RESEARCH ARTICLE

Binge Eating Disorder Pharmacotherapy Clinical Trails—Who Is Left Out?

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Abstract

Objective: This report examined the characteristics of subjects interested in binge eating disorder (BED) pharmacotherapy trails who were ineligible for participation.

Methods: Data on 2685 potential subjects interested in participating in five different placebo-controlled monotherapy trails of BED were analysed.

Results: Of the 2685 potential subjects, 1230 (45.8%) were ineligible because they did not meet entry criteria, 586 (21.8%) were eligible for participation, 531 (19.8%) were not interested in the study and 338 (12.6%) were not contacted. Among the 1230 ineligible candidates, 525 (42.7%) were taking exclusionary psychotropic medication, 305 (24.8%) did not meet specified BED criteria, 157 (12.7%) were out of the required age ($n = 83$) or weight ($n = 74$) range, 212 (17.2%) had prohibited medical ($n = 78$) or psychiatric ($n = 134$) disorders and 31 (2.5%) were participating in weight loss programmes.

Discussion: Given the complexity of BED, future pharmacotherapy studies should examine a broader range of subjects, including subjects with subthreshold forms of BED, those with comorbid disorders and elderly subjects.

Keywords

binge eating; placebo-controlled; pharmacotherapy; inclusion criteria

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Introduction

Binge eating disorder (BED), classified as an eating disorder not otherwise specified (EDNOS) in DSM-IV, is characterised by recurrent episodes of binge eating without inappropriate compensatory weight loss behaviours (A.P.A, 1994) and is associated with a chronic course, obesity and other medical morbidity, psychopathology and disability (Hudson, Hiripi, Pope, & Kessler, 2007; Pope et al., 2006; Yanovski, Nelson, Dubbert, & Spitzer, 1993). Its lifetime prevalence in the United States is estimated to be 1–3% (Hudson et al., 2006; Striegel-Moore & Franko, 2003).

Although several psychotherapies have been shown to be effective in reducing eating and associated psychopathology in BED (Brownley, Berkman, Sedway, Lohr, & Bulik, 2007; Wilfley et al., 2002), growing research suggests several pharmacotherapies (Brownley et al., 2007; Carter, Hudson, Lalonde, Pindyck, McElroy, &Pope, 2003; Stefano, Bacaltchuk, Blay, & Appolinario, 2008) may also be effective. Selective serotonin-reuptake inhibitor (SSRI) antidepressants

(Arnold, McElroy, Hudson, Welge, Bennett, & Keck, 2002; Guerdjikova et al., 2008; Hudson et al., 1998; McElroy et al., 2000; McElroy, Hudson, Malhotra, Welge, Nelson, & Keck, 2003), antiepileptic drugs (McElroy, Hudson, Capece, Beyers, Fisher, & Rosenthal, 2007; McElroy et al., 2006), the selective norepinephrine reuptake inhibitor atomoxetine (McElroy, Guerdjikova, Kotwal, Welge, Nelson, & Lake, 2007) and antiobesity medications (Appolinario et al., 2003; Grilo, Masheb, & Salant, 2005; W. Milano, Petrella, Casella, Capasso, Carrino, & L. Milano, 2005; Wilfley et al., 2008) have all shown promise in reducing binge eating symptoms. Some of these treatments may also be helpful in reducing the overweight that often accompanies BED. The patient groups examined in those studies, however, were subjected to rigorous inclusion and exclusion criteria, thus limiting the generalisibility of the obtained results. It therefore would be of clinical and research importance to examine individuals who expressed interest in participating in BED pharmacotherapy treatment studies in general, and what prevented potential candidates from participating.

Indeed, relatively few treatment studies of BED to date have systematically described the entire screened population excluded from participation and the reasons potential candidates did not participate. These include several placebo-controlled trails of cognitive-behavioural therapy (CBT) with and without pharmacotherapy (Devlin et al., 2005; Grilo, Masheb, & Salant, 2005; Grilo, Masheb, & Wilson, 2005), and several randomised trials comparing different psychotherapy (Munsch et al., 2007; Wilfley et al., 2002) or self-help techniques (Grilo, Masheb, & Salant, 2005). Among the most common reasons for subject ineligibility in all studies were not meeting specified BED criteria, being outside the required weight range, use of disallowed psychotropic medications, being medically unstable and reasons of a practical nature such as time commitment, length of study, scheduling difficulties, or lack of transportation. However, to our knowledge, no studies published to date have provided information on the ineligibility of candidates expressing interest in placebo-controlled monotherapy pharmacological trials for BED, despite Consolidated Standards of Reporting Trails (CONSORT) (Begg et al., 1996) recommending description of such potential subjects.

