

Pharmacological Profile of SSRIs and SNRIs in the Treatment of Eating Disorders

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Abstract: Bulimia Nervosa (BN) and Binge Eating Disorder (BED) are some of the most common eating disorders (ED) in industrialized societies, characterized by uncontrolled binge eating and self-induced purging or other compensatory behaviours aiming to prevent body weight gain. It has been suggested that reduced serotonergic and noradrenergic tone triggers some of the cognitive and mood disturbances associated with ED. In fact in the active phase of ED the concentration of serotonin and noradrenaline in cerebral fluid is reduced. For these reasons, the pharmacologic treatment of ED consists mainly of selective serotonin reuptake inhibitors (SSRIs) or selective noradrenaline reuptake inhibitors (SNRIs). At present, the physiologic basis of this disorder are not yet completely understood. In this review we evaluate several randomized controlled trials to compare the efficacy of several SSRIs and SNRIs in patients with a diagnosis of ED as defined by the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* [DSM IV]). These findings indicate that both SSRIs and SNRIs are well tolerated and reduce effectively the bulimic crisis and purging episodes in patients with ED.

INTRODUCTION

Bulimia Nervosa

The term bulimia nervosa (BN) refers to an eating behavior characterized by episodes of compulsive, greedy, uncontrolled ingestion of large quantities of highly-caloric easily digested foods [1-4]. Compensatory behaviors to control body weight often follow these episodic crises and include self-induced vomiting or the abuse of laxatives or diuretics. Even if the patient with BN is nearly always of normal weight or slightly overweight, weight stability is very fragile and the fear of gaining weight becomes a dominant emotion [1-4].

In 1994, the peculiarities of the bulimic crisis (binge eating) were defined in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* on the basis of the quantity of food ingested and the patient's lack of control of the eating impulse [2]. Moreover, the *DSM-IV* identifies 2 BN subtypes: BN with purging behaviors (self-induced vomiting, misuse of laxatives or diuretics, etc) and without purging behaviors, ie, use of fasting or excessive physical exercise rather than medications or vomiting [2]. The first subtype is obviously the more serious one.

The clinical complications of BN are associated mainly with chaotic eating behavior, especially the compensation behaviour for the overeating, which can cause side effects such as the erosion of dental enamel or inflammation of the esophageal mucosa, as well as electrolyte imbalances that can cause arrhythmias, cardiac and renal failure [5]. Patients with BN nearly always demonstrate mood disorders (depression), alcohol or drug addiction, self-damaging behaviors,

panic, symptoms of obsessive-compulsive disorder, or other abnormal behaviours [1-5].

Recent theories about the underlying pathology in BN have focused on serotonergic activity [6]. Neurochemical, endocrinologic and comorbidity studies have indicated a reduction in serotonergic transmission in the etiology of BN [6].

Bulimic behavior can be considered a mechanism of compensating for the effects of abnormal central serotonergic activity, considering that serotonin is involved in creating the signal for repletion [6].

The bulimic crisis is, in theory, compatible with the hypothesis of a reduction in serotonergic tone because patients with BN have a reduced sensation of fullness and a stronger sensation of hunger [6].

In the active phase of BN, the concentration of serotonin in cerebrospinal fluid, plasma, and urine is normal or reduced, as is the global turnover of serotonin and 5-hydroxyindoleacetic acid (5-HIA). During the quiescent phase, serotonin levels are high [7-11]. The sensitivity of postsynaptic serotonergic receptors has been shown to be reduced [7-11].

In psychoendocrinologic studies of pre- and postsynaptic serotonin receptors, investigators found a reduced response or no response to serotonin, which indicates reduction in the release of serotonin and in the response of postsynaptic serotonergic receptors to serotonin [7-11].

These findings suggest that these specific alterations in serotonergic transmission not only occur because of a nutritional deficits, but also may represent a potential biochemical substratum with possible therapeutic implications [12-14]. The serotonin-based theory would also explain other psy-

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chopathologic characteristics often linked to eating behavior disorders [15-22].

