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Current drug treatment of patients with bulimia nervosa and binge-eating disorder: selective serotonin reuptake inhibitors versus mood stabilizers

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Received 14 February 2004; accepted for publication 17 July 2004

Our aim was to review and compare findings from controlled trials and previous reviews concerning current drug treatment of patients suffering from bulimia nervosa (BN) and binge eating disorder (BED). Thus we selected published articles quoted over the last 10 years in the databases of Medline and Cochrane Library. The combination of pharmacological and psychological treatments is superior to the single psychotherapeutic approach, which in turn is superior to single drug treatment (just superior to placebo). Among drug treatments, SSRIs are the first line choice treatments, especially in primary care. They are more acceptable and tolerated by patients, moreover effective even if investigations on long-term outcomes are lacking. A number of patients, however, do not respond to these drugs. For them it is necessary to find new therapeutic strategies. Mood stabilizers are promising in this regard. In particular, topiramate seems to allow reduction of binge eating and weight in SSRI non-responder patients. (*Int J Psych Clin Pract* 2004; **8:** 235–243)

Keywords
bulimia ***binge-eating disorder***
drug treatment ***antidepressants***
stabilizers

INTRODUCTION

The bulimia nervosa (BN) and binge eating disorder (BED) are independent psychiatric diagnoses according to the DSM-IV nosography, but share important clinical aspects – the binge eating episodes show, in fact, the same characteristics in both pathologies: that is, compulsive ingestion of huge amounts of food in a short time, feelings of loosing control over the eating behaviour, consequent feelings of guilt, shame and poor self-esteem. The BN diagnosis is differentiated by the necessary presence of compensatory behaviours. Moreover, BN and BED seem to converge in responsiveness to drugs, and perhaps in some neurobiological implications. The apparently effective drugs in treating these disorders are basically the same, even if more active for BN than for BED. The binge eating episodes can become very frequent and disturbing for patients, to strongly interfere with completion of daily life activities and to cause important medical problems. A primary goal for the physician in taking care of these patients must be to eliminate or at least to reduce the frequency of binge eating symptomatology. Treatment of BN and BED involves many difficulties, as the aspects of impulsiveness affecting many patients often prevent them from complying steadily with a therapeutic program. Moreover, among the experimental strategies, on both a psychotherapeutic and drug treatment level, only a few have been demonstrated to be really effective. The treatment of BN has been studied more deeply. Fluoxetine was initially the only approved drug by the Food and Drug Administration for the treatment of BN in the USA. As for BED, available data are still scarce, and at present there are no established or completely effective therapies. The selective serotonin-reup take inhibitors are the first option, but other molecules are under research consideration because of encouraging outcomes: one of these is a mood stabilizer named topiramate.

Thus, by means of a critical review of controlled trials quoted in Medline or Cochrane databases, the aim of this study was to compare antidepressants, particularly single-acting (e.g. SSRIs) and dual-acting (e.g. SNRIs) antidepressants, with innovative, though less investigated

DOI: 10.1080/13651500410005621

drugs, like topiramate. Consequent purposes were to elicit comparative effectiveness, tolerability and patient eligibility.

REVIEW OF THE LITERATURE

ANTIDEPRESSANTS

On the basis of the rationale provided by the observation that eating disorders (ED) are often associated with symptoms of mood disorders, and especially of depressive ones, antidepressants are the most investigated drugs.[1] There are four different possibilities with regard to the relationships between bulimia and depression: first, bulimia may be the equivalent of a mood disorder, for example a kind of atypical depression. The second possibility is that bulimia can lead to depression; and the third is that a primary mood disorder can develop into bulimic symptoms as a part of the depressive syndrome. Finally, it is possible that the two disorders simply coexist in the same patient. The observations that there is a high prevalence of mood disorders among first-degree relatives of bulimic patients and, moreover, that neuroendocrinological investigations show similar aspects in the two pathologies, and that bulimic patients are good responders to antidepressant drugs, support the link between bulimia and depression.[2]

