); moreover, specific questions concerning possible side effects were also posed.

In clinical practice, combined treatment with sibutramine and SSRI drugs is usually avoided due to the risk for serotonergic crisis (23). In the present study, five patients taking SSRI drugs at relatively low doses were included. The reason they were included was that their quality of life was very poor and their weight gain was alarming. To allow early detection of serotonergic symptoms in these individuals, they or their parents were contacted by telephone once each week.

The study was approved by the Ethics Committee of Karolinska

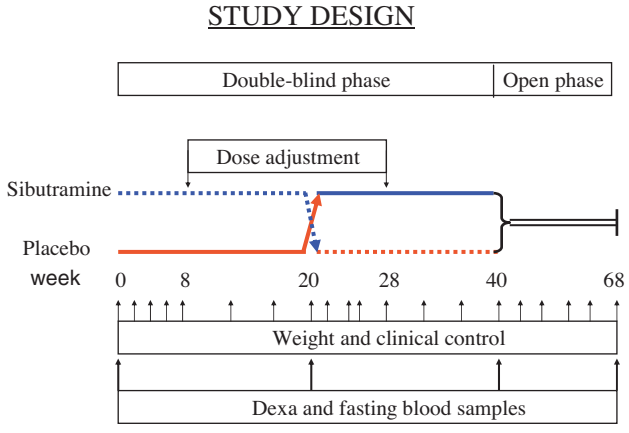

FIG. 1. Study design. The study consisted of a blinded, randomized, placebo-controlled phase and an open phase.

Institute and the Swedish Medical Products Agency. Parents gave written consent to the study and were aware of its design in terms of randomization to active drug or placebo.

Statistical analysis

The data for all patients included in this investigation were included in the analysis. The last-observation-carried-forward approach was used for the data collected within each study period. All data are presented as means with SDS, SEMS, or ranges where appropriate.

All statistical analyses were performed using the SAS 8.2 or STATISTICA 6.0 (Statsoft Inc., Tulsa, OK) software; all tests were two sided; and $P < 0.05$ was regarded as being statistically significant. The null hypothesis used for testing the primary variable of efficacy was that the mean change in the BMI SDS value for the patients receiving sibutramine did not differ from the corresponding value for patients administered the placebo. This hypothesis was evaluated using the ANOVA repeated-measures design, together with corresponding planned comparisons within and between treatment periods. The analysis included the baseline levels as a covariate as well as the treatment as an explanatory factor. The hypotheses concerning the secondary variables of efficacy were tested with the same approach. The Pharma Consulting Group (Uppsala, Sweden) carried out these statistical analyses.

Results

Of the 50 patients initially included, 49 received at least one dose of sibutramine or the placebo and were also evaluated with respect to possible side effects and safety. There were five withdrawals from the study during the first randomized phase: three subjects with hypothalamic obesity withdrew because of tumor recurrence and two subjects with nonhypothalamic obesity failed to comply satisfactorily. Thus, 45 patients (90%) completed the randomized, double-blind phase, of whom 24 received the placebo initially and thereafter sibutramine and 21 sibutramine initially. These two groups were closely similar with respect to background characteristics (data not shown).

The results of the randomized phase of the study with respect to change in weight are depicted in Fig. 2. Treatment of both the first and second groups with sibutramine caused a significant decrease in BMI SDS, compared with the placebo ($P < 0.001$). This decrease in BMI SDS was approximately the same, regardless of whether treatment with sibutramine came first or second, *i.e.* 0.7 U (Fig. 2).

In contrast, administration of placebo during the two study periods was associated with significantly different effects. The subjects receiving the placebo during the first period demonstrated no significant change in weight, whereas during placebo treatment preceded by administration of sibutramine, a rebound in BMI SDS was observed (Fig. 2). This difference was found to be statistically significant ($P = 0.002$) when the interaction between placebo treatment and time was analyzed.