Binge Eating Disorder (BED)

Until the late 1970s, anorexia nervosa was the only eating disorder defined by specific diagnostic criteria [3,23,24]. In the 1980s, the *Diagnostic and Manual of Mental Disorders*, 3rd edition (DSM-III) included the diagnostic criteria for bulimia nervosa [3,23,24]. By 1994, however, a significant number of cases of eating disorder had been described that did not meet the DSM-IV diagnostic criteria of either anorexia nervosa or bulimia nervosa [3,23,24]. Diagnosed as nonspecific eating disorders, these conditions did in fact share specific psychopathologic characteristics not addressed in established criteria [4,5,25]. In all such cases, the patients held distorted beliefs regarding food and diet and body weight and shape and demonstrated ritualized behavior in their eating behavior. Among these patients were those who frequently demonstrated the same bingeing pattern observed in patients with bulimia nervosa but, unlike that group, did not engage in inappropriate compensatory behavior, such as fasting, purging, or excessive exercise, after an episode of excessive eating [4,5,25]. This particular disorder, now referred to as binge-eating disorder, has in recent years aroused increasing interest, particularly as it is closely related to obesity [4,5,25]. In 1959, Albert Stunkard was the first to identify this disorder. In his studies of subgroups of obese patients who presented with binge eating as the characteristic symptom, he recognized binge eating as a compulsive attack during which a patient eats food in great quantity without control [7,8, 26,27]. Today, the term binge-eating disorder is used to indicate both the symptom of binge eating and the symptomatology that distinguishes the disorder from bulimia nervosa [9-11, 28-30]. In the general population, binge-eating disorder is quite rare. Its reported prevalence ranges from 0.7% to 4.6%. The disorder is quite common in patients undergoing treatment for obesity, however [9-11, 28-30]. In fact, approximately two thirds of patients with binge-eating disorder have above-average weight, and among obese patients, the prevalence of binge-eating disorder tends to increase in proportion to the severity of the weight disorder. Recent statistics on binge-eating disorder show a prevalence of 16% among patients who follow nonmedical weight-loss programs, 30% among those who undergo specialized outpatient treatments, and 70% among hospitalized obese patients [9-11, 28-30]. The prevalence among men and women is similar, but among those who follow a specialized diet, the prevalence is greater among women. The disorder is frequently diagnosed in adults between 30 and 40 years of age, and most of these have a history of an eating disorder beginning, on average, between the age of 15 and 20 years. Obese patients with binge-eating disorder also tend to have a life-long history of obesity and early struggles with low-calorie diets [9-11]. In addition, patients suffering from binge-eating disorder are more likely than the general population to have a lifetime history of mental disorders, such as depression and dysthymia (in more than 60% of the cases), anxiety disorders, and alcohol and drug dependence [9-11, 28-30]. They are also susceptible to the same conditions and sequelae linked to obesity, such as diabetes mellitus, arterial hypertension, cardiovascular disease, and neoplasia. Again, the risk

and severity of these conditions correlate with the seriousness of the obesity.

The treatment of binge-eating disorder in most patients is particularly difficult because therapy must address both the eating disorder and obesity simultaneously [6-8]. Currently, no standard protocol has been established for the pharmacologic treatment of binge-eating disorder. The major studies conducted thus far have focused on the use of antidepressants, both tricyclic agents (especially desipramine and imipramine) and selective serotonin reuptake inhibitors [6-11, 31-33] which have demonstrated only short-term efficacy in reducing the frequency of binge episodes and minimal efficacy in reducing weight. Recently, the antiobesity medication, sibutramine, has been used to treat binge-eating disorder [20-23, 33-37]. Sibutramine is a tertiary amine originally developed as a potential antidepressant, but it has also demonstrated the ability to induce weight loss [20-23, 33-37]. It inhibits the reuptake of the neurotransmitters serotonin [5-HT] and noradrenaline by the nerve cells of the brain [20-27, 33-41]. Its activity is evidenced mainly through 2 metabolic processes (the supplementation of the physiologic process of satiation and the stimulation of thermogenesis) that induce weight loss by affecting both the hunger impulse and energy consumption. These processes increase the activity of the sympathetic effectors in the thermogenically active brown adipose tissue [25-27, 39-41].

