High-dose escitalopram in the treatment of binge-eating disorder with obesity: a placebo-controlled monotherapy trial

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Objective The purpose of this study was to evaluate the efficacy and safety of high-dose escitalopram in the treatment of binge-eating disorder (BED) associated with obesity.

Method Forty-four outpatients with BED by DSM-IV criteria and obesity were randomized to receive either escitalopram (N = 21) or placebo (N = 23) in a 12-week, double-blind, flexible dose (10–30 mg/day) study.

Results In the primary analysis, escitalopram (mean dose 26.5 mg/day) and placebo had similar rates of reduction of binge episodes, binge days and obsessive-compulsive symptoms of BED. However, escitalopram was associated with statistically significant reductions in weight, body mass index (BMI), and global severity of illness scores. In a secondary analysis, escitalopram was associated with statistically significant reductions in frequency of binge episodes and binge days, weight, BMI and severity of illness, but not in obsessive-compulsive symptoms of BED. No changes in metabolic variables, including measures of ghrelin and leptin, were observed. High-dose escitalopram was well tolerated.

Conclusion High-dose escitalopram was not efficacious in reducing obsessive-compulsive symptoms of BED, but was efficacious in reducing weight and global severity of illness. No definitive conclusions about its efficacy in reducing binge-eating frequency could be drawn due to limitations related to statistical power. Copyright © 2007 John Wiley & Sons, Ltd.

Key words—binge-eating disorder; escitalopram; obesity; randomized clinical trial; serotonin reuptake inhibitors; obsessive-compulsive

INTRODUCTION

Growing evidence suggests binge-eating disorder (BED), characterized by recurrent episodes of binge eating without inappropriate compensatory weight loss behaviors (APA, 1994) is an important public health problem. Its lifetime prevalence in the United States (U.S.) is estimated to be 1–3% (Hudson et al., 2006; Striegel-Moore and Franko, 2003) and it is associated with medical and psychiatric comorbidity (Hudson et al., 2007; Javaras et al., 2007; Peterson et al., 2005; Yanovski et al., 1993), impaired quality of life and disability (Gruca et al., 2007; Hudson et al., 2006; Rieger et al., 2005).

Regarding medical comorbidity, BED has a strong association with obesity (Gruca et al., 2007; Hudson et al., 2007; Yanovski et al., 1993). There is an increased prevalence of BED in persons requesting weight management and bariatric surgery (Busetto et al., 2005; Dymek-Valentine et al., 2004; Niego et al., 2007; White et al., 2006; Yanovski, 2003), and conversely, an increased prevalence of obesity among
individuals with BED (Grucza et al., 2007; Hudson et al., 2006). In addition, abnormalities of the brain-gut axis, including dysregulation of the hormones leptin and ghrelin, may occur in persons with BED and obesity (Adami et al., 2002; Geliebter et al., 2005; Hellstrom et al., 2004; Monteleone et al., 2004).

Regarding psychiatric comorbidity, BED has strong associations with anxiety and mood disorders (Javara et al., 2007). In the National Comorbidity Survey Replication study, 65% of respondents with BED had a co-occurring anxiety disorder and 46% had a mood disorder (Hudson et al., 2007).

