Serotonin and Norepinephrine Reuptake Inhibition and Eating Behavior

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ABSTRACT: **Brain neurotransmitters, serotonin and norepinephrine, play an important role in the central nervous control of energy balance and are involved in symptomatology related to both obesity and depression. Therefore both serotonin and norepinephrine neural pathways have been paid a special attention as targets for the antiobesity drugs, antidepressants, and drugs used in the treatment of eating disorders. Selective serotonin reuptake inhibitors (SSRI) have been used in the treatment of depression and eating disorders but have failed to achieve sustained weight loss in the treatment of obesity. Sibutramine, a serotonin and norepinephrine reuptake inhibitor, which induces satiety and prevents decline in metabolic rate associated with a hypocaloric diet, is currently the sole centrally acting drug indicated for the long-term treatment of obesity. Depression, dietary disinhibition (evaluated by the Eating Inventory [EI]), and stress are associated with the accumulation of abdominal fat and the development of metabolic syndrome and related diseases. Subjects with abdominal obesity demonstrate neuroendocrine abnormalities which result in disturbances in hypothalamo-pituitary-adrenal (HPA) function. Treatment with SSRI might interrupt the vicious circle which leads to endocrine abnormalities and the accumulation of abdominal fat. Obesity treatment with sibutramine results, not only in significant weight loss, but also in reduction of abdominal fat and in the improvement of health risks associated with metabolic syndrome (lipid profile, blood glucose, insulin, HbA1c, and uric acid), as well as in the decline in disinhibition score of the EI. In a 1-year sibutramine trial, only a decrease in the disinhibition score remained a significant correlate of weight loss among the psychobehavioral and nutritional factors which were taken into account.**

KEYWORDS: **serotonin; norepinephrine; eating behavior; dietary disinhibition; sibutramine; abdominal obesity; metabolic syndrome**

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CENTRALLY ACTING DRUGS THAT AFFECT SEROTONIN AND NOREPINEPHRINE PATHWAYS (TABLE 1)

Obesity reached epidemic proportions at the beginning of the new millennium in both developed and developing countries. Therefore intensive research has been focused on the development of new antiobesity agents in order to control the increasing epidemic of obesity. Central nervous control of eating consists of two separate neuroregulatory systems. Regulation of satiety and hunger is mediated by neurotransmitters and hormones, such as serotonin, norepinephrine, leptin, neuropeptide Y/agouti-related peptide, proopiomelanocortin/MSH/CART, orexins, ghrelin, peptide YY, glucagon-like peptide- 1, etc. On the other hand, in the regulation of hedonic responses (eating represents a source of pleasure and addiction) dopamine, endo-cannabinoids, opioids, and glutamate are involved. Drugs affecting energy balance through the central serotonin and norepinephrine pathways have been paid a special attention in the treatment of obesity. Amphetamines and phentermine act as releasing agents for norepinephrine and dopamine. Because of serious side effects associated with norepinephrine-induced tachycardia and hypertension and dopamine-induced addiction, amphetamines do not have any indication for the treatment of obesity. Phentermine exhibits less addiction properties than amphetamines, but still exerts adverse cardiovascular side effects. Therefore phentermine is indicated only for short-term use as an antiobesity agent in some countries and was withdrawn from the market in other countries. Fenfluramine and dexfenfluramine act as both serotonin-releasing agents and serotonin reuptake inhibitors and were used as antiobesity agents which induced a significant weight loss by suppression of the appetite.[1] They were withdrawn from the market because of the development of heart valve disease associated with stimulation of the heart serotonin 2b receptors. A new generation of selective serotonin (2C) agonists (ADP356, Ro 60-0175, Org 12962, VER-3323, BVT-933, YM348) have been developed that induce satiety and have been devoid of cardiotoxicity.[2] ADP356 is currently undergoing clinical trials. ADP356 administered for 1 month in a daily dose of 15 mg induced a highly significant weight loss in comparison with placebo. The drug was well tolerated and there were no apparent harmful side effects on the heart as assessed by echocardiograms. Selective serotonin reuptake inhibitors (SSRI) used as antidepressant agents (fluoxetine, sertraline, citalopram) induced weight loss during the short-term period, but failed to achieve sustained weight loss in the treatment of obesity. Sibutramine is currently the only centrally acting drug that is indicated for the long-term treatment of obesity. Sibutramine acts as a serotonin and norepinephrine reuptake inhibitor, which induces satiety and prevents a hypocaloric diet-induced decline in metabolic rate.[3] Venlafaxine, milnacipran, and duloxetine as serotonin and norepinephrine reuptake inhibitors represent a new treatment option for depression, anxiety, and stress urinary incontinence, as well as painful physical symptoms.[4,5] Their use in the treatment of obesity

has not been reported. However, even the long-term treatment of depression with serotonin–norepinephrine reuptake inhibitor, duloxetine, is not associated with substantial weight gain.