In the present review we evaluate several randomized controlled trials to compare the efficacy and tolerability of several SSRIs (fluoxetine, fluvoxamine, citalopran and sertraline) and SNRIs (Sibutramine) [28-30, 42-44] in patients with a diagnosis of ED as defined by the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DMS IV).

MATERIALS AND METHODS

Fluvoxamine in BN

This 12-week randomized, placebo-controlled study was conducted in 12 female patients aged 21 to 34 years with a diagnosis of BN with purging behaviors (BN-binge purging), according to DSM-IV. The patients, under previous consent, were randomly assigned to 2 groups of 6 women each. The patients in the first group received fluvoxamine 200 mg daily; patients in the second group received placebo. All of the women were monitored on an outpatient basis twice a week throughout the treatment period for the clinical effect of therapy and for side effects. The patients had to accurately record in a diary their food choices, bulimic episodes, weight, and compensatory behaviors.

Citalopram in BN

The study included 20 female patients, aged between 19 and 28 who suffered from BN with purging behaviours (BN - binge purging) according to the DSM IV and the BITE scale's diagnostic criteria. The patients, with their consent, were randomly divided into two groups of 10 women in each. The patients in the first group were given citalopram of 20 mg/day for the first week and 40 mg/day during the following seven weeks. The patients in the second group were given placebo. The study went on for eight weeks. All pa-

tients were subjected to clinical check-up (twice-a-week for the period of 8 weeks) in order to monitor the clinical development and the possible side effects if any. The patients had maintained an accurate diary of their food choices, bulimic seizures, weight and the possible compensatory behaviours.

Sertraline in BN

The study included 20 female patients, aged between 24 and 36 years, who suffered from purging type BN according to DSM-IV. The patients, all of whom had given their consent to participate in the study, were randomly divided into two groups of 10 women each. The patients in the first group were given sertraline 100 mg/day. The patients in the second group were given placebo. The study duration was 12 weeks. All subjects were followed up as outpatients twice a week for the duration of the treatment period to monitor any clinical developments and side effects. The patients had to accurately record in a diary their food choices, bulimic seizures, weight, and any compensatory behaviors.

Fluoxetine in BN

In this study we have inserted 20 patients, all of female sex, with age included between 18 and 34 years (middle age 26 years), suffering from purging type BN in according with the diagnostic criteria of DSM IV. They randomly divided in 2 groups of 20 patients each.

The patients received fluoxetine at the doses of 60 mg/day for 10 weeks. All patients have been controlled, in outpatient regime, twice a week for all the treatment for to monitor of clinical the trend and the possible collateral effects. All the patients record an accurate alimentary diary where they registered the alimentary choice, the bulimic episodes, the weight and the possible compensatory behaviours.

Sertraline in BED

The study included 20 female patients, aged between 24 and 36, who suffered from BED with purging behaviours (BED-binge purging). The patients with their consent, were randomly divided into two groups of 10 in each. The patients in the first group were given sertraline of 100 mg/day. The patients in the second group had placebo. The treatment was continued for twelve weeks. Patients were monitored twice a week for twelve weeks to observe the clinical development and the possible side effects if any. The patients maintained the diary recording their food choices, bulimic seizures, weight and the possible compensatory behaviours.

Sibutramine in BED

The study included 20 female patients, aged between 24 and 36 years old, who suffered from binge-eating disorder, defined according to the DSM-IV criteria. Ten of these patients were randomly assigned to receive sibutramine 10 mg/kg/day for 12 weeks and the other 10 were given placebo. During the study, the participants were instructed to maintain daily diaries in which they recorded their food choices, bulimic seizures, weight, and any compensatory behaviors and their clinical status was monitored at twice weekly outpatient visits. The primary outcome measure was the binge frequency, defined as the average number of days per week during which at least 1 binge-eating episode occurred. In addition, the patients' Body Esteem Scale (BES)

scores and consistency of weight control throughout the study were assessed.