Comparison of treatment during wk 0–8 with treatment during wk 8–20 within a given treatment period revealed no significantly enhanced response ($P = 0.51$) when the dose of sibutramine was increased (see *Subjects and Methods*). Furthermore, the response to sibutramine was linear with time.

To examine whether children exhibiting hypothalamic obesity were resistant to the weight-lowering effect of sibutramine, these subjects (n = 19) were compared with the children with nonhypothalamic obesity (n = 26). As seen in Fig. 3, both the subgroups with hypothalamic ($P = 0.005$) and nonhypothalamic obesity ($P = 0.001$) demonstrated significant reductions in weight while receiving sibutramine in comparison with the placebo. However, the effect of sibutramine on the subjects with nonhypothalamic obesity was more pronounced, indicating that hypothalamic obesity is associated with partial resistance to this drug. The number of subjects whose dosage of sibutramine was, according to the study design, increased to 15 mg daily was 17 in the group with hypothalamic obesity (94%) *vs.* 16 in the patients demonstrating nonhypothalamic obesity (66%).

The total body fat percentage, measured by dual-energy x-ray absorptiometry, was decreased by treatment with sibutramine in comparison with administration of the placebo (change during sibutramine treatment from 48.6 ± 1.3 to 46.7 ± 1.4% and during placebo from 47.9 ± 1.3 to 47.8 ± 1.4%; $P = 0.003$). At the end of the open study phase, a further decrease of fat percentage was observed (44.0 ± 1.9%; $P =$

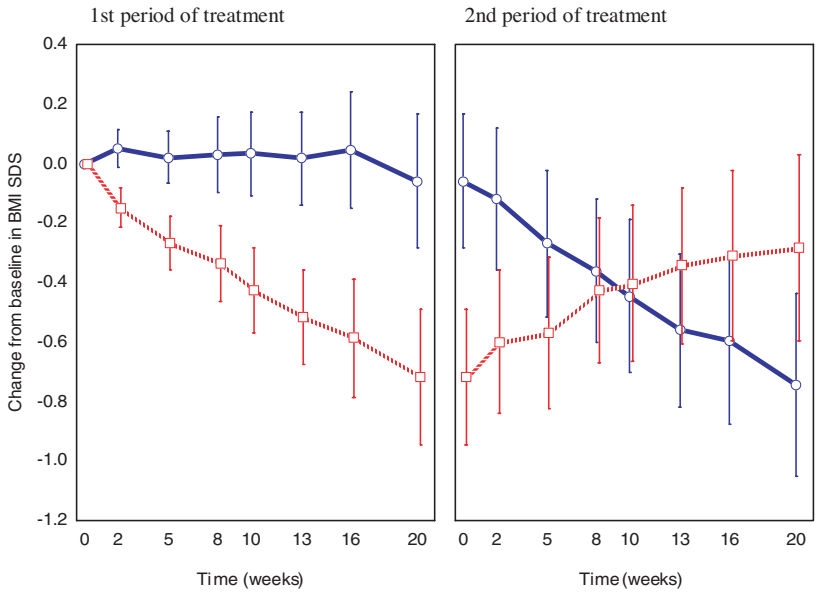

FIG. 2. Effects of sibutramine or placebo on the BMI SDS of the patients during the blinded phase of the study. Twenty-four patients (*solid line*) received the placebo during the first period of treatment and sibutramine during the second period and 25 patients (*dotted line*) initially received sibutramine. The data presented are means and 95% confidence intervals.