As for BED, because of the partial overlapping of its symptoms with BN, most of the relevant psychopharmacological studies focused on drugs effective in bulimics, and therefore on antidepressants.[3,4] In addition, patients with BED have a high lifetime prevalence of major depression diagnosis and often present depressive symptoms coincident with ED.[4,5] Furthermore, concerns about food and body weight are almost always found in patients with BED, and many studies involve other kinds of obsessive–compulsive symptoms in these patients. Such evidence suggests that SSRIs, which are effective in the therapy of obsessive–compulsive disorder, may be useful in BED as well.[4] In their review, Bacaltchuk and Hay[6] investigated whether the use of antidepressants is effective for the treatment of BN compared to placebo. They also examined whether different types of antidepressants could have different effects with regard to tolerability and effectiveness. They considered 18 randomised placebo-controlled trials with tricyclics, SSRIs, MAOI and others antidepressants. So the medication with a single antidepressant, as compared to placebo, was found to be effective for the treatment of BN, with a greater overall remission rate but a higher rate of dropouts. However, a conspicuous number of patients showed a lower than 50% reduction of bulimic symptoms. All classes of antidepressants were effective in reducing ED symptoms in a significant number of patients. A major reduction, compared to placebo, of the frequency of binge episodes and depressive symptoms has been noted.[7] Concerns about body weight and shape also seemed to decrease.

Recommended dosages and plasma drug levels are in general similar to those established for the treatment of depression, with the exception of fluoxetine, involving higher doses (60–80 mg/d.i.e.). But Stahl[8] states that the starting dosages of all SSRIs used for ED are higher than the ones used for other diagnoses; moreover, the drug responses can begin earlier for ED than for other disorders. The degree of mood improvement during antidepressant treatment does not seem to be related to the level of effectiveness in reducing pathological eating behaviours. This observation, together with the fact that antidepressants seem to be effective also in eating disorder patients without comorbid depressive symptoms, indicates a possible different mechanism of action for these drugs in the two pathologies.[2,9,10] It is not yet possible to establish firm conclusions about the mechanism of action of these drugs, whether it is primarily antidepressant, tranquilizing, appetite suppressant, improving impulse control, or if it is a different mechanism, specific for binge eating, perhaps through increased serotonin levels.[1] The results of short-term studies are encouraging, but there is a necessity to verify whether the beneficial effects of these drugs are maintained for a longer time.[6]

Antidepressants may be used for treating BN in adolescents, but they are not licensed for this age group and there is no evidence for this practice. Thus they should not be considered as a first-line treatment in bulimic adolescents. As for BED, adolescent patients should receive the same type of treatment as adults but adapted to the developmental level and with family involvement.[7]

From the literature review, it appears that SSRIs are, of the antidepressants, the drugs of first choice. So we decided to directly compare serotonin-reuptake inhibitors and the recently suggested topiramate. The introduction of SSRIs has represented an improvement in the therapy of these disorders. Notwithstanding their side effects, they are often less dangerous and better tolerated compared to prior antidepressants.[11] Pharmacological and experimental evidence support the thesis of a hypofunction of the brain serotoninergic system as the basis of BN.[8,12,13] As is well known, the SSRIs are highly selective inhibitors of serotonin reuptake, inducing possible side effects significantly different from those of tricyclic antidepressants. The specificity of SSRIs, however, is not absolute, and little differences in overall drug actions may have clinical consequences and differentiate the members of the same pharmacological class.[11] The increased serotoninergic transmission is responsible for the possible early onset of side effects (akathisia, agitation, nausea, anxiety, insomnia, sexual dysfunction, gastrointestinal cramps, diarrhoea, headache) and for later onset of good tolerance.[13] According to NICE practice guidelines for ED, there is limited but positive evidence from five trials favouring SSRIs over placebo with regard to treatment acceptability. On the contrary, acceptability of tricyclic antidepressants is inferior to that of placebo. Moreover, with regard to tolerability, there is insufficient evidence as to whether or not a specific class of antidepressants is superior to another.[7] The clinical use of some SSRIs is associated with appetite and weight decrease. Many SSRIs were studied for their effect of decreasing body weight in

depressed and non-depressed obese subjects. The decrease in body weight is, usually, a dose-dependent effect, and relatively high dosages, proportional to the potency of the drug in serotonin reuptake inhibition, are required to obtain a significant effect.[2,14] Some of them, with the exception of fluoxetine, may also present a weight-gain side effect by an independent mechanism of that inducing decreased appetite and food ingestion. The observed effects in each patient will depend on either balancing these two actions or the prevalence of one of them.