Obtaining more information about this group might increase knowledge of persons with BED interested in pursuing pharmacotherapy, shed light on their treatment preferences and assist in better design of future pharmacotherapy clinical trails by helping to define study entry criteria that are more representative of the general BED population. Therefore, we attempted to characterise the subgroup of individuals who expressed interest in participating in placebo-controlled monotherapy trails in BED, but were ineligible, by analysing 2685 potential subjects who contacted our programme in response to advertisements for BED pharmacotherapy studies over a three and a half year period.

Methods

Between September 2003 and May 2007, the Psychopharmacology Research Programme at the University of Cincinnati, the largest academic institution in the region, recruited participants for five double-blind, placebo-controlled monotherapy studies in BED by DSM-IV criteria (Table 1). Four studies were investigator initiated. None but the most recent study (lamotrigine) provided monetary compensation for participation (20$ per visit for time and travel). Funding for study advertisements was provided by pharmaceutical companies supporting the trials. Throughout that period, studies were advertised on the local radio ($n = 2$), TV ($n = 4$), largest daily newspaper ($n = 39$), free printed media ($n = 10$) and two local fitness centres. Recruitment consisted of advertisements seeking participants who had 'eating out of control' and were 'eating large amounts of food', for placebo-controlled treatment studies. The Cincinnati/Northern Kentucky metropolitan area includes 15 counties in the states of Ohio, Kentucky and Indiana and has a population of over two million people.

Name and contact information from all potential participants who contacted the office regarding the trails was entered in one confidential database. The outcome of the phone contact (subject eligible, subject scheduled for screen visits, subject ineligible or contact status), along with detailed reason for ineligibility, if applicable, was recorded. If the subject was found ineligible for one reason (e.g. he or she was receiving a prohibited psychotropic medication), the phone screen process was discontinued at that time (i.e. there was no further data collection on other exclusionary criteria).

The inclusion criteria were similar, though not identical, for all five studies and are presented in Table 1. The exclusion criteria for all five studies were very similar, namely: (1) concurrent anorexia nervosa

Table 1 Description of five monotherapy placebo-controlled trails that took place at UC between September 2003 and May 2007

Study title	Recruitment period	Patients randomised	Screen fails	Inclusion criteria
High-dose escitalopram in the treatment of binge-eating disorder with obesity: a placebo-controlled monotherapy trial (Guerdjikova *et al*., 2008)	January 2003–July 2003	40	12	18–65 years of age; BED with at least 2 episodes/week; BMI $\geq$ 30
Topiramate for the treatment of binge eating disorder associated with obesity: a placebo-controlled study (McElroy, Hudson, et al., 2007)*	November 2003–September 2004	53	19	18–65 years of age; BED with at least 3 episodes/week; BMI between 30 and 50
Zonisamide in the treatment of binge eating disorder with obesity: a randomised controlled trial (McElroy *et al*., 2006)	September 2003–October 2004	60	23	18–65 years of age; BED with at least 2 episodes/week; BMI $\geq$30
Atomoxetine in the treatment of binge-eating disorder: a randomized placebo-controlled trial† (McElroy, Guerdjikova, et al., 2007)	September 2004–November 2005	40	36	18–65 years of age; BED with at least 3 episodes/week; weight 85% of the midpoint of ideal body weight for that height
Lamotrigine in the treatment of binge eating disorder with obesity: a randomized controlled trial (ongoing)*,‡	April 2006–May 2007	38	12	18–65 years of age; BED with at least 2 episodes/week; BMI $\geq$ 30

* Subjects with clinically significant depression (defined as a Montgomery–Åsberg Depression Rating Scale [MADRS] score >24 at baseline visits) (Montgomery & Asberg, 1979) were excluded from the study.
† Subjects with BMI < 30 were included in the study; the mean BMI of the 40 randomised subjects was 39.3.
‡ Subjects with stable bipolar disorder (YMRS < 8) (Young, Biggs, Ziegler, & Meyer, 1978) were included in the study.

