

Short-term difference in mood with sibutramine versus placebo in obese patients with and without depression

Kristina Elfhag[†] &
Stephan Rössner

[†]Author for correspondence
Karolinska University
Hospital, Obesity Unit, M73,
SE-141 86 Stockholm,
Sweden
Tel.: +46 858 582 478
Kristina.Elfhag@medhs.ki.se

Background: Sibutramine is an anti-obesity satiety-enhancing drug which elicits its effect by inhibiting the reuptake of serotonin and noradrenalin. **Objective:** The aim of this study was to test the short-term effect on mood with sibutramine versus placebo in obese patients with and without depressive features. **Materials & methods:** The participants consisted of 36 obese patients with a mean body mass index of 39 kg/m². Depressive features were measured with the Comprehensive Psychopathological Rating Scale (CPRS). Sibutramine (15 mg) and placebo were administered daily in a cross-over design over 14-day periods. At baseline, 19 (53%) patients demonstrated depressive features. **Results:** A significant short-term difference, implying lower mood with sibutramine versus placebo, was observed for depressed patients, in particular, in the CPRS subscale for anxiety. This result persisted as statistically significant also when removing an item on increased sleeping difficulties in the CPRS anxiety scale. Sleeping difficulties, which are common side effects of anti-obesity drugs, were also greater with sibutramine in depressed patients. No differences were found in the nondepressed population. **Conclusion:** Patients with depressive features can be more susceptible to experiencing a relatively higher initial discomfort with sibutramine compared with placebo at onset of treatment.

Sibutramine is an anti-obesity drug which primarily enhances satiety through a process of serotonin and noradrenalin reuptake inhibition [1]. It is a well-documented drug for long-term weight reduction [2]. Sibutramine was initially developed as an antidepressant, characterized by a rapid onset of neurotransmitter changes which were demonstrated in animal brain tissue and human plasma [3–5]. The pharmacological profile has been thoroughly reviewed by Heal [1].

Antidepressive effects observed in subsequent human Phase II clinical trials were, however, discouraging. Due to the unexpected side effect of weight loss, the compound was instead further developed as an anti-obesity drug. The unsuccessful results of sibutramine as an antidepressant were reported only as an abstract [6]. Since then, little attention has been attributed to a possible mood effect of sibutramine. We have found only two placebo-controlled studies reporting results on depression in obese samples treated with sibutramine for weight reduction. In a 12-week study examining obese binge eaters, a reduction in depression was reported with sibutramine versus placebo [7]. No difference in depression was found after 14 days with sibutramine versus placebo in an obese non-patient sample [8]. Non-placebo-controlled mood

improvements in sibutramine treatment have been reported in an additional study of obese binge eating patients and in a general clinical sample of obese patients [9,10]. Improvements in mood are however, commonly found in various obesity treatments [11]. In our previous research, we found incidences of remission of depression during sibutramine treatment and one new incidence of depression in a patient who thereafter dropped out of treatment, aside from the overall significantly positive mood effect [10].

Sibutramine has well-documented rapid neurotransmitter effects [5]. The negative side effects of sibutramine treatment are most pronounced during the first weeks of treatment. Side effects related to the CNS most commonly include insomnia and dry mouth, and less commonly, anxiety, headache and dizziness [12–14]. The rapid CNS effects of sibutramine have been tested in previous work examining the acute abuse potential of sibutramine. In these experiments, sibutramine was found to be less preferred than placebo at both doses tested (20 and 30 mg) in experienced stimulant abusers [15]. With 30 mg of sibutramine, a subscale for dysphoria was even greater than with placebo. In all other psychological measures, sibutramine was statistically indistinguishable from placebo.

Keywords: anti-obesity drug, depression, insomnia, pharmacological treatment, psychology, side effects



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Depression and depressive features are known to be very common in obese patients [16]. We have earlier reported that there were no differences for depressed and non-depressed patients in non-placebo-controlled mood changes during prolonged sibutramine treatment [10]. We have found no prior research evaluating short-term differences in mood with sibutramine in depressed and non-depressed patients. More knowledge of potential short-term effects on mood with a drug used for patients with a high incidence of depression is of obvious clinical importance.

