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Antidepressants in short-term treatment of binge eating disorder: Systematic review and meta-analysis

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Abstract

Objective: To evaluate the effects of antidepressant interventions for patients with Binge Eating Disorder (BED).
Method: A systematic review and meta-analysis of available randomized controlled trials including a quality appraisal was conducted. Six databases: PUBMED, EMBASE, PSYINFO, LILACS, The Cochrane Collaboration Controlled Trials Register and The Cochrane Depression, Anxiety and Neurosis Group Database of Trials were searched using an electronic search strategy. Articles published during the period from January 1994 to December 2005 were included.
Results: From the 3357 articles initially identified, 19 full manuscripts were selected and analyzed and 7 studies fulfilled the inclusion criteria and were included in the final analysis. Data from the meta-analysis revealed that binge-eating remission rates were higher in patients receiving antidepressants when compared with placebo. No difference in body weight has been found as measured by short-term change in body mass index. Most studies were short-term trials (median duration: 8 weeks). The only 16-week duration study did not show superiority of antidepressants over placebo.
Conclusion: Available data are not sufficient to formally recommend antidepressants as a single first line therapy for both short-term remission of binge-eating episodes and weight reduction in patients with BED. BED is a chronic condition and very short-term studies (8 weeks) may be of limited value.

Keywords: Eating disorders; Binge eating; Antidepressants; Meta-analysis

Contents

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1. Introduction

BED is a proposed diagnostic category included in DSM-IV (APA, 1994) as an Eating Disorder Not Otherwise Specified (EDNOS) and characterized by recurrent episodes of binge eating followed by a sense of loss of control over eating in the absence of inadequate compensatory behaviors, such as diuretic and laxative ingestion, commonly experienced by Bulimia Nervosa patients in order to avoid a possible weight gain.

BED strikes individuals of both genders, being more common among women than men (3 females to 2 males), from all ethnicities, usually beginning by the end of adolescence (Grilo, 2002). Subjects with this condition usually display a body mass index (BMI = weight in kg / height squared) higher than those not presenting BED, as well as more frequent weight oscillations. Some authors found that they frequently base their self-evaluation on their weight and shape and have higher scores for depressive symptomatology, with an average of 50% of them have clinical depression (Borges & Jorge, 2000). This disturbed eating pattern usually begins by the age of twenty (Spitzer et al., 1993), and 2/3 of obese with BED report that it begins before the development of obesity (Wilson, Nonas & Rosenblum, 1993). A group of evidences suggests that the severity of binge eating would be related to a higher severity of obesity, which makes those individuals more prone to medical complications (Spitzer et al., 1993).

Beyond the health implications of obesity and the association with psychiatric disorders, patients with BED also suffer from discrimination in job and housing opportunities, receive lower earnings, have difficulty to be accepted to university, and boast a lesser number of friends and romantic relationships (Husted & Shapira, 2005).

As for the treatment, BED patients show higher levels of attrition, and gain weight faster than obese not presenting BED (Marcus, Wing & Hopkins, 1988; Telch et al., 1990).

Although in Bulimia Nervosa we have several evidences that a combination of Cognitive-Behavior Therapy (CBT) and antidepressants show good results (Bacaltchuk, Hay & Trefiglio, 2005), the evidence of efficacy of the different therapeutic approaches for treating BED still needs to be confirmed. For BED the most extensively studied interventions are antidepressants, CBT and Inter-personal therapy.

The rationale of the use of antidepressants for BED patients was, among others, the positive results observed with these agents in BN a condition close related to BED and the high co-morbidity with depressive psychopathology (Salzano & Cordás, 2004).

McElroy, Casuto and Nelson (2000) compared Sertraline and placebo with 34 BED patients during 6 weeks, and observed a binge remission pattern of 38.8% for the experimental group, and 12.5% for the placebo group. In 2003, McElroy et al. tested the antidepressant Citalopram versus a placebo during 6 weeks with a sample of 38 BED patients, and obtained the remission in binge-eating episodes of 47.3% in the Citalopram group, against 21% in the placebo group (McElroy et al., 2003). However, Grilo, Masheb and Wilson (2005) obtained a negative result in terms of binge frequency when comparing Fluoxetine to placebo during 16 weeks in a study involving 54 BED patients, in which the remission was of 22.2% for the experimental group and of 25.9% for the placebo group.