or bulimia nervosa (by DSM-IV criteria); (2) concurrent or recent (within 1 year of study entry) substance abuse or dependence (by DSM-IV criteria); (3) a lifetime history of psychosis, mania or hypomania or dementia (by DSM-IV criteria), except for the lamotrigine study which allowed patients with bipolar disorder; (4) a history of any personality disorder that could interfere with diagnostic assessment, treatment or compliance; (5) posing significant suicide risk; (6) receiving interpersonal, CBT or dialectal behavioural therapy for BED within 3 months of study entry; (7) clinically unstable medical illness; (8) history of seizures; (9) clinically significant laboratory abnormalities; (10) monoamine oxidase inhibitors (MAOIs) within 4 weeks of randomisation; (11) other psychotropic medication within 2 weeks of randomisation. Females were excluded if they were pregnant, lactating or if fertile, not practicing a medically accepted form of contraception. Two of the studies (McElroy et al. McElroy, Hudson, et al., 2007) excluded patients with clinically significant depression (defined as a Montgomery– Asberg Depression Rating Scale [MADRS] (Montgomery & Asberg, 1979) score >24 at the baseline visits).

Results

From the 2685 potential subjects who contacted our programme, 2347 were interviewed by phone (Figure 1). A total of 338 people were left messages at least twice but did not return calls after their initial phone contact. Of the 2347 potential subjects who were interviewed over the phone, 586 were scheduled for a face-to-face screening evaluation; of these 231 were randomised, 102 were screen fails (Table 2) and 253 were eligible, but either wanted to take more time before committing to participate ($n = 135$), or did not appear for their screening visit ($n = 118$). The remaining 1761 potential subjects were determined to be either ineligible for participation ($n = 1230$) or not interested ($n = 531$) in the study during the phone interview. Among the former, current antidepressant use ($n = 379$; 30.8%) was the most common reason for ineligibility, followed by not meeting DSM-IV criteria for BED ($n = 305$; 24.8%), use of other psychotropic medications ($n = 146$; 11.8%), being out of the age range ($n = 83$; 6.7%), having an unstable medical condition ($n = 78$; 6.3%), having a body mass index (BMI) below 30 ($n = 74$; 4.2%), being previously