The objective of this study was to analyze short-term changes in mood with sibutramine versus placebo in depressed and non-depressed obese patients for whom we have earlier reported non-placebo-controlled positive mood effect at month 2 through to 6 for patients who subsequently remained on treatment [10].

Materials & methods

Participants

The participants were 36 patients included in a clinical trial at the Obesity Unit, Karolinska University Hospital, Sweden. Of these, 27 were female and nine male, with a mean age of 43 ± 12 years, standard deviation, (SD) ranging from 20 to 64 years. The mean body mass index (BMI) was 39 ± 4 kg/m² and ranged from 30 to 45 kg/m². More information on this sample, including medical exclusion criteria for participation and drop-outs, has been provided in a previous publication [17]. Treatment with drugs that could interfere with the action of sibutramine was not allowed in the study. Treatment with selective serotonin re-uptake inhibitor (SSRI) drugs was likewise an exclusion criterion. The study was approved by the local ethics committee at the Karolinska Institute and patients gave their informed consent to participate.

Assessment methods

Comprehensive Psychopathological Rating Scale (CPRS-S-A) was used for the assessment of depressive symptoms. The CPRS is a validated self-rating scale measuring depression [18], and is suggested to capture mild features of depression and to be sensitive to change [19]. A CPRS score of greater than or equal to 6 indicates depressive features, albeit not full clinical depression. Reduction in appetite was excluded as a symptom of depression when calculating depression scores, as this was obviously not a relevant element of depression

in the present study. The CPRS can be further subdivided into three subscales describing depression, anxiety and obsessive symptoms [18], of which the scales for depression and anxiety were further considered as relevant in the prevailing study. Insomnia as a sign of depression was also considered separately, as sleeping difficulties are one of the major side effects of sibutramine.

Procedure

A placebo-controlled cross-over design was utilized, including 14-day periods with daily administration of 15 mg sibutramine and placebo respectively, with a 14-day washout period in-between [17]. The patients were randomized to the order of administration, with half of the patients starting with sibutramine and the other half with placebo. The CPRS was administered at day 14 in each drug condition. After the experimental phase, all patients received sibutramine in a prolonged open-label treatment period. This study concerns only the experimental phase.

Statistics

A nonparametric statistical method – the Wilcoxon signed rank test – was chosen for measuring changes in CPRS scores as there were statistical outliers and a high SD on CPRS. A p-value of less than 0.05 was chosen as the level of statistical significance.

Results

Effects of sibutramine on changes in mood

According to the suggested CPRS cut-off score of greater than or equal to 6, 19 (53%) of the 36 patients had signs of depressive features at baseline. The CPRS scores after 14 days of sibutramine versus placebo were tested for the 'depressed' and the 'non-depressed' patients and the results are displayed in Table 1. A significant negative mood effect measured by the total CPRS score was observed for the depressed patients but not in the non-depressed. Of the depressed patients, 12 (63%) out of the 19 reported a negative mood with sibutramine versus placebo, compared with 6 (35%) out of the 17 non-depressed.

In particular, the CPRS subscale anxiety was higher with sibutramine in the depressed patients, with 68% of this group reporting higher anxiety according to Table 1. For the non-depressed, there was no significant difference in anxiety. The CPRS subscale for depression alone did not reach a level of statistical significance for the depressed patients.

Table 1. Wilcoxon signed rank test for CPRS scores with sibutramine versus placebo for depressed and non-depressed patients.