This paper aims to evaluate, through a systematic review of the literature and meta-analysis, the efficacy of the use of antidepressants compared with a placebo for treating BED, in randomized clinical trials during at least 4 weeks.

2. Method

2.1. Study selection

In this review were included only randomized clinical trials comparing antidepressants and placebo for the treatment of BED patients, according to the diagnostic criteria proposed by DSM-IV (APA, 1994).

2.2. Data sources

We searched the electronic databases MEDLINE, EMBASE, PsycINFO, LILACS, The Cochrane Collaboration Controlled Trials Register, and The Cochrane Depression, Anxiety and Neurosis Group Database of Trials. In addition, we did a manual search in the International Journal of Eating Disorders from January/94 to December/2005 to identify randomized clinic trials using antidepressants versus placebo with patients diagnosed with BED.

The search thread was based on the search strategy for randomized clinic trials developed by the Cochrane Depression, Anxiety and Neurosis Group, and on the following MeSH Terms (Medical Subject Heading): "Eating Disorders", "Bulimia Nervosa" and "Antidepressant Agents".

The bibliographic references of the selected papers were revised for papers not localized by the electronic search for possible inclusion in this study.

The abstracts of the papers identified by the electronic search were examined by a reviewer. The complete texts of randomized clinical trials for possible inclusion in this review were evaluated by two independent reviewers (SCS, JB), who were not blind for the names of authors, institutions and publishing medias.

2.3. Measurements of outcome

The main outcome measures considered in this systematic review were: total remission of BED symptoms (defined as a 100% reduction of the binge-eating episodes by the end of the study), change of the BED symptoms, change of the body weight and abandoning levels. Besides these outcome measurements, whenever possible we also evaluated the depression scales' scores, when they were used.

2.4. Quality assessment

The trials included in this review were rated as quality A or B according to the randomization procedure of allocation concealment, following the Cochrane Collaboration Manual for methodological quality evaluation (Mulrow & Oxman, 1997).

They are as follows:

A. "Low risk of bias". Adequate allocation concealment (e.g., central randomization by phone computer).
B. "Moderated bias risk". Unclear or doubtful allocation concealment.
C. "High bias risk". Inadequate allocation concealment (for instance, the use of alternate numbers, date of birth, etc.).

2.5. Data extraction and analysis

Data were entered into a spreadsheet program, and into the Cochrane Collaboration Review Manager (REVMAN) analysis software (Higgins & Green, 2005).

Dichotomous outcomes (remission and dropouts) were analyzed by calculating relative risks (RR) and 95% confidence intervals (CI) for each trial. The RRs from the individual trials were combined using appropriate methods of meta-analysis. The estimates of RR were based on more conservative DerSimonian–Laird (Dersimonian & Laird, 1996) estimate of pooled RR, the random effects model. This model takes into account both within-study sampling

error and any between-studies variations in the assessment of the CI of the results (even if there was no statistically significant heterogeneity) and gives the same result as the fixed effects model when there is no between study variance. If the RR equaled 1, this indicated no difference between the compared groups.

For continuous outcomes the mean and standard deviations of these measures were assessed. They were analyzed according to their difference in mean treatment effects and its standard differences. Then the standardized mean differences (SMDs) were calculated.

Data were extracted by two reviewers (SCS and JB) who reached 100% agreement in all instances by consensus. In some instances, and to help to achieve consensus, the study authors were contacted to provide the necessary information to clarify the situation (Laederach-Hofmann et al., 1999; Arnold et al., 2002; Pearlstein et al., 2003).

2.6. Heterogeneity analysis

Chi-square tests for homogeneity were done at 5% level of significance and the *I*-square. The latter provides an estimate of the percentage of variability due to heterogeneity, rather than chance alone. In addition negative values are equated to zero, so that I^2 lie between 0% and 100%. A value of 0% indicates no observed heterogeneity, larger values show increasing heterogeneity, and a value greater than 50% considered substantial heterogeneity (Higgins et al., 2003).