Norepinephrine reuptake inhibitor, GW320659, that possesses antidepressant activities is also investigated as an antiobesity agent and a drug for the management of attention-deficit/hyperactivity disorder. Reboxetine, a potent and selective norepinephrine reuptake inhibitor, has been approved for the treatment of major depression[6] as well as for the treatment of chronic pain in patients with depression.[7] In healthy volunteers, an administration of reboxetine stimulates cortisol secretion and this cortisol response is higher in males than in females.[8] Reboxetine has not been evaluated in obese patients. However, a case of significant weight loss in normal weight woman treated with reboxetine was described.[9]

ROLE OF PSYCHOLOGICAL FACTORS IN BODY WEIGHT REGULATION AND HEALTH RISKS OF OBESITY

Body weight, fat accumulation, and fat distribution, as well as the subsequent health risks are influenced by the interaction of genetic and environmental factors. This process is under a complex control of neurotransmitters and hormones which could affect health risks either directly or indirectly through their influence on body fat accumulation and/or body fat distribution. Psychological factors affecting eating behavior and physical activity are influenced not only by genes and environment, but also by neurotransmitters, hormones, fat accumulation, and by the health risks manifested by obesity-related diseases. Psychological factors might exert their influence on health risks either directly or indirectly by neurohormonal pathways or through their influence on fat accumulation.

DEPRESSION, OBESITY, AND ABDOMINAL FAT ACCUMULATION

Per Björntorp emphasized the following main characteristics of the "Civilization Syndrome":[10]

(1) High stress,
(2) poor coping,
(3) increased alcohol and tobacco consumption,
(4) overeating, and
(5) physical inactivity.

According to Bjornorp, the characteristics of the "Civilization Syndrome," together with depression, lead to the accumulation of abdominal fat, a major

TABLE 1. Centrally acting drugs affecting serotoninergic and adrenergic pathways

	Releasing agents			Reuptake inhibitors	
	5-HT	NE	DA	5-HT	NE
Dexamphetamine		√	√		
Phentermine		√	√		
Fenfluramine	√			√	
Dexfenfluramine	√			√	
ADP 356*	√				
Fluoxetine				√	
Sibutramine				√	√
Duloxetine				√	√
Milnacipran				√	√
Venlafaxine				√	√
Atomoxetine					√
Reboxetine					√

*Selective 5-HT (2C) agonist.
NOTE: 5-HT = serotonin; NE = norepinephrine; DA = dopamine.

feature of the metabolic syndrome.[10] Depression could be one of the causal factors resulting in abdominal obesity. Ahlberg *et al*. classified abdominal obesity according to the waist to hip ratio (WHR) and evaluated depression by three different depression inventories: Hamilton Depression Scale, Montgomery–Asberg Depression Rating Scale, and Beck Depression Inventory.[11] He found that individuals with the WHR ≥ 1 exhibited significantly higher depression scores in all three depression scales than individuals with the WHR < 1 (TABLE 2). Recent study in overweight premenopausal women demonstrated a significant positive association of depressive mood with visceral and not with subcutaneous adipose tissue measured by computed tomography at the level of vertebral body L4-L5.[12] Depression could be a consequence of obesity in females who negatively perceive weight discrimination and weight teasing. In contrast, obesity is not usually accompanied by depression in males, as men do not perceive obesity as a psychosocial obstacle. Major depression in adolescents predicted a greater body mass index in adult life. Adverse childhood experiences promote the development of both depression and obesity and their co-occurrence. A genetic susceptibility to both depression and obesity may be expressed by environmental influences.[13] However, it is unclear whether the co-occurrence of depression and obesity is functionally related. Brain serotonin is involved in the regulation of appetite, mood, and other neuroendocrine functions. Reduction of brain serotonin might result in hyperphagia, depression, and pertubation of the pituitary–adrenal axis, suggesting that there may be common pathophysiology elements between obesity and depression.[14] The role of the serotoninergic system in body weight regulation is further supported by the observed association between polymorphism of serotonin 2C receptor[15]