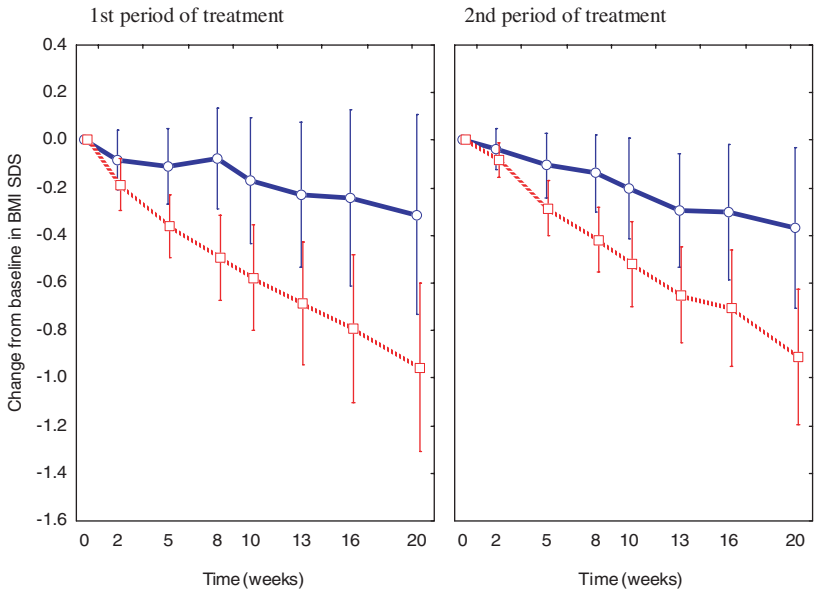

FIG. 3. Comparison of the effects of sibutramine treatment on children with hypothalamic (*solid line*) and nonhypothalamic (*dotted line*) obesity. The data presented are means and 95% confidence intervals.

0.01) Furthermore, during the placebo-controlled phase of this study, sibutramine treatment decreased plasma levels of triglycerides by the end of the treatment periods in both groups ($P = 0.04$), from 1.3 ± 0.1 to 1.1 ± 0.2 mmol/liter. During placebo no significant change was observed (1.2 ± 0.2 mmol/liter before and 1.3 ± 0.1 mmol/liter after placebo treatment). Cholesterol, insulin, and glucose levels were not significantly changed during the study period.

During the second, open-study phase of the investigation, there were another three withdrawals: two subjects with ADHD/mental retardation refused to take the drug and one patient with hypothalamic obesity was referred to a psychiatric clinic for severe mental illness. Thus, 42 patients (84%) completed the entire 68-wk-long study. During the open-study phase, a continuous reduction in weight was observed (Fig. 4), and the pattern of this reduction was similar for subjects who first received the placebo and those who were administered sibutramine first. However, the rebound effect observed during placebo treatment of the subjects who initially received sibutramine (Fig. 2) was not followed by any pronounced reduction in weight when these same individuals again received the drug.

The adverse events observed during the first phase of the present investigation are summarized in Table 2. During the placebo-controlled phase of the study, there was no significant difference in the numbers of patients who demon-