3. Results

3.1. Search

The search strategy identified 3357 articles. They were first reviewed through their titles to exclude those that did not fulfill in the aims of this review, such as articles on other eating disorders like anorexia and bulimia nervosa. 1808 abstracts were left. They were evaluated and we excluded those not related to BED, non-interventional studies, epidemiological studies, case reports or case series, etc. Finally, 19 papers were analyzed in more detail, and 7 studies fulfilled the criteria for inclusion in this systematic review.

A double-blind randomized clinical trial comparing Fluoxetine to placebo by Greeno and Wing (1996) was excluded from this review because it had a treatment period phase lasting only 6 days.

The Milano, Petrella and Capasso (2005) study was also excluded from this review, although it is a clinical randomized trial comparing Sertraline to placebo, because it mixed patients with BED and Bulimia Nervosa in the sample, and did not presented the results separately.

3.2. Study characteristics

Out of the 7 included studies, only one of them (Laederach-Hofmann et al., 1999) used a tricyclic antidepressant (ADT); the remaining 6 studies evaluated selective inhibitors of serotonin recapture (SSRI).

Table 1
Characteristics of the selected trials

Study	Intervention (no. of patients)	Daily dose (mean)	Control (no. of patients)	Duration of intervention (weeks)	Randomization
Arnold et al., 2002	Fluoxetine (30)	71.3 mg	Placebo (30)	6	B
Grilo et al., 2005	Fluoxetine (27)	60 mg	Placebo (27)	16	A
Hudson et al., 1998	Fluvoxamine (42)	260 mg	Placebo (43)	9	B
Laederach-Hoffman et al., 1999 [a]	Imipramine (15)	75 mg	Placebo (16)	8	B
McElroy et al., 2000	Sertraline (18)	50–200 mg (flexible dose)	Placebo (16)	6	B
McElroy et al., 2003	Citalopram (19)	57.9 mg	Placebo (19)	6	B
Pearlstein et al., 2003	Fluvoxamine (9)	239 mg	Placebo (11)	12	B

[a] Data from the first phase A — "Low risk of bias": Adequate allocation concealment. B — "Moderated bias risk": Unclear or doubtful allocation concealment.

Table 2
Remission rates [a]

Number of people who show remission (100% binge free)					
Study	Antidepressants		Placebo		RR (random) 95% CI
	n/*N*	Percentage [b]	*n*/*N*	Percentage [b]	
Arnold et al., 2002	13/30	43.3%	5/30	16.6%	0.68 [0.48, 0.97]
Grilo et al., 2005 [c]	6/27	22.2%	7/27	25.9%	1.05 [0.78, 1.42]
Laederach-Hoffman et al., 1999	8/15	53.3%	2/16	12.5%	0.53 [0.30, 0.94]
Hudson et al., 1998	15/40	37.5%	11/43	25.5%	0.84 [0.62, 1.13]
McElroy et al., 2000	7/18	38.8%	2/16	12.5%	0.70 [0.46, 1.05]
McElroy et al., 2003	9/19	47.3%	4/19	21%	0.67 [0.41, 1.08]
Pearlstein et al., 2003	6/9	66.6%	5/11	45.4%	0.61 [0.21, 1.78]
Total (95% CI)	64/158	40.5%	36/162	22.22%	0.77 [0.65, 0.92]
Test for heterogeneity: $Chi^2=7.32$, $df=6$ ($P=0.29$), $I^2=18.0\%$					
Test for overall effect: $Z=2.95$ ($P=0.003$)					

n=number of events, *N*=number of people randomized.
[a] Statistically significant $P<0.05$.
[b] Percentage of patients in remission.
[c] Duration of study: 16 weeks.

All studies included in their samples patients with BED diagnosed according to the DSM-IV (APA, 1994) criteria.

Regarding to the adequacy of the randomizing procedures, the quality of the studies was good, including 6 studies classified with a B criterion and one with an A criterion according to the concealment allocation (Mulrow & Oxman, 1997). The characteristics of the studies included in this review are shown in Table 1.