Fluoxetine in BED

The study included 40 female patients, aged between 20 and 26, who suffered from BED with purging behaviours (BED-binge purging). The patients with their consent, were randomly divided into two groups of 20 in each.

The patients received fluoxetine at the doses of 60 mg/die for 10 weeks. All patients have been controlled, in outpatient regime, twice a week for all the treatment for to monitor of clinical the trend and the possible collateral effects. All the patients have kepted an accurate alimentary diary where they registered the alimentary choice, the bulimic episodes, the weight and the possible compensatory behaviours.

Citalopram in BED

The study included 40 female patients, aged between 20 and 26, who suffered from BED with purging behaviours (BED-binge purging). The patients with their consent, were randomly divided into two groups of 20 in each. The patients, with their consent, were randomly divided into two groups of 10 women in each. The patients in the first group were given citalopram of 20 mg/day for the first week and 40 mg/day during the following seven weeks. The patients in the second group were given placebo. The study went on for eight weeks. All patients were subjected to clinical check-up (twice-a-week for the period of 8 weeks) in order to monitor the clinical development and the possible side effects if any. The patients had maintained an accurate diary of their food choices, bulimic seizures, weight and the possible compensatory behaviours.

Results

The Effects of SSRIs on BN

At the end of the treatment period, the fluvoxamine, fluoxetine, citalopram and sertraline groups showed a significative reduction in the severity of bulimic episodes and in purging episodes (Table 1A). During the treatment period, none of the patients discontinued therapy because of serious side effects (Table 1B).

The Effects of SSRIs and SNRIs in BED

At the end of the of the treatment period, the group given sertraline, fluvoxamine, citalopram or sibutramine showed a decrease in the bulimic seizures and reduction in the purging behaviour (Table 2A). The patients also lost their weight (Table 2A). None of the patient went out of the trial because of any side effects (Table 2B).

DISCUSSION

In the present review we have evaluate several randomized controlled trials to compare the efficacy and tolerability of several SSRIs (fluoxetine, fluvoxamine, citalopran and sertraline) and SNRIs (Sibutramine) [28-30, 42-44] in patients with a diagnosis of ED as defined by the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DMS IV).

A. Treatment	Purging Behavior (% of reduction)	Bulimic Episodes (% of reduction)	Body Weight (% of reduction)	Caloric Intake (% of reduction)
Fluvoxamine	47.0 ± 5.00	52.0 ± 7.00	46.0 ± 5.00	51.0 ± 4.00
Citalopram	45.0 ± 3.00	55.0 ± 4.00	49.0 ± 3.00	54.0 ± 5.00
Sertraline	44.0 ± 2.00	47.0 ± 2.00	52.0 ± 2.00	49.0 ± 3.00
Fluoxetine	50.0 ± 3.00	49.0 ± 4.00	51.0 ± 3.00	47.0 ± 2.00
B. Treatment	Nausea (% of control)	Sedation (% of control)	Headache (% of control)	Mouth Dryness (% of control)
Fluvoxamine	2	1	2	3
Citalopram	3	2	1	2
Sertraline	1	3	2	1
Fluoxetine	1	1	1	2

Table (1A). The effects of SSRIs on BN behaviours. **Table (1B).** The tolerability in patients treated with SSRIs. Results are expressed as mean±SEM. ** $P < .01$ vs placebo. Student's t test for paired data.

The clinical data reported in the present review indicate that both SSRIs and SNRIs induce significant clinical effects on ED. The patients with BN or BED treated with SNRI (sibutramine) or SRRIs (Citalopram, Sertraline and Fluoxetine) demonstrated a statistically significant decrease in the number of binge-eating crises and purging episodes, as well as a slight decrease in weight, which we attribute to a significant reduction in their cravings for carbohydrates and modest average caloric intake. The placebo group did not show these effects. Moreover, none of the patients in these trials showed significant side effects enough to interfere with treatment, thus indicating a high tolerability for both SSRIs and SNRIs. These encouraging results suggest that both SSRIs and SNRIs may serve as a useful alternative to TCAs in the treatment of the symptoms of BN and BED.