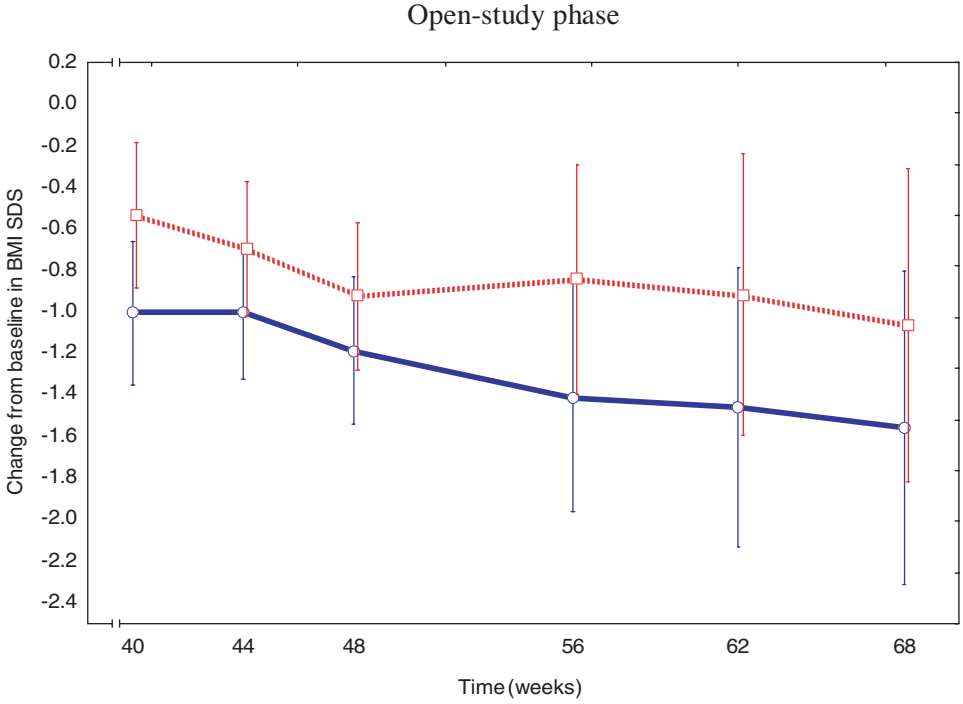

FIG. 4. Effect of sibutramine treatment during the open-study phase for patients who initially received the placebo (*solid line*) and those who were administered sibutramine first (*dotted line*). The data presented are means and 95% confidence intervals.

TABLE 2. Adverse events reported during the placebo-controlled phase of the study

Event	Sibutramine	Placebo
Constipation	7	5
Xerostomia	6	1
Fluctuations in mood	8	5
Insomnia	4	0
Fatigue	4	5

strated adverse effects among those receiving the placebo or sibutramine. The blood pressures and heart rates of the patients in both groups varied considerably, but no differences in the means were observed. During the second phase, adverse events were generally mild and of the same nature and frequency as during phase 1. Altogether, six serious adverse events were reported: two children exhibited signs of depression, both during placebo treatment; three suffered tumor recurrences; and one developed type 2 diabetes while receiving the placebo. Even with especially careful monitoring, we did not observe any enhanced frequency of adverse events among the children being treated concomitantly with SSRI drugs during the study period.

Discussion

In the present investigation, a clinically and statistically significant effect of sibutramine on BMI SDS of children previously treated unsuccessfully with behavioral therapy was observed. During the first, blinded 20 + 20-wk portion of our study, sibutramine reduced the BMI SDS of these subjects by approximately 0.7 U. Administration of the placebo in combination with repeated advice regarding diet and physical activity had little effect, demonstrating once again the resistance of obese children with aggravating syndromes to behavioral treatment. During the open-trial phase, the BMI SDS continued to decrease so that the total reduction for the group that was initially administered the placebo and therefore treated with the drug for 48 consecutive wk was approximately 1 BMI SDS unit.

The group of subjects who received sibutramine during the first period demonstrated a pronounced rebound increase in weight when placed on the placebo. Readministration of the drug to these individuals did not cause weight reduction any more rapidly than for the group that received the placebo first, followed by continuous drug treatment. Thus, the final outcome was less beneficial for the former group. Apparently, for this type of patients, continuous treatment with sibutramine may be more beneficial than intermittent administration.

Five of our patients were being treated concomitantly with SSRI drugs, despite the fact that such treatment is generally considered to be a contraindication for the use of sibutramine (23). The study nurse maintained weekly contact with the parents of these children in an attempt to detect possible adverse serotonergic events as early as possible. However, no such events were observed.

Patients suffering from hypothalamic obesity constitute a special medical problem. In most cases the specific mechanisms underlying their morbid obesity is unknown. In addition to the common view that disturbances of the centers in the hypothalamus that regulate appetite may lead to hyperphagia and obesity, it has been proposed that primary hyperinsulinemia in response to food intake may be of pathophysiological significance in this context (24). This proposal gains support from the observation that treatment of patients suffering from hypothalamic obesity with octreotide can reduce the amount of weight they gain (25, 26).