3.3. Meta-analysis

The available data allowed 5 different analyses:

3.3.1. Remission of binge-eating episodes

In terms of remission, using a more conservative statistical procedure (models of random effects), we found a statistically significant difference favoring the groups receiving antidepressants, when compared to the placebo group: 40.50% vs. 22.22% (RR = 0.77 [95% CI = 0.65, 0.92]).

It must be noted that when analyzing individually the studies' results we found a wide variation of the remission pattern, and the only study with 16-week duration (Grilo et al., 2005) showed that the placebo was superior to the antidepressant (Table 2).

Table 3
Mean binge-eating episodes at the end of the treatment

Difference in mean binge-eating frequency at the end of treatment					
Study	Antidepressants		Placebo		SMD (random) 95% CI
	N	Mean (SD)	*N*	Mean (SD)	
Arnold et al., 2002	23	1.80 (2.90)	13	2.70 (3.80)	−0.27 [−0.95, 0.41]
Grilo et al., 2005	27	10.30 (11.10)	27	7.20 (9.20)	0.30 [−0.24, 0.84]
Laederach-Hoffman et al., 1999	15	2.80 (3.00)	16	5.40 (5.10)	−0.60 [−1.32, 0.12]
McElroy et al., 2000	13	1.13 (1.56)	13	3.85 (3.81)	−0.90 [−1.72, −0.09]
McElroy et al., 2003	16	1.70 (3.10)	15	3.40 (3.00)	−0.54 [−1.26, 0.18]
Pearlstein et al., 2003	9	3.11 (4.20)	11	7.31 (9.31)	−0.54 [−1.44, 0.36]
Total (95% CI)	103		95		−0.36 [−0.74, 0.01]
Test for heterogeneity: $Chi^2=8.29$, $df=5$ ($P=0.14$), $I^2=39.7\%$					
Test for overall effect: $Z=1.90$ ($P=0.06$)					

Table 4
Mean difference scores on depression rating scale at the end of treatment

Mean difference scores on depression rating scale at the end of treatment					
Study	Antidepressants		Placebo		SMD (random) 95% CI
	N	Mean (SD)	*N*	Mean (SD)	
Arnold et al., 2002	23	2.60 (3.00)	13	5.50 (4.10)	−0.83 [−1.54, −0.12]
Laederach-Hoffman et al., 1999	15	9.80 (7.00)	16	16.00 (10.30)	−0.68 [−1.41, 0.05]
McElroy et al., 2000	13	6.40 (3.90)	13	7.50 (8.40)	−0.16 [−0.93, 0.61]
McElroy et al., 2003	16	1.40 (2.30)	15	1.90 (3.10)	−0.18 [−0.89, 0.53]
Pearlstein et al., 2003	8	9.38 (9.71)	8	7.38 (6.16)	0.23 [−0.75, 1.22]
Total (95% CI)	75		65		−0.38 [−0.74, −0.03]
Test for heterogeneity: Chi^2=4.29, *df*=4 (*P*=0.37), I^2=6.7%					
Test for overall effect: *Z*=2.13 (*P*=0.03)					

All studies used the Hamilton Depression Scale (HAM-D).

3.3.2. Change on the mean frequency of binge-eating episodes

Analyzing the difference in the mean frequency of binge-eating episodes at the end of treatment, we did not find a statistically significant difference between groups (SMD = − 0.36 [95% CI = − 0.74, 0.01]) (Table 3).

3.3.3. Adherence to the treatment

In terms of discontinuation of the treatment for any reason, we did not find a statistically significant difference between groups. On the antidepressant group, 27.5% of the subjects withdrew the study compared to 21.6% of the placebo group (RR=1.35 [95% CI=0.61, 3.00]).

3.3.4. Weight change

There was no statistically significant difference between groups in terms of BMI difference of the patients by the end of the study period (SMD=0.03 [95% CI=−0.49, 0.55]).

3.3.5. Change of depressive symptoms evaluated by scale

Comparing the studies using the Hamilton Scale for Depression (HAM-D) to evaluate the improvement of depressive symptoms of patients, we have found a statistically significant difference between groups (SMD=−0.38 [95% CI=−0.74, −0.03]) (Table 4).