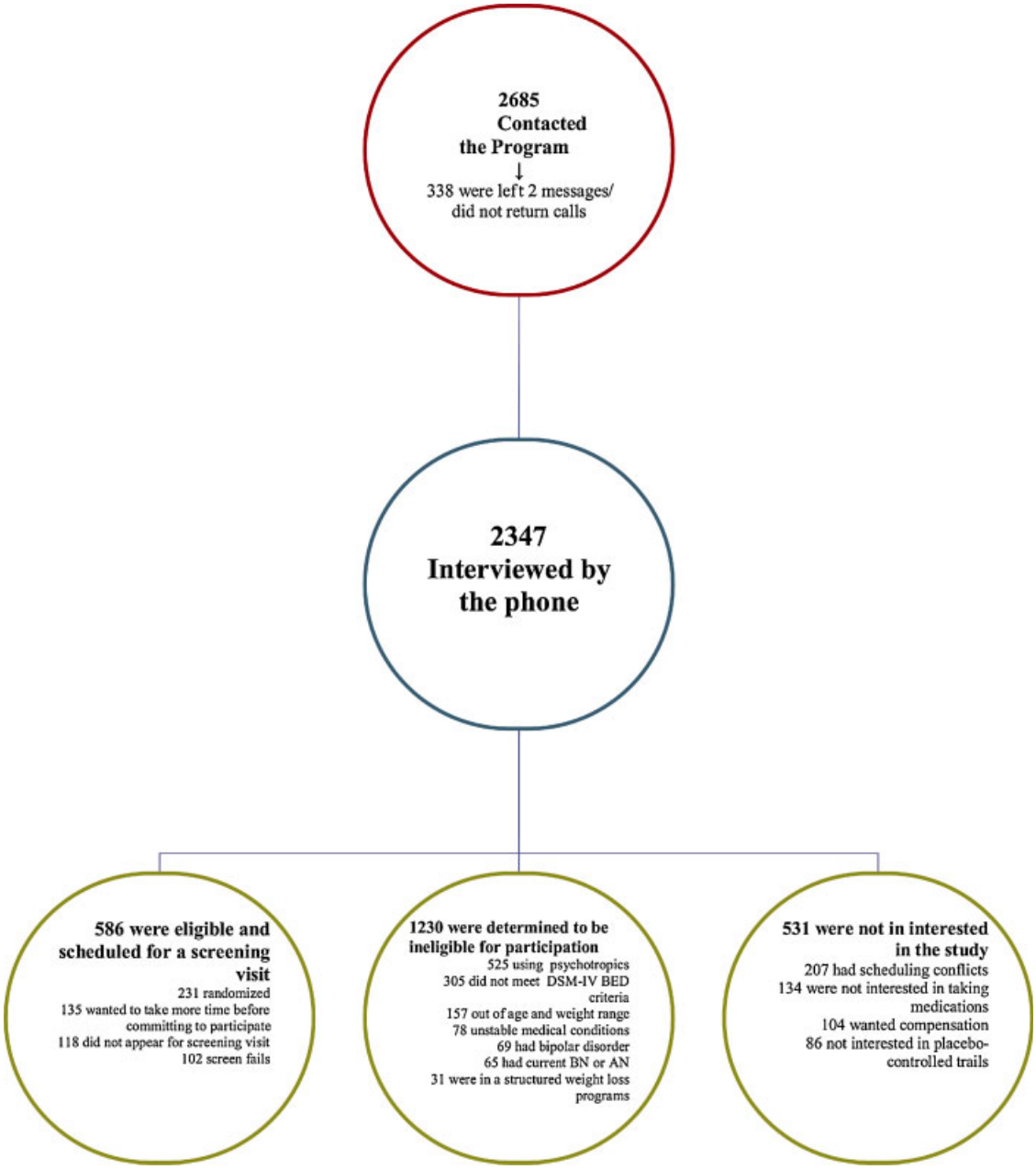

Figure 1 Flow of subjects interested in participating in pharmacotherapy trails for BED and obesity

diagnosed with bipolar disorder ($n = 69$; 6%), having current bulimia nervosa ($n = 53$; 4.3%) or anorexia nervosa ($n = 12$; 0.9%) or participating in structured weight loss programmes or psychotherapy ($n = 31$; 2.5%). Of the 83 potential subjects who were out of the age range, all were too old: 46 (3.7%) were in the 66–70 year age range; 25 (2%) were in the 71–75 year age range; 5 (0.4%) were in the 76–85 year age range and 7 (0.6%) self-classified as 'too old' after being given the age range for the study. Of the 531 potential subjects not interested in study participation after obtaining more information, 207 (38.9%) had scheduling conflicts; 134 (25.2%) did not want to take medication; 104 (19.6%) wanted compensation for time and travel and 86 (16.2%) did not want to participate in a placebo-controlled trial.

Table 2 Description of screen fails during recruitment for five monotherapy placebo-controlled trails that took place at UC between September 2003 and May 2007

Study title	Screen fails	Reasons for screen fails
High-dose escitalopram in the treatment of binge-eating disorder with obesity: a placebo-controlled monotherapy trial (Guerdjikova *et al*., 2008)	12	Exclusionary psychiatric diagnosis, bipolar disorder ($N=5$); unstable medical conditions ($N=3$); failed to meet DSM-IV criteria for BED ($N=1$) or had <2 binge days in the week before randomisation ($N=2$); withdrew consent to participate ($N=1$)
Topiramate for the treatment of binge eating disorder associated with obesity: a placebo-controlled study (McElroy, Hudson, et al., 2007)	19	Chose not to participate ($N=8$); unstable medical conditions ($N=6$); failed to meet DSM-IV criteria for BED ($N=3$); exclusionary psychiatric diagnosis ($N=2$)
Zonisamide in the treatment of binge eating disorder with obesity: a randomized controlled trial (McElroy et al., 2006)	23	Chose not to participate (N = 12); exclusionary psychiatric diagnosis (N = 4); failed to meet DSM-IV criteria for BED ($N=4$); unstable medical conditions ($N=3$)
Atomoxetine in the treatment of binge-eating disorder: a randomized placebo-controlled trial* (McElroy, Guerdjikova, et al., 2007)	36	Exclusionary psychiatric diagnosis ($N=10$); unstable medical conditions ($N=9$); placebo responders ($N=6$); chose not to participate ($N=6$); exclusionary medication ($N=5$)
Lamotrigine in the treatment of binge eating disorder with obesity: a randomized controlled trial (McElroy et al.) (ongoing)**	12	Exclusionary psychiatric diagnosis ($N=3$); lost to follow-up ($N=3$); unstable medical conditions ($N=2$); failed to meet DSM-IV criteria for BED ($N=1$); exclusionary medication ($N=1$); no appropriate birth control ($N=1$); insufficient monetary compensation for time and travel ($N=1$)

*Subjects with BMI<30 were included in the study; the mean BMI of the 40 randomized subjects was 39.3.