The administration of SSRIs can also be useful for controlling such comorbid disorders as depression, obsessive–compulsive disorder, panic disorder, general anxiety disorder, post traumatic stress disorder, phobias and, moreover, such personality characteristics as aggressiveness, impulsiveness and tendency to substance abuse. They are frequently present in eating disordered patients, being related to serotoninergic impairment.[15,16]

Despite the evidence of a short-term good effectiveness of antidepressants, and in particular of SSRIs, long-term outcomes are not encouraging. Table 1 shows a survey of the main and most recent controlled studies on SSRI utilization for treating patients with BN and BED. With regard to the main efficacy indicator, which is reduced number of binge-eating episodes, positive results have been obtained in the following studies: Fluoxetine Bulimia Nervosa Collaborative Study Group (1992),[17] Goldstein et al (1995),[18] Walsh et al (1997),[19] Walsh et al (2000),[20] Romano et al (2002),[21] Fichter et al (1996),[22] Hudson et al (1998),[23] McElroy et al (2000),[24] Arnold et al (2002)[25] and McElroy et al (2003).[26] On the contrary, negative or not significant results were found in the studies by Fichter et al (1991),[27] Beumont et al (1997).[28]

There is another class of antidepressants, the serotonin and noradrenalin reuptake inhibitors (SNRIs), e.g. venlafaxine, nefazodone, milnacipran and mirtazapine, selective towards both serotonin and the noradrenergic system.[8] These drugs are partially similar to tricyclic antidepressants, but lacking in the anticholinergic and particularly cardiovascular side effects. Some results from open-label trials seem quite encouraging[29–32] (Tables 1 and 2).

Mood Stabilizers

Many studies indicate that ED becomes chronic in a considerable percentage of patients.[36] Moreover, many patients do not respond to evidence-based treatments. Thus, there is the opportunity to try different therapeutic strategies. The discovery of the possible effectiveness of new drugs in the therapy of BN and BED is intriguing. A fascinating class is that of mood stabilizers, in particular, topiramate. However, many doubts about their use, mechanism of action and efficacy seem to call for further investigations and controlled trials. According to Bacaltchuk and Hay[6] the "relative low efficacy of antidepressants" has induced investigators to assess some new drugs, including topiramate. It is a recent antiepileptic drug, with an unknown mechanism of action responsible for its anticonvulsant activity. Electrophysiological and biochemical studies on neuron cultures identified three properties which may contribute to the antiepileptic effects: a state-dependent sodium channel-blocking activity, a strengthening of GABA inhibitory transmitter activity, inhibition of some carbonic anhydrase isoenzymes and blocking of glutamate receptors. In addition to its anticonvulsant properties, topiramate suppresses appetite, is associated with weight decrease[37] and seems to have mood stabilizing properties.[38–40] The most common side effects are sleepiness, dizziness, ataxia, language disorders, psychomotor slowing down and paresthesias. Some authors have described very rare but serious side effects, such as nephrolithiasis or acute angle glaucoma.[41] Its mechanism of action in ED is not yet clear. It could act by suppressing appetite or increasing sense of repletion and, consequently, reducing binges. These effects do not seem to be mediated by an influence on serotoninergic transmission. On a basis of a glutamate receptor antagonism, since glutamate and its agonists stimulate increased food ingestion, topiramate could reduce the need to binge. Taste alterations, gastrointestinal disturbance and nausea are fairly common side effects of the drug. It is possible that these effects contribute to decreased food ingestion in some patients. Preliminary data suggest that reduced weight associated with topiramate is due to loss of fat rather than to lean mass loss. In animal models, topiramate inhibits fat deposition, both reducing caloric intake and promoting energy expenditure. The exact mechanisms involved in increasing energy expenditure and metabolism, however, remain unknown.[41] The activity of mood stabilization may be important for therapeutic effects, since such personality features as impulsiveness might play a role in eliciting binge eating episodes.[40] Further controlled trials will be necessary to confirm the first findings on topiramate effectiveness in treating patients with BN and BED. In Table 2 the main studies on the topiramate use for ED are listed. Since many data about controlled trials are not yet available, open-label trials have been mentioned as well (Table 3).

DISCUSSION AND CONCLUSIONS

The therapeutic approach to ED is very complex and presents a number of problems. Such a disorder is often hidden or denied for a long while by patients, and is revealed only when symptoms are exacerbated and therefore importantly interfere with daily life. The pathology, by then, evident for itself or for its complications, arrives for the psychiatrist's observation. Subsequently, on the basis of unrealistic expectations, patients demand an immediate solution of their problems, which can also be approached by pharmacotherapy.