	Depressed				Non-depressed			
	<i>n</i> = 19	Mean rank	Sum of ranks	<i>p</i> -value	<i>n</i> = 17	Mean rank	Sum of ranks	<i>p</i> -value
CPRS total score				0.041				0.573
Sibutramine > Placebo	12	10.2	122.5		6	6.3	37.5	
Sibutramine < Placebo	6	8.1	48.5		7	7.6	53.5	
Sibutramine = Placebo	1				4			
CPRS depression				0.317				0.959
Sibutramine > Placebo	10	9.8	97.5		5	5.4	27.0	
Sibutramine < Placebo	7	7.9	55.5		5	5.6	28.5	
Sibutramine = Placebo	2				7			
CPRS anxiety				0.004				0.860
Sibutramine > Placebo	13	9.5	124.0		6	7.2	43.0	
Sibutramine < Placebo	3	4.0	12.0		7	6.9	48.0	
Sibutramine = Placebo	3				4			

As the anxiety subscale contains a reference to sleeping difficulties, the tests were repeated for the scale with this factor removed to exclude the influence of insomnia as a likely side effect. This showed that 58% of the depressed group had higher anxiety, which was still significant (Table 2).

Effects of sibutramine on sleeping difficulties

Next, the separate CPRS factors on sleeping difficulties, which are known side effects of the drug, were tested for depressed and non-depressed patients (Table 3). Significantly, more sleeping difficulties with sibutramine were

found for the depressed but not for the non-depressed patients. Of the depressed patients, 12 (63%) out of 19 reported more sleeping difficulties with sibutramine versus placebo, whereas only four (24%) out of the 17 non-depressed did so.

Expert opinion

Many patients in our sample – 53% – had signs of depressive features at baseline, consistent with the common occurrence of depression and impaired mental health found in obese patient samples [16]. In this study we tested short-term differences in mood with sibutramine versus placebo in patients with and without depressive features at baseline.

Table 2. Wilcoxon signed rank test for the CPRS anxiety scale without the sleeping difficulties for depressed and non-depressed patients.

	Depressed			Non-depressed		
	<i>n</i> = 19	Sum of ranks	<i>p</i> -value	<i>n</i> = 17	Sum of ranks	<i>p</i> -value
Sibutramine > Placebo	11	105		6	33	
Sibutramine < Placebo	4	15		5	33	
Sibutramine = Placebo	4		0.010	6		1.00

Table 3. Wilcoxon signed rank test for the CPRS items sleeping difficulties in sibutramine versus placebo for depressed and non-depressed patients.

	Depressed				Non-depressed			
	<i>n</i> = 19	Mean rank	Sum of ranks	<i>p</i> -value	<i>n</i> = 17	Mean rank	Sum of ranks	<i>p</i> -value
CPRS sleeping difficulties				0.009				0.943
Sibutramine > Placebo	12	7.8	93.5		4	4.6	18.5	
Sibutramine < Placebo	2	5.8	11.5		4	4.4	17.5	
Sibutramine = Placebo	5				9			

As a cross-over design was used, the patients were their own controls for the comparisons. The 'depressed' group reported a more negative effect on mood with sibutramine than with placebo, and this was revealed in particular in the CPRS anxiety subscale. For the 'non-depressed' patients, there were no mood effects at all with sibutramine.

The known side effects of sibutramine should first be noted. Patients who had depressive features at baseline were more prone to experience sleeping difficulties with sibutramine than those who lacked signs of depression. Hence, depressive patients may be more susceptible to this very common side effect at onset of sibutramine treatment. Anxiety was furthermore higher for the depressed patients with sibutramine, a result that persisted after removing the scale factor on sleeping difficulties. Frank anxiety as an adverse effect is less common and in our sample was reported by only two of the patients receiving sibutramine [17]. Our result for the more depressive patients can thus reflect the relatively higher discomfort at onset of treatment with sibutramine as compared with the generally positive effects expected with placebo [20].

The literature thus far provides little reason to assume negative effects on mood in prolonged sibutramine treatment. Rather, positive placebo-controlled mood improvement has been noted for obese binge eaters but with a main treatment effect of reduction in binges [7]. The non-placebo-controlled improvements in mood for the depressed patient in the prevailing sample in their subsequent treatment phase were further similar to the non-depressed patients [10]. Weight loss results were also similar for the two groups. Literature on noradrenergic antidepressants having a similar method of action as sibutramine has furthermore shown promising results in treating anxiety [21].

The finding of relatively higher initial anxiety with sibutramine could be interpreted as a secondary psychological reaction rather than as a direct biological effect. Depressive patients seem more sensitive in experiencing a side effect such as sleeping difficulties, which would be accompanied by a lower level of well-being. Depressive patients could also be more sensitive in their psychological reaction to the overall sensations and alterations in the early phase of treatment. Psychological factors are known to interact with pharmacological actions in a complex manner [22], and this could be more pronounced in patients suffering from depression. However, a direct CNS-mediated short-term effect on mood in obese depressed patients cannot be excluded with sibutramine. Similar study designs including anti-obesity drugs with other pharmacological modes of actions could provide more clarity on some aspects of this issue.

A lack of differences in short-term depressive features following treatment with sibutramine vs placebo were reported in an earlier, similar study design, with 14-day assessments in an obese non-patient sample [8]. As obese people in the community are generally not found to have elevated levels of mood disorders [16], this result is compatible with our findings – the non-depressive participants do not seem to experience negative short-term effects.

Some caution regarding our results concerns possible influences on the statistics. The depressed patients, having overall higher levels of depression, may be more prone to alter their CPRS responses, whereas the non-depressed patients may report lower and more stable levels. Conversely, such instability in depressed patients may also reflect the nature of depression with a greater sensitivity to the influences on mood. As the patients were randomized to the order of

Highlights

- Sibutramine is an anti-obesity drug which inhibits the reuptake of serotonin and noradrenalin and was initially tested as an anti-depressant.
- Little is known about the short-term effects of sibutramine on mood in obese patients who have a high incidence of depression.
- We tested the difference in mood with sibutramine versus placebo over 14-day periods in obese patients.
- Obese patients with depressive features at baseline experienced a more negative short-term mood effect with sibutramine versus placebo, whereas no difference was found for the non-depressed.
- The result was at least partly accounted for by a common side effect such as insomnia, which was more pronounced with sibutramine in the depressed patients.
- Although there is no reason to expect adverse long term effects on mood in obese depressed patients on sibutramine treatment, there is need for more research of psychological aspects in this medical treatment.

administration, an artefact such as regression toward the mean was, however, controlled for.

Our results suggest that early side effects with sibutramine may have clinical implications. A risk–benefit assessment of sibutramine is clearly positive [23]. Patients with mood impairments in particular may however not experience the overall immediate benefits of treatment that are expected with a placebo. Sibutramine is used in obese clinical samples who have high frequencies of depression and has recently also been tested in patients with Binge Eating Disorder (BED) [7,24,25], known to have the highest vulnerability

for mood dysfunctions among obese patients [26]. Further investigations of the psychological aspects of sibutramine are needed. Screening for mood dysfunctions may turn out to be warranted before administration of an anti-obesity drug such as sibutramine. Providing information that prepares patients for some transient discomfort in the short-term phase may, for example, be considered. It would also be clinically helpful if future research could determine when there is a turning point with a shift in balance from discomfort to an equalization, or even improvement in mood, with sibutramine versus placebo.

Outlook

There is currently a vast amount of research on compounds targeting food intake and body weight. Within a few years there will be several new anti-obesity drugs available to help us more effectively treat obesity. From a clinical perspective, it will become increasingly important to learn more about the specific profiles of each drug. With more knowledge on psychological aspects, predictors and effects, we will be more able to make optimal individual treatment choices. Depression is common in obese patients and is one of the key factors to take into account. More careful matching of patients to optimal treatments may improve compliance and hence, long-term clinical outcome.

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Affiliations

*Dr Kristina Elfhag, Lic Psychologist, PhD
Karolinska University Hospital,
Obesity Unit, M73, SE-141 86
Stockholm, Sweden
Tel.: + 46 858 582 478
Kristina.Elfhag@medhs.ki.se*

*Dr Stephan Rössner, MD, PhD
Karolinska University Hospital,
Obesity Unit, M73, SE-141 86
Stockholm, Sweden*