Treatment objectives for BED include reduction of binge eating and associated psychopathology, as well as weight loss, or at least prevention of further weight gain, when there is comorbid obesity (Appolino and McElroy, 2004; Carter et al., 2003; Devlin et al., 2005; Grilo et al., 2005; Leombruni et al., 2006; Willey et al., 2002). Selective serotonin reuptake inhibitor (SSRI) antidepressants have been shown to have some efficacy in BED, in several of the psychiatric (e.g., major-depressive disorder, obsessive-compulsive disorder [OCD], generalized anxiety disorder) conditions that co-occur with BED, and also in obesity without associated psychopathology (Appolino and McElroy, 2004; Bielski et al., 2005; Fontenelle et al., 2007; Golden, 2004; Norris et al., 2004). Specifically for BED, the SSRIs (fluvoxamine (Hudson et al., 1998), sertraline (McElroy et al., 2000), fluoxetine (Arnold et al., 2002) and citalopram (McElroy et al., 2003)) were associated with statistically significant reductions in binge eating and weight in short-term (6–9 week) double-blind, placebo-controlled, two-arm monotherapy trials. A meta-analysis of these four trials found SSRIs to be superior to placebo in reducing binge-eating frequency and in increasing global improvement (Carter et al., 2003). Similarly, in the longest SSRI trial conducted to date, a 6-month open-label trial of sertraline, the reduction of binge eating and weight symptoms and weight loss obtained at 8 weeks was maintained at 6 months (Leombruni et al., 2006). By contrast, in the longest placebo-controlled trial (16 weeks) of an SSRI in BED, which compared SSRI monotherapy with cognitive-behavioral therapy (CBT), fluoxetine at 60 mg/day failed to separate from placebo regarding remission of binge eating and weight loss and CBT was found superior to both fluoxetine and placebo for decreasing binge eating, but not for weight loss (Grilo et al., 2005). This trial was limited, however, by lack of blinding of CBT relative to pharmacotherapy.

The above studies of SSRIs in BED have several specific limitations. First, despite findings that BED frequently co-occurs with obesity, which has been shown to respond to SSRIs at least over the short-term, only one study (Leombruni et al., 2006) required subjects to have comorbid obesity (body mass index [BMI] ≥ 30 kg/m²). Although this study found sertraline was associated with weight loss and weight maintenance, it was not controlled. Second, despite the overlap of BED with anxiety disorders, including OCD (Jarry and Vaccarino, 1996; McElroy et al., 1994), which sometimes responds only to ‘supratherapeutic’ doses of SSRIs (Bejerot and Bodlund, 1998; Byerly et al., 1996; Ninan et al., 2006), no SSRI studies in BED have yet evaluated such doses. Indeed, two early studies of fluoxetine in subjects with obesity suggested a dose-response relationship for both weight loss and weight maintenance (Goldstein et al., 1993; Levine et al., 1989). It could therefore be hypothesized that SSRIs at higher, or ‘supratherapeutic’, doses might be associated with greater decreases in the compulsive features of binge eating and possibly greater weight loss. A third limitation of available SSRI studies in BED is that none assessed effects on metabolic variables, including leptin and ghrelin, despite preliminary data suggesting that SSRIs may improve metabolic parameters in obese subjects even with minimal or no weight loss (Ljung et al., 2001; Norris et al., 2004).

In order to address some of these limitations, we conducted a randomized, double-blind, placebo-controlled, 12-week trial to assess the efficacy and safety of high-dose escitalopram (up to 30 mg/day) in subjects with BED and obesity. Escitalopram is the S-stereoisomer of citalopram and is characterized by high selectivity of serotonin reuptake inhibition. Since it was first approved in Denmark in 1989, escitalopram has been prescribed in 26 countries. It is currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of major depressive disorder and generalized anxiety disorder, and has been shown to be efficacious for the long-term treatment of OCD (Stein et al., 2007). In addition to escitalopram’s effects on binge-eating symptoms, obsessive-compulsive features of BED and weight, we also assessed its effects on metabolic variables, including leptin and ghrelin.

MATERIALS AND METHODS

Subjects

Subjects were outpatients who were recruited from advertisements for a medication trial for persons with binge eating and obesity. They were eligible for the
study if they met DSM-IV criteria for BED (APA, 1994) were obese, defined as having a BMI ≥ 30 kg/m²; and were 18 through 60 years of age. Subjects were excluded if they met any of the following criteria: (1) had concurrent anorexia nervosa or bulimia nervosa (by DSM-IV criteria), (2) had concurrent or recent (within 1 year of study entry) substance abuse or dependence (by DSM-IV criteria), (3) had a lifetime history of psychosis, mania or hypomania or dementia (by DSM-IV criteria), (4) had a history of any psychiatric disorder that could interfere with diagnostic assessment, treatment or compliance, (5) posed a significant suicide risk