According to Bacaltchuk et al,[48] combined pharmacological and psychological treatments are superior to the single psychotherapeutic approach alone, which in turn is superior

Table 1
Controlled trials with SSRI for the treatment of BN

Authors	*Diagnosis*	*No. of patients*	*Weeks*	*Drug*	*Dose (mg/d.i.e.)*	*Change in binge-eating episode frequency*	*EDE total score*		*% Remission*	*BMI*	
							Pre	*Post*		*Pre*	*Post*
Fichter et al[27]	BN	40	5	Fluoxetine *placebo*	60						
FBNCSG[17]	BN	387	8	Fluoxetine *placebo*	20	−45%				22	
					60	−67%					
						−33%					
Goldstein et al[18]	BN	398	16	Fluoxetine *placebo*	60	−50%			18.3	21	20.93
						−18%			*12*		*21.15*
Beumont et al[28]	BN	67	8	Fluoxetine + nutritional counselling *placebo*	60						
Walsh et al[19]	BN	120	16	Fluoxetine + desipramine + CBT + SP *placebo*	60	(+CBT)	3.23	1.52	48	21.6	21.5
					300 (max)	−87%					
						(+SP)	3.31	2.01	9	21.7	21.2
						−51%					
						−69%	3.34	2.01	21	22.3	21.7
						(+CBT)	*3.15*	*1.65*	*20*	*22.1*	*22.6*
						−65%					
						(+SP)	*3.02*	*1.96*	*14*	*21.7*	*22.1*
						−46%					
Walsh et al[20]	BN	22	8	Fluoxetine *placebo*	60	−82%	2.5	1.7	38	22.0	21.8
						+20%	*2.6*	*2.6*	*0*	*23.0*	*22.8*
Romano et al[21]	BN	150	8 single blind 52 double blind	Fluoxetine *placebo*	60	−76%			17.7	22.5	
						−67%				*23.0*	
Fichter et al[22]	BN	72	12	Fluvoxamine *placebo*		−?					
Fichter et al[35]	BN	72	15	Fluvoxamine *placebo*							
Clarck and Rosenblatt 1989	BN	80	8	Sertraline *placebo*							

EDE, Eating Disorder Examination; BMI, body mass index; FBNCSG, Fluoxetine Bulimia Nervosa Collaborative Study Group; CBT, cognitive-behavioural therapy; SP, supportive psychotherapy.

Table 2
Controlled trials with SSRI for the treatment of BED

Authors	*Diagnosis*	*No. of patients*	*Weeks*	*Drug*	*Dose (mg/d.i.e.)*	*Change in binge-eating episode frequency*	*EDE (total score)*		*% Remission*	*BMI*	
							Pre	*Post*		*Pre*	*Post*
Marcus et al[33]	BED + obesity	11	52	Fluoxetine + IBT *placebo*	60						
Arnold et al[25]	BED	60	6	Fluoxetine *placebo*	20–80	− 70% *− 56%*			45 *24*	39.6 *36.7*	40 *39.5*
DeZwann et al[34]	BED + obesity	15	18	Fluvoxamine + CBT *placebo*	100						
Hudson et al[23]	BED	85	9	Fluvoxamine *placebo*	260 (50–300)	− 80% *− 61%*			38 *26*	35.5	
McElroy et al[24]	BED	34	6	Sertraline *placebo*	50–200	− 85% *− 47%*			47 *14*	36.4 *35.8*	
McElroy et al[26]	BED	38	6	Citalopram *placebo*	20–60	− 82% *− 51%*			47 *21*	37.8	

EDE, Eating Disorder Examination; BMI, body mass index; IBT, individual behavioural therapy.

Table 3
Controlled trials with topiramate for the treatment of BN and BED

Authors	*Trial*	*Diagnosis*	*No. of patients*	*Weeks*	*Drug*	*Dose (mg/d.i.e.)*	*Change in binge-eating episode frequency Post*	*EDE (total score)*		*% Remission*	*Weight (kg)*	
								Pre	*Post*		*Pre*	*Post*
Shapira et al[42]	Open-label	BED	13		Topiramate	100–1400	–?				99.3	–11.8
Knable[43]	Open-label	BN	1		Topiramate	150	–?					
Felstrom & Blackshaw[44]	Open-label	BN	1	12	Topiramate	75	–100%			100		
Appolinario[40]	Open-label	BED	8	16	Topiramate	150 (max)	–?			66		–4.1
Barbee[45]	Open-label	BN	5		Topiramate	90–400	–?					
McElroy et al[41]	Placebo-controlled	BED	61	14	Topiramate	75–600	–92%			64	120.4	–5.9
					placebo		*–66%*			30		
											123.4	–1.2
Hedges, Hoopes et al[46,47]	Placebo-controlled	BN	69	10	Topiramate	100	–49%				61.5	
					placebo	(25–400)	*–25%*				67.4	