4. Discussion

The remission rates were higher on the antidepressant group when compared to the placebo group. However, most of the studies were of short duration (an average of 8 weeks). The only study with 16-week duration (Grilo et al., 2005) did not show a superiority of the antidepressant over the placebo. Thus, the short-term follow up, used in the majority of the studies, could not capture the real effect of medication. The study of Grilo et al. (2005) which doubled the medium duration of observation, might have power to demonstrate this difference.

In view of these findings it must be considered, as proposed by Carter, Hudson and Lalonde (2003), that BED patients can show a short-term improvement of their condition when many types of intervention are used, as a result of suggestion or by other non-specific factors. A number of drug treatments to Bulimia Nervosa and BED 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 present frequently relapse even after successful treatments (Bellini & Merli, 2004).

Despite we have not found a statistically significant difference between the groups, the adherence to the treatment was worse with the individuals exposed to the active drug, when compared to the placebo group, most likely due to the emergence of collateral effects caused by the antidepressants.

The antidepressant mean daily dosages used in the included studies are in line with the usual dosage suggested in the literature (Husted & Shapira, 2005).

The meta-analysis of the outcome "mean difference of the HAM-D depression scale scores" showed a statistically significant difference pro the interventional group. However, from the five studies included in this meta-analysis, only three included in their samples patients who, on the beginning of the studies, had a diagnostic of existing depression (McElroy et al., 2000, 2003; Arnold et al., 2002). This result must be interpreted with caution because of the small number of studies included, sample size and non-standardization of the inclusion criteria related to depression of these studies. Therefore, we cannot conclude that the improvement of the depressive symptoms is due to the BED improvement or to the antidepressant action of the drugs.

Still regarding the antidepressants used as intervention on the studies included in this meta-analysis, they are all serotoninergic; one study used a tricyclic antidepressant (Laederach-Hofmann et al., 1999), and the other six studies used selective inhibitors of serotonin recapture (SSRI). It would be important to investigate, in future studies, the action of other antidepressants with other action mechanisms on the BED symptoms.

We did not find a statistically significant difference in terms of weight change evaluated by BMI. Maybe such difference was not evident due to the short duration of the studies. Other parameters relevant to the patients' evaluation, as the waist/hip measurement, insulin, and lipidic profile could, along with the weight and the BMI, offer more information on the metabolic action of these agents.

The methodological quality of the studies was overall good. Most of them were evaluated as B according to the Cochrane Collaboration evaluation criteria; i.e. "Moderated bias risk" (Unclear or doubtful allocation concealment).

Although BED is a common clinical condition, the samples included in the studies were small, with studies including from 20 to 85 subjects. This might have influenced the results found since larger samples tend to obtain more precise effect estimations, and greater chance to detect an effect when it already exists.

The distribution by gender of the selected samples differs from the one found at the general population (3 females to 2 males). For instance, 88% of the subjects included in the studies were female, which reduces the generalization of the findings to the general population. Most of the studies was underwent at only one center, with exception of the Hudson, McElroy and Raymond (1998) study, which was underwent at 3 centers simultaneously. Future studies including several centers and a larger collective of patients might overcome the sample bias.

The results presented in our meta-analysis agree with a classic literature review by Husted and Shapira (2005), who state that the efficacy of BED treatment with long-term ISRS is still unknown.

5. Conclusions

This study revealed that controlled clinical trials for BED treatment with antidepressant pharmacotherapy showed positive results when measured according to the short-term remission index. The outcome criteria difference of the mean frequency of binge episodes, weight, and adherence to the treatment did not show differences between the groups. The improvement of the depressive symptoms obtained in the studies must be examined with care, because those studies were underpowered to assess this kind of symptomatology.

New studies are necessary to evaluate the effect of antidepressants on the binge-eating episodes. Such studies should consider: study designs with longer intervention periods (at least 16 weeks) and follow-up measures after the end of the study. In addition, these studies should include larger samples, more detailed and uniform binge definition criteria, a larger standardization of instruments and evaluation criteria for the patients, more clinical and metabolic parameters, and be held simultaneously at different research centers. Thus, the data obtained by this meta-analysis are not enough to indicate the use of antidepressants as the only and first choice therapy for remission of binge-eating episodes and weight reduction of patients being treated for BED.

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