Discussion

Of 2685 potential subjects expressing initial interest in participating in five pharmacotherapy studies in BED over a three and a half year period, 1230 (45.8%) were deemed ineligible in the initial phone interview, 1122 (41.8%) stated they were uninterested in participating for various reasons, 102 (3.8%) met exclusion criteria upon a face-to-face screen evaluation and 231 (8.6%) met entry criteria and were randomised. Similarly to previous studies examining combined pharmacotherapy and psychotherapy treatment for BED (Devlin et al., 2005; Grilo, Masheb, & Salant, 2005; Grilo, Masheb, & Wilson, 2005), using psychotropic medication, most commonly antidepressants, not meeting DSM-IV BED criteria, having prohibited or unstable medical or psychiatric conditions, or being out of the age and weight range were among the most common reasons for ineligibility as determined at initial phone interview. Other important reasons for ineligibility found in our sample were not wanting to take medication or to participate in a placebo-controlled trial, as well as various reasons of a practical nature.

Use of antidepressants and other psychotropics was high in this population (22.3% among contacted potential subjects) and is consistent with existing data on the overlap among BED and mood and anxiety disorders (Hudson et al., 2007; Peterson, Miller, Crow, Thuras, & Mitchell, 2005). The high rate of antidepressant use might also be consistent with long-term studies (Devlin et al., 2005; Grilo, Masheb, & Wilson, 2005; Ricca et al., 2001) showing that the beneficial effects of SSRIs demonstrated in short-term clinical trails on BED and body weight (Carter et al., 2003) may not persist with long-term treatment.

A substantial portion (12.9%) of contacted candidates did not qualify because they did not meet strict DSM-IV BED criteria. It was our clinical impression that many of these candidates had subthreshold BED because they often reported less than two binge eating episodes per week (Striegel-Moore, Dohm, Solomon,

Fairburn, Pike, & Wilfley, 2000). As growing research shows EDNOS is the most prevalent, but least studied, category of eating disorders (Fairburn, Cooper, Bohn, O'Connor, Doll, & Palmer, 2007; Grilo et al., 2007; Machado, Machado, Goncalves, & Hoek, 2007), methodologically sound pharmacological studies examining different forms of EDNOS, including subthreshold BED, may be warranted.

Another interesting observation was that 3.5% of all contacted candidates did not qualify for participation because they were 65 years of age and older. Indeed, despite recent research suggesting BED may be a chronic condition (Pope et al., 2006), we were unable to find any published data on BED in the elderly. Empirical studies of BED in elderly subjects may represent a research priority, especially in light of the increasing lifespan and improving quality of life in the last decades of life.

About 2.9% of all contacted candidates had been previously diagnosed with bipolar disorder. This is consistent with clinical and epidemiological studies reporting elevated rates of bipolar disorder in individuals with BED (Hudson et al., 2007; McElroy, Kotwal, Keck, & Akiskal, 2005) and supports the use of structured diagnostic interviews to assess comorbid psychopathology in persons with BED participating in clinical trials.

Regarding treatment preferences, 5.7% of contacted candidates stated that they did not want to take medication for their BED. No studies to date have compared psychotherapy versus pharmacotherapy treatment preferences in BED subjects. The only systematic comparison of treatment preferences that we located found that CBT was preferred by two-thirds of obese BED subjects who responded to advertisements for treatment studies looking for persons who wanted to 'stop binge eating and lose weight' (Brody, Masheb, & Grilo, 2005). The other one-third of subjects preferred behavioural weight loss therapy. Treatment preferences were independent of subjects' demography: histories of obesity, dieting, binge eating or weight cycling; and current BMI, eating disorder features or psychological functioning (Brody et al., 2005). Randomised trails in BED that include pharmacotherapy arms might consider comparing treatment preferences and explore whether such preferences have an impact on treatment outcomes.

The findings of this study are tempered by several important limitations. First, potential subjects did not receive in-person structured interviews and it is unknown how many truly met DSM-IV criteria for BED. Second, ineligible candidates were classified based on the first exclusion criterion that they met; it is thus likely that some met other exclusion criteria which were not accounted for. Third, to some extent our advertisements may have influenced the results of the study. For example, the proportion of candidates with possible subthreshold BED may have been artificially inflated because required frequency and chronicity of binge eating episodes were not explicitly stipulated in the advertisement.

In sum, most potential subjects who responded to advertisements for placebo-controlled pharmacotherapy studies of BED were ineligible for participation for a variety of reasons. Future studies with broader entry criteria should examine subjects with subthreshold forms of BED, subjects with comorbid medical conditions other than obesity, and elderly subjects with binge eating symptoms. Future pharmacotherapy trails in BED should follow CONSORT guidelines and include detailed information about subjects' flow starting with the initial contact with potential participants.

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