EDE, Eating Disorder Examination.

to the single pharmacological treatment (being superior to placebo). Moreover, some authors think that pharmacological treatment can be a first line therapy, especially in primary care.[7] It seems to be feasible to let patients take advantage of reduced binge episodes. Patient eligibility for drug treatment has not been completely studied and clarified. Summarizing some key-points, we would list: (1) to be non-responders to psychotherapy; (2) presence of remarkable symptoms; (3) refusal of psychotherapy; (4) presence of conspicuous emotional instability which prevents the initiation of psychotherapy; (5) presence of comorbid depressive symptomatology requiring concomitant antidepressant drugs; (6) as a first line therapy in primary care.[1,7]

According to NICE practice guidelines, the SSRIs, and specifically fluoxetine, are the first choice drugs for the treatment of BN in terms of acceptability, tolerability and reduction of symptoms.[7] These drugs allow a reduction in symptomatology without significant side effects when instructions for use are followed.[7]

Drugs can play a very important role in the short-term improvement of the negative psychosocial consequences of BN and BED. In fact, bingeing often becomes frequent and induces a marked social impairment, so that it becomes highly disabling. In such occurrence it can be difficult to start psychotherapy because of impaired patient compliance. Thus, drug treatment may induce a short-term relief, increased compliance, and facilitated adherence to a concomitant or subsequent psychotherapeutic program. A number of drug treatments have been demonstrated to be beneficial in acute conditions, but very little is known about long-term outcomes. To a large extent, eating disorders actually tend to become chronic, and quite frequently relapse even after successful treatments. Further controlled trials with longer observation periods and higher numbers of patients are needed to verify outcome stability over time. The pharmacological treatment should be extended for at least 1 year, and future trials should include patients with comorbid major depression, personality disorders, substance abuse and other relevant clinical conditions.[6]

Nevertheless, no effective drug achieves positive outcomes in all patients. It therefore becomes necessary to indicate innovative strategies for non-responder patients.[49] In this regard topiramate is promising, but it involves problems of titration in addition to some unfavourable side effects. A very slow and gradual titration (approximately 25 mg/d.i.e.) is necessary.

With regard to the comparison of the use of SSRIs or topiramate, it can be seen from the literature that so far very little is known about assignment methods. At present, predictors for the relevant prescription have not been found. For example, depression or seriousness of obesity, binge episode frequency, age of onset, illness duration and the relationships involved among these variables could allow the identification of patient subgroups, responding differently to each typology of treatment. Thus it will be useful to address research on non-responder patients.[50,51]

Concluding remarks may be, however, available: according to the opinion of most experts, the first choice drug should be an SSRI. If it fails, it is possible to consider the use of an SNRI.[4] Antidepressants should be used in the presence of a concomitant or previous mood disorder (in particular unipolar depression), and possibly in the presence of a positive depressive family history. In partial agreement with other authors, we could say that mood stabilizers like topiramate should be indicated for non-responder patients, those intolerant to antidepressants or suffering from a comorbid bipolar disorder, an impulse control disorder, a severe borderline personality disorder or from marked emotional instability.[5,40] A new pharmacological approach, the 5-HT3 inhibitor ondansetron, has been recently considered for BN, and preliminary data seem interesting, even if controlled trials are still too scarce.[52,57]

CONFLICT OF INTEREST

No funding sources supporting the work, no commercial or other associations are present.

KEY POINTS

- Combined pharmacological and psychological treatments are superior to single psychotherapeutic approach alone, which in turn is superior to single pharmacological treatment
- Pharmacological treatment can be a first-line therapy, especially in primary care
- The SSRIs, and specifically fluoxetine, are the first choice drugs for the treatment of BN in terms of acceptability, tolerability and reduction of symptoms
- A mood stabilizer like topiramate seems to allow reduction of binge eating and weight in SSRI non-responder patients

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