In the present study, sibutramine caused a significant and long-lasting reduction in the weight of subjects with hypothalamic obesity. However, this effect was less pronounced in such children than in those with uncomplicated obesity together with aggravating syndromes, which indicates that the underlying cause of hypothalamic obesity may be associated with partial resistance to sibutramine (25). It is unclear whether this resistance can be overcome by increasing the dose of sibutramine. The higher of the two daily doses (10 and 15 mg) administered here, in accordance with the protocol, to 18 of the 19 patients with hypothalamic obesity after 8 wk on the lower dose gave rise to only minor adverse events. On the other hand, this increase in dose did not appear to improve weight reduction in these individuals.

In conclusion, administration of sibutramine to children exhibiting obesity together with syndromes that aggravate this condition and also make behavioral treatment difficult resulted in a significant reduction in their BMI SDS. Even in children with hypothalamic obesity, a statistically and clinically significant reduction in the degree of obesity was observed, despite partial resistance to sibutramine treatment. However, because no long-term sibutramine studies are available in children and particularly in children with hypothalamic disorders, caution is warranted.

Acknowledgments

The invaluable and excellent assistance of research nurses Sofia Trygg-Lycke and Charlotta Westlund is highly appreciated. We also thank all of our colleagues in Sweden for their confidence in referring their patients to us as well as statistician Jan Kowalski for his excellent support.

Received April 12, 2007. Accepted August 17, 2007.

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This was an investigator-sponsored study that was supported financially by the Swedish Research Council (project 9941), the Swedish Children's Cancer Foundation, the Stockholm Free Mason's Foundation for Children's Welfare, and the Jerring Foundation. We are also grateful to the Abbott Sweden Company for generously supplying us with both the drug and placebo during the initial phase of this investigation as well as for a grant covering part of the salary of one of our research nurses.

Disclosure Statement: The authors have nothing to disclose.

References

1. **Lobstein T, Baur L, Uauy R** 2004 Obesity in children and young people: a crisis in public health. Obes Rev 5(Suppl 1):4–104
2. **Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, Allen K, Lopes M, Savoye M, Morrison J, Sherwin RS, Caprio S** 2004 Obesity and the metabolic syndrome in children and adolescents. N Engl J Med 350: 2362–2374
3. **Dietz WH, Robinson TN** 2005 Clinical practice. Overweight children and adolescents. N Engl J Med 352:2100–2109
4. **Lindgren AC, Barkeling B, Hagg A, Ritzen EM, Marcus C, Rossner S** 2000 Eating behavior in Prader-Willi syndrome, normal weight, and obese control groups. J Pediatr 137:50–55