The use of SSRIs or SNRIs as a pharmacologic approach in the symptomatologic treatment of BN or BED clearly has clinical value. We may suggest that the use of some SSRIs and SNRIs for the treatment of ED, in according with the most recent international literature, induces both a reduction of the bulimic episodes and a reduction of the compensatory behaviours that, as we have previously reported, induce various organic diseases. We think useful, in the symptomatological treatment of ED, the use of SSRIs or SNRIs that act on the mechanism of the serotonergic and noradrenergic neurotransmission, respectively.

In recent years, knowledge in the field of food physiopathology behaviour have widely increased leading to design of molecules safer and targeted for pharmacological correction of ED and weight: in this respect, studies on leptin as well as on SSRI and SNRI are very encouraging [45-47].

However, the use of other means, such as psychotherapy, to explore the core psychopathology underlying this eating disorder or the use of nutritional counseling to promote the healthy use of food, should be considered.

At today, the biological knowledge are still far from explaining the complexity of the ED phenomena as well as the

integration processes between basic and higher mental functions in the pathology of food intake. This complexity is related to the fact that there is no single cause behind the ED [48-60].

The few studies available show that the nutritional counseling after the intervention hospital for rinutrizione is less than the structured cognitive psychotherapy in preventing relapses and improving aspects psychopathologic and medical syndrome [61,62]. The percentage of patients who stop treatment prematurely remains very high (around 35%) in each therapeutic intervention is confronted with the lack of motivation to treatment [63]. Some authors have proposed the introduction of techniques for increase motivation as a specific phase of treatment [64-66].

For ED are certainly more evidence of the effectiveness and superiority of structured cognitive psychotherapy compared to drug treatment and other forms of psychotherapy [63-66]. Again, however, the percentage of patients that normalizes the pattern food is equal to 50% of those who complete treatment, and only 29% if you consider all recruited patients [63-66]. A limit of efficacy studies of psychological treatments in ED is the lack of standardized approaches that does not allow the generalization of the results in the context of clinical practice [63-66]. The widespread belief in the centres with more experience is that often the application of standardized treatment is very difficult and that the studies are not very representative of clinical reality with which we confront every day traders.

In conclusion, in our ED clinical studies, both SSRIs and SNRIs have been remarkably and significantly successful, however, apart from pharmacotherapy, the utilization of cognitive behavioural treatments either individually or in group, have been of significant help in improving eating behaviour and attitude about body shape and weight. Recent studies has shown the superiority of combined drug and cognitive behavioural therapy over behaviour therapy. Thus, the future management of ED patients lies in combined thera-

A. Treatment	Purging Behavior (% of reduction)	Bulimic Episodes (% of reduction)	Body Weight (% of reduction)	Caloric Intake (% of reduction)
Sertraline	40.0 ±3.00	43.0 ±2.00	40.0 ±4.00	45.0 ±5.00
Sibutramine	42.0 ± 2.00	40.0 ± 5.00	41.0 ± 2.00	43.0 ± 3.00
Citalopram	47.0 ± 5.00	42.0 ± 3.00	43.0 ± 3.00	42.0 ± 4.00
Fluoxetine	41.0 ± 3.00	41.0 ± 2.00	44.0 ± 5.00	41.0 ± 2.00
B. Treatment	Nausea (% of control)	Sedation (% of control)	Headache (% of control)	Mouth Dryness (% of control)
Sertraline	1	2	1	2
Sibutramine	2	1	2	1
Citalopram	1	2	2	1
Fluoxetine	1	1	1	2

Table (2A). The effects of SSRIs and SNRIs on BED behaviours. **Table (2B).** The tolerability in patients treated with SSRIs and SNRIs. Results are expressed as mean±SEM. ** $P < .01$ vs placebo. Student's t test for paired data.

pies, which include pharmacotherapy, cognitive behaviour therapy and dietary advice.

This integrated approach to the treatment of ED is the distinctive advantage of SSRIs as well as SNRIs, which, owing to their unique mechanism of action, addresses the 3 main goals in the treatment of ED: reducing the frequency of binge eating, promoting and maintaining weight loss, and treating the comorbid psychiatric conditions.

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