TABLE 2. Depression rating and abdominal obesity classified according to the WHR

Depression scale	WHR < 1.0	WHR ≥ 1.0	*P* value
Hamilton depression scale	1.2 ± 1.8	4.1 ± 4.1	<0.001
Montgomery–Asberg depression rating scale	0.9 ± 1.1	3.0 ± 4.0	0.007
Beck depression score	2.7 ± 2.7	4.9 ± 4.7	0.044

NOTE: According to Ahlberg *et al*.[11]

and body weight gain in response to treatment with antipsychotic drugs, as well as by the finding of differential expression of serotonin receptors among mice, prone or resistant to chronic high-fat diet-induced obesity.[16]

It is also important to note that stress and depression represent barriers to the initiation and maintenance of healthy behaviors. P.Rhode *et al*. found that that higher stress and depression scores at the termination of a 6-month weight loss intervention predicted an increase in the percentage of total fat intake at 9 and 12 months, a trend that continued at 18 months.[17] Energy-deficient diets exert changes in the serum cortisol level which predict changes in appetite and weight loss during the subsequent follow-up.[18] However, it should be taken into account that changes in serum cortisol levels induced by a negative energy balance are also significantly determined by hereditary factors. This was demonstrated in our study of monozygotic twins who underwent 1-month treatment with very-low-calorie diet (VLCD). Significant within-pair resemblance in VLCD-induced changes in serum cortisol level was demonstrated throughout the day.[19]

An apparent overlap of obesity and depression is being frequently observed. Both diseases frequently exhibit increased appetite, hypersomnia, psychomotor retardation, and fatigue or loss of energy. Furthermore, both abdominal obesity and major depression are associated with coronary heart disease (CHD) and represent an increased risk of mortality. Depressive symptoms constitute an independent risk factor for the development of CHD and total mortality.[20] Major depression was also recognized as an independent risk factor that accelerated the development of CHD in diabetic women.[21] On the other hand, depressive patients treated with specific serotonin reuptake inhibitors have a significantly lower risk of death or nonfatal myocardial infarction.[22] Depression is associated with hyperglycemia in patients with diabetes.[23] Serum concentration of adiponectin, an adipose tissue hormone which is involved in the prevention of the development of metabolic syndrome, is negatively related to a depression score evaluated by the Beck Depression Inventory.[24] Norepinephrine and serotonin as brain neurotransmitters are involved in symptomatology related to both obesity and depression. Brain norepinephrine deficiency might be related to lethargy, decreased alertness, decreased energy, and abnormal feeding, whereas deficiency of serotonin might be related to obsessive and compulsive symptoms, dysphoria, abnormal feeding, eating disorders, and binge eating.

ABDOMINAL OBESITY, PERTUBATION OF HYPOTHALAMO-PITUITARY-ADRENAL AXIS AND TREATMENT WITH SSRI

Subjects with abdominal obesity demonstrate neuroendocrine abnormalities resulting in disturbances in the hypothalamo-pituitary-adrenal (HPA) function. A normal HPA function is characterized by high variability and high morning cortisol levels and a clear postprandial response in the cortisol level after lunch ingestion, as well as by an appropriate suppression with dexamethasone.[25] Low morning serum cortisol levels[26–29] and a decreased dexamethasone-induced suppression of cortisol release[28] characterize a pertubation of HPA axis in abdominal obesity. Dysfunction of the HPA axis as a consequence of frequently repeated or chronic stressful stimuli is associated with abdominal obesity and increased risks for cardiovascular disease, type 2 diabetes, and stroke.[25] Treatment with the SSRI citalopram, induced an increase in morning serum cortisol concentrations, suggesting a change toward normalization of the pertubed HPA axis activity.[29] Improvement in plasticity of the HPA axis by treatment with citalopram was also demonstrated by the increased cortisol levels in response to stimulation with corticotropin-releasing hormone (CRH) and stress.[29] Rosmond and Björntorp suggested to use the SSRI antidepressants in order to interrupt the vicious circle of pertubed HPA axis leading to an increasing abdominal obesity and endocrine abnormalities that, in turn, lead to progressive accumulation of intra-abdominal fat.[30] Administration of dexfenfluramine (an antiobesity drug which was withdrawn from the market), acting both as serotonin reuptake inhibitor and serotonin-releasing agent, was shown to induce a specific reduction of abdominal fat stores when assessed by magnetic resonance imaging (MRI). In the trial of Marks *et al*., treatment of obesity with dexfenfluramine for 3 months was accompanied by a significant reduction of the visceral fat area ($-21.0 \pm 4.0\%$ in the dexfenfluramine group versus $-6.7 \pm 2.2\%$ in the placebo group, $P < 0.01$), although there was no significant difference between placebo and dexfenfluramine groups with regard to a reduction in the subcutaneous fat area.[31] The role of the serotoninergic system in the development of abdominal obesity and metabolic syndrome was recently demonstrated by an association of the low central nervous system serotoninergic responsivity with the metabolic syndrome and physical inactivity.[32]

EATING DISORDERS, SEROTONINERGIC SYSTEM, HPA AXIS AND TREATMENT WITH SSRI

Eating disorders, such as anorexia nervosa and bulimia nervosa, are diseases characterized by aberrant patterns of feeding behavior and weight regulation, as well as disturbances in the attitudes toward the perception of body weight and body shape. Both disturbances in the HPA axis and alterations in the central serotoninergic mechanisms were observed in patients with bulimia nervosa.

About one-third of women with bulimia nervosa failed to suppress the salivary cortisol level after dexamethasone and bulimic nonsuppressors exhibited elevated basal salivary cortisol levels.[33] Lester *et al*. described that an exacerbation of bulimic symptoms was followed by an elevated cortisol secretion.[34] On the other hand, the blunted response of cortisol and prolactin to administration of the partial serotonin agonist, meta-chlorophenylpiperazine (m-CPP), was demonstrated in patients with bulimia nervosa in comparison to healthy subjects.[35] The blunting of neuroendocrine responses was most remarkable in bulimic women who reported in their history a self-destructiveness. Serotoninergic abnormalities in bulimia nervosa might be therefore most characteristic of individuals with self-destructive potential.[35] Studies using brain positron emission tomography with serotonin-specific radioligands revealed alterations of 5-HT1A and 5-HT2A receptors and the 5-HT transporter in eating disorders.[36] Alterations of these circuits may affect mood and impulse control as well as the motivating and hedonic aspects of feeding behavior. It has been suggested that reduced serotonin activity triggers some of the cognitive and mood disturbances associated with bulimia nervosa and therefore, the pharmacological treatment of bulimia nervosa is focused mainly on SSRI. SSRIs are effective in reducing binge eating, as well as purging episodes in patients with bulimia nervosa.[37] Elevated concentrations of 5-hydroxyindoleacetic acid in the cerebrospinal fluid observed after recovery suggest that altered serotonin activity in eating disorders is a trait-related characteristic.[38] Treatment with SSRI reduces the clinical symptoms of eating disorders independently of their antidepressant effects. However, effectiveness of SSRIs in the treatment of anorexia nervosa requires an adequate supply of nutrients, which are essential to the appropriate synthesis and function of serotonin. This is the reason why the treatment with SSRI fails in malnourished and severely underweight anorectic patients, but is effective after weight restoration and improvement of nutritional status.[38]

Binge-eating disorder (BED) is characterized by recurrent episodes of binge eating in the absence of compensatory behaviors to avoid weight gain, such as vomiting or laxative abuse, usually seen in bulimia nervosa.[39,40] Related characteristics include eating until uncomfortably full, eating alone, eating when not physically hungry, as well as consequent depressive and guilty feelings. BED is associated with depression and personality disorders. Almost 30% of obese patients manifest BED.[40] Stress is the most frequently reported trigger of binge eating. Cortisol response to a cold pressor stress test positively correlated with abdominal obesity in obese women with BED.[41] Hyperactivity of the HPA axis related to abdominal obesity persisted even after cognitive-behavioral treatment, suggesting that cortisol might play an essential role in the pathogenesis of this disorder.[41] SSRI, such as fluoxetine, fluvoxamine, sertraline, and citalopram, have been used in the treatment of BED, reducing binge-eating frequency and body weight over the short term.[42]

The *night eating syndrome* is an eating disorder characterized by morning anorexia, evening hyperphagia and insomnia, as well as night awakenings

accompanied by eating of small amounts of food with rapid return to sleep.[43] Stress is closely related to night eating. An abnormal eating behavior, as observed in night eaters, is associated with an activation of the HPA axis, resulting in higher diurnal salivary cortisol levels,[44] as well as with disturbances in the HPA axis manifested by an attenuated adrenocorticotropic hormone (ACTH) and cortisol response to CRH.[45] According to Stunkard, coincidence of the night eating syndrome with psychiatric disorders, especially depression, is very high.[44,46] The role of the serotoninergic system in the pathogenesis of the night eating syndrome was confirmed by the effective treatment with SSRI. Administration of sertraline to patients with the night eating syndrome significantly reduced evening hyperphagia, awakenings, and night eating episodes.[44,46]

SIBUTRAMINE IN THE TREATMENT OF OBESITY AND BED

Sibutramine is a combined reuptake inhibitor of both serotonin and norepinephrine which has a dual mode of action on energy balance. It reduces food intake by enhancing satiety and attenuates the weight loss-induced decline in energy expenditure.[47] Mechanism of action, that is, inhibition of the reuptake of serotonin and norepinephrine in the target tissues, clearly differentiates sibutramine (as well as the antidepressant duloxetine) from amphetamine and fenfluramine, which act as releasing agents.[3,4] Sibutramine has been shown to produce dose-dependent weight loss.[48] Weight loss achieved at week 4 was predictive of weight loss achieved at week 24. Clinical trials clearly demonstrated that two-thirds of patients taking sibutramine lose $\geq$5% of initial body weight.[47] Simultaneously with weight loss, patients treated with sibutramine demonstrate significant improvement in lipid profile, blood glucose, HbA1c, and uric acid and those with hypertension at base line exhibit a significant decline in blood pressure.[49,50] Sibutramine is an efficient antiobesity drug not only for weight loss but also for the long-term maintenance of weight loss. In the STORM study, an individualized weight management program achieved weight loss in 77% of obese patients and sustained weight loss in most patients continuing therapy for 2 years.[51] A 2-year weight management with sibutramine resulted in a significant decrease in waist circumference, as well as in improvement in lipid profile. Changes in concentrations of high-density lipoprotein (HDL) cholesterol, very-low-density lipoprotein (VLDL) cholesterol, and triglyceride observed in the STORM study exceeded those expected from the weight loss alone.[51] It appears, therefore, that there is an independent effect of sibutramine on the HDL cholesterol level, beyond weight loss, that requires further elucidation. Efficacy of pharmacotherapy for weight loss in adults with type 2 diabetes was evaluated in meta-analysis conducted by Norris.[52] Weight loss in patients with diabetes was modest and achieved 4.5 kg in response to a 26-week treatment with sibutramine, 5.8 kg in response to a 52-week treatment with SSRI fluoxetine, and 2.6 kg in response to a 26-week treatment

with lipase inhibitor, orlistat. Diminished drug treatment-induced weight loss in obese patients with diabetes might be caused by genetic and metabolic factors, as well as by the concomitant drug therapy. Glycosylated hemoglobin was also only modestly reduced with each drug included in the meta-analysis. A randomized trial of sibutramine in the management of obese, type 2 diabetic patients treated with metformin demonstrated that glycemic control improves with corresponding weight loss.[53] Patients who lost $\geq$10% initial body weight showed a mean 1.2% decrease in HbA1c. Because sibutramine treatment may lead to both increased blood pressure and heart rate, its use is contraindicated in patients with uncontrolled hypertension, dysrhythmias, and congestive heart failure.[54] Recent combined analysis of two placebo-controlled trials concludes that sibutramine treatment is unlikely to elicit a critical increase in blood pressure in hypertensive patients because a sibutramine-induced central nervous system blockade of norepinephrine reuptake attenuates the sympathetic outflow through activation of α-2 adrenoreceptors ("clonidine-like effect").[55]

It is important that intermittent treatment with sibutramine was equally effective as continuous treatment during a 48-week randomized, placebo-controlled trial.[56] The proportion of adverse events was lowest in the group receiving intermittent therapy. Sibutramine was also used in the treatment of adolescent obesity and its administration was associated with a higher weight loss in comparison with a placebo or behavioral therapy alone.[57] Sari *et al*. demonstrated that an addition of orlistat to sibutramine did not lead to a greater weight loss than the treatment with sibutramine alone.[58]

Long-term weight maintenance after weight loss in the STORM trial was significantly determined by a higher leisure-time activity index.[59] We confirmed the role of sibutramine treatment in increasing the habitual physical activity: the increase in reported daily walking time during the 4-month placebo-controlled period was significantly higher in the sibutramine-treated than in the placebo group.[60] Spontaneous locomotor activity was also significantly increased in experimental animals following the administration of sibutramine.[61]

As mentioned before, SSRI have exhibited efficacy in reducing the frequency of binge-eating episodes and ameliorating depressive symptomatology in BED, but they have not demonstrated the ability to achieve long-term weight reduction.[42] On the contrary, the sibutramine treatment of BED resulted not only in a decreased frequency of binge eating and an improvement of comorbid conditions as depressive symptoms, but also in the reduction of body weight.[62,63]

OBESITY TREATMENT WITH SIBUTRAMINE AND EATING BEHAVIOR

Weight loss in response to weight management is influenced by genetic, metabolic, neurohormonal, nutritional, and psychobehavioral factors. Weight loss in response to a short-term nutritionally well-defined weight reduction

program is determined by energy efficiency, substrate oxidation, sympathetic nervous system activity, and insulin sensitivity,[64] as well as by the levels of hormones involved in energy balance regulation.[65] Psychobehavioral factors, such as depression, anxiety, and eating behavior, do play an important role in the adherence to weight management and thus in weight loss maintenance. Depression represents a negative prognostic marker for weight reduction.[66,67]

Psychobehavioral predictors of weight loss have been evaluated during the pharmacotherapy of obesity which employed the combined administration of drugs (fenfluramine + phentermine, fenfluramine + mazindol), most of which have now been withdrawn from the market.[68] The Eating Inventory (EI), also known as the Three Factor Eating Questionnaire, has usually been used for evaluation of the eating behavior.[69] The EI assess three behavioral traits: (*a*) cognitive dietary restraint—deliberate control of intake, (*b*) disinhibition—measure of the loss of control over food intake which might be triggered, for example, by stress, depression, anxiety, and alcohol intake, and (*c*) perceived hunger—awareness of and susceptibility to hunger. In the Womble's study, base line values of dietary restraint and hunger predicted weight loss at 6 and 12 months of drug treatment.[68] High base line scoring on dietary restraint and hunger was associated with lower weight loss after a 6-month treatment, whereas only high hunger scoring at base line predicted lower weight loss at 12 months. A high restraint score at base line was also associated with a lower weight loss at 1 year after gastric banding.[70] In the STORM study, which evaluated a 2-year weight loss maintenance in response to sibutramine/placebo treatment, the baseline body weight, mode of treatment, and age, explained 9% of the variation in weight change over a 2-year period of follow-up.[71] In the same study gender, resting metabolic rate, smoking history, previous attempts to lose weight, and the age of the onset of obesity did not affect the weight change at a 2-year follow-up, however, psychobehavioral and nutritional parameters were not considered. In our study, obese women were followed for 12 months and treated either with sibutramine alone for the whole period of 12 months, or with a placebo and sibutramine (a placebo was administered over an initial 4 months and sibutramine was given in a subsequent period of 8 months).[60] The role of baseline BMI, psychobehavioral, and nutritional parameters on weight loss in patients treated with 10 mg sibutramine/day was evaluated at 4-month and 12-month follow-ups. Three factors of the EI, Beck depression score, energy, and macronutrient intake were assessed before the trial started, and at 4-month and at 12-month follow-ups. Baseline values for BMI and dietary restraint, together with the mode of treatment, predicted body weight change after a 4-month treatment ($r^2 = 30.8\%$). Higher initial BMI and lower baseline dietary restraint and treatment with sibutramine predicted a better outcome during a 4-month placebo-controlled period of the trial. Baseline values for BMI, depression score, restraint score, and energy intake were significant predictors of body weight change after a 12-month treatment and explained 43.8% of the variance in the BMI change (TABLE 3). It means that

TABLE 3. BMI after 12-month treatment

Method	Independent variables	Parameter	Standard error	*t*-statistics	*P* value
Backward stepwise regression (Fisher's statistics>3 was chosen as a selection criterion)	Constant	4.8	1.44	3.33	0.001
	Depression$^{0.11}$	−1.63	0.58	−2.79	0.007
$R = 0.662$	Restraint$^{0.90}$	−0.0552	0.0206	−2.67	0.010
$P < 0.0001$	Energy$^{0.32}$	−0.201	0.082	−2.46	0.017
	Protein$^{0.21}$	1.64	0.95	1.73	0.088
	− (BMI$^{-3.86}$)	683, 722	126, 175	5.42	0.000

Backward stepwise regression of the relations between the change in BMI after a 12-month treatment with sibutramine/placebo, and the mode of treatment, baseline BMI, and the psychobehavioral and nutritional characteristics.

NOTE: According to Hainer *et al*.[60]

patients with higher depression and dietary restraint scores at base line lost less weight at the 12-month follow-up. High dietary restraint at the pretreatment period might be associated with dieting and weight control before the trial started, and therefore these patients did not lose as much weight in response to treatment, compared to those with low restraint initially who increased their dietary restraint during the treatment. The impact of the changes in psychobehavioral and nutritional parameters seen after 4 and 12 months of treatment on BMI changes was also investigated. The BMI decrease over a 4-month treatment period was significantly associated with the mode of treatment and changes in dietary restraint and disinhibition, as well as with changes in protein and fat intake. These variables accounted for 56.6% of the variance in weight change after a 4-month treatment. Sibutramine administration, increases in dietary restraint and protein intake, and reductions in dietary disinhibition and fat intake resulted in a greater weight loss. However, among the changes in the psychobehavioral and nutritional parameters over the 12-month period of the sibutramine trial, only the change in the disinhibition score remained the sole significant factor related to the BMI decrease (TABLE 4). A significant relation between the decrease of the disinhibition score and the decrease of the BMI is shown in FIGURE 1. The association between weight loss and decline in the disinhibition score in response to the sibutramine treatment might be related to the previously described beneficial effects of sibutramine treatment on obesity-related health risks.[49–51] Our recent study using a quota sample of the Czech population demonstrated that the disinhibition score was closely related, not only to the BMI and waist circumference, but also to cardiovascular disease, hypertension, and hyper(dys)-lipidemia.[72] The revealed association between the factors of EI and these diseases remained significant even when the BMI and age were considered. The relationships between dietary disinhibition and diseases were especially pronounced in middle-aged persons. Prevalence of hypertension, cardiovascular disease, and hyper(dys)-lipidemia

TABLE 4. The relations between the BMI change after a 12-month treatment with either sibutramine alone or placebo/sibutramine, and changes in the psychobehavioral and nutritional parameters

Method	Independent variables	Parameter	Standard error	*t*-statistics	*P* value
Backward stepwise regression (Fisher's statistics>3 was chosen as a selection criterion) $R = 0.541$ $P < 0.0001$	Constant	1.019	0.086	11.91	0.000
	Δ Disinhibition	0.0911	0.0211	4.31	0.000

In the backward stepwise regression, a change in the disinhibition score remained the sole significant factor associated with the BMI change.

NOTE: According to Hainer *et al*.[60]

(%) in middle-aged males and females (33- to 44-years old) was significantly higher in subjects scoring high (upper quartile) than in those scoring low (lower quartile) on the disinhibition score (FIG. 2). There is no doubt that a decrease in the disinhibition score as a correlate of sibutramine-induced weight

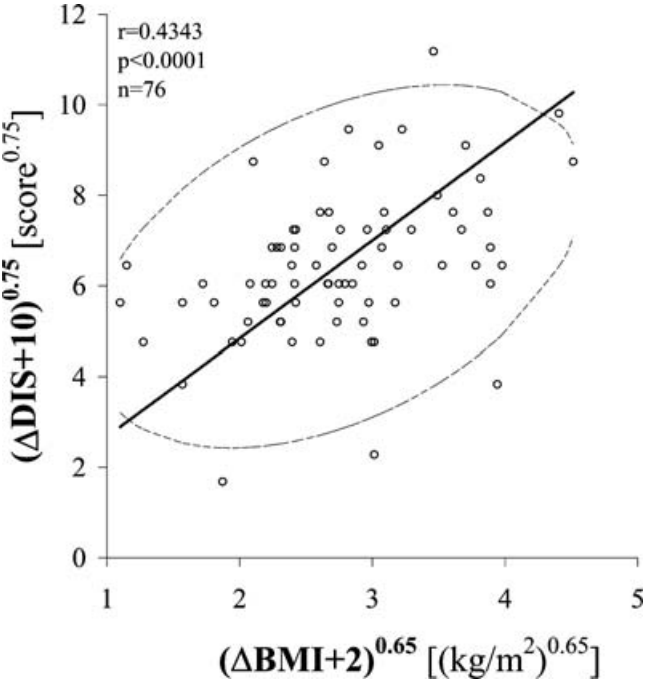

FIGURE 1. Relationship between the change of BMI and change of the disinhibition score at a 12-month follow-up in patients treated either with sibutramine alone for 12 months or with a placebo (initial 4 months) and sibutramine (subsequent 8 months) (unpublished figure according to Hainer *et al.*[60]).

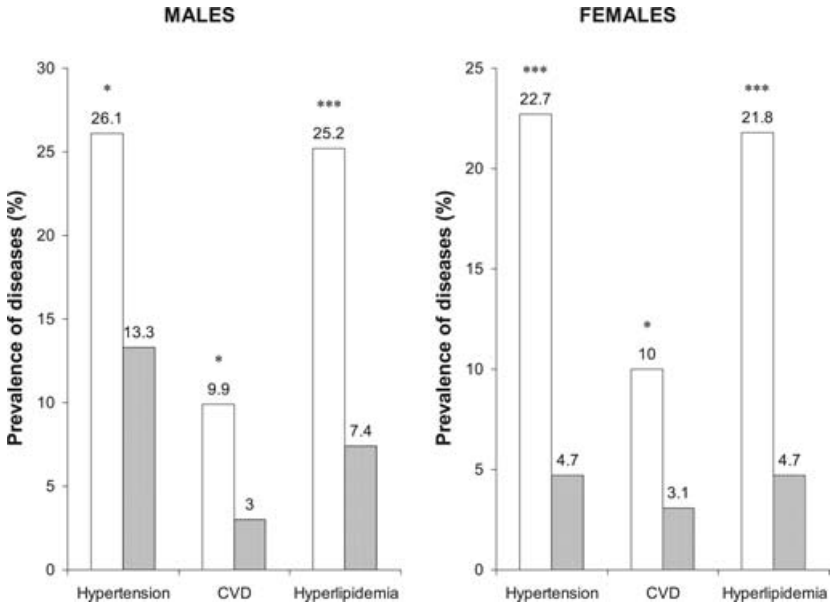

FIGURE 2. Prevalence of diseases (%) in middle-aged (33- 44-years old) males and females characterized by high and low disinhibition scores (upper versus lower quartile) (unpublished figure according to Hainer *et al.*[72]).

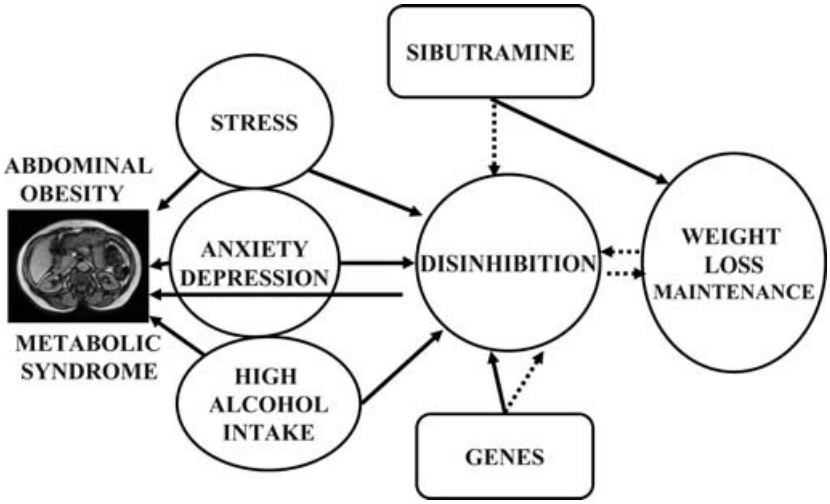

FIGURE 3. Dietary disinhibition is frequently triggered by stress, anxiety, and depression, but is also greatly influenced by genetic factors. Disinhibition is significantly related to abdominal obesity and to diseases associated with the metabolic syndrome. Demonstrated association of sibutramine-induced weight loss maintenance with changes in eating behavior characterized by a decrease in the disinhibition score might partly explain beneficial metabolic effects of sibutramine treatment.

loss does play an important role in the amelioration of health risks linked to the abdominal obesity and lifestyle-associated pathologies (FIG. 3). However, it should be mentioned that disinhibition as an eating behavior which reflects opportunistic eating is significantly genetically determined, whereas dietary restraint is most strongly influenced by environmental factors.[73–76]

In conclusion, among the drugs targeting central serotonin and norepinephrine pathways, only serotonin and norepinephrine reuptake inhibitor, sibutramine, has been approved as an efficient tool for both the long-term treatment of obesity and amelioration of obesity-related health risks. Other drugs affecting brain norepinephrine and serotonin pathways are mainly used in the treatment of depression and eating disorders. However, novel agents, possessing a high selectivity, are being investigated as potential antiobesity drugs, too.

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