5. **Sorva R** 1988 Children with craniopharyngioma. Early growth failure and rapid postoperative weight gain. Acta Paediatr Scand 77:587–592
6. **Geffner M, Lundberg M, Koltowska-Haggstrom M, Abs R, Verhelst J, Erfurth EM, Kendall-Taylor P, Price DA, Jonsson P, Bakker B** 2004 Changes in height, weight, and body mass index in children with craniopharyngioma after three years of growth hormone therapy: analysis of KIGS (Pfizer International Growth Database). J Clin Endocrinol Metab 89:5435–5440
7. **Karavitaki N, Brufani C, Warner JT, Adams CB, Richards P, Ansorge O, Shine B, Turner HE, Wass JA** 2005 Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up. Clin Endocrinol (Oxf) 62:397–409
8. **Farooqi IS, O'Rahilly S** 2005 Monogenic obesity in humans. Annu Rev Med 56:443–458
9. **Bray GA** 1984 Syndromes of hypothalamic obesity in man. Pediatr Ann 13: 525–536
10. **Muller HL, Bruhnken G, Emser A, Faldum A, Etavard-Gorris N, Gebhardt U, Kolb R, Sorensen N** 2005 Longitudinal study on quality of life in 102 survivors of childhood craniopharyngioma. Childs Nerv Syst 21:975–980
11. **Poretti A, Grotzer MA, Ribi K, Schonle E, Boltshauser E** 2004 Outcome of craniopharyngioma in children: long-term complications and quality of life. Dev Med Child Neurol 46:220–229
12. **Asp NG, Björntorp P, Britton M, Carlsson P, Kjellström T, Marcus C, Nerbrand C, Näslund I, Rössner S, Sjöström L, Östman J** 2004 Treating and preventing obesity. In: Östman J, Britton M, Jonsson E, eds. Weinheim, Germany: Wiley-VCH Verlag GmbH & Co.
13. **Summerbell CD, Ashton V, Campbell KJ, Edmunds L, Kelly S, Waters E** 2003 Interventions for treating obesity in children. Cochrane Database Syst Rev CD001872
14. **Ryan DH, Kaiser P, Bray GA** 1995 Sibutramine: a novel new agent for obesity treatment. Obes Res 3(Suppl 4):553S–559S
15. **Berkowitz RI, Wadden TA, Tershakovec AM, Cronquist JL** 2003 Behavior therapy and sibutramine for the treatment of adolescent obesity: a randomized controlled trial. JAMA 289:1805–1812
16. **Godoy-Matos A, Carraro L, Vieira A, Oliveira J, Guedes EP, Mattos L, Rangel C, Moreira RO, Coutinho W, Appolinario JC** 2005 Treatment of obese adolescents with sibutramine: a randomized, double-blind, controlled study. J Clin Endocrinol Metab 90:1460–1465
17. **Berkowitz RI, Fujioka K, Daniels SR, Hoppin AG, Owen S, Perry AC, Sothern MS, Renz CL, Pirner MA, Walch JK, Jasinsky O, Hewkin AC, Blakesley VA** 2006 Effects of sibutramine treatment in obese adolescents: a randomized trial. Ann Intern Med 145:81–90
18. **Daniels SR, Long B, Crow S, Styne D, Sothern M, Vargas-Rodriguez I, Harris L, Walch J, Jasinsky O, Cwik K, Hewkin A, Blakesley V** 2007 Cardiovascular effects of sibutramine in the treatment of obese adolescents: results of a randomized, double-blind, placebo-controlled study. Pediatrics 120:e147–e157
19. **Garcia-Morales LM, Berber A, Macias-Lara CC, Lucio-Ortiz C, Del-Rio-Navarro BE, Dorantes-Alvarez LM** 2006 Use of sibutramine in obese Mexican adolescents: a 6-month, randomized, double-blind, placebo-controlled, parallel-group trial. Clin Ther 28:770–782
20. **Van Mil EG, Westerterp KR, Kester AD, Delemarre-van de Waal HA, Gerver WJ, Saris WH** 2007 The effect of sibutramine on energy expenditure and body composition in obese adolescents. J Clin Endocrinol Metab 92:1409–1414
21. **Rolland-Cachera MF, Sempe M, Guilloud-Bataille M, Patois E, Pequignot-Guggenbuhl F, Fautrad V** 1982 Adiposity indices in children. Am J Clin Nutr 36:178–184
22. **Cole TJ, Bellizzi MC, Flegal KM, Dietz WH** 2000 Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 320:1240–1243
23. **Yanovski SZ, Yanovski JA** 2002 Obesity. N Engl J Med 346:591–602
24. **Jeanrenaud B** 1985 An hypothesis on the etiology of obesity: dysfunction of the central nervous system as a primary cause. Diabetologia 28:502–513
25. **Lustig RH, Hinds PS, Ringwald-Smith K, Christensen RK, Kaste SC, Schreiber RE, Rai SN, Lensing SY, Wu S, Xiong X** 2003 Octreotide therapy of pediatric hypothalamic obesity: a double-blind, placebo-controlled trial. J Clin Endocrinol Metab 88:2586–2592
26. **Lustig RH, Rose SR, Burghen GA, Velasquez-Mieyer P, Broome DC, Smith K, Li H, Hudson MM, Heideman RL, Kun LE** 1999 Hypothalamic obesity caused by cranial insult in children: altered glucose and insulin dynamics and reversal by a somatostatin agonist. J Pediatr 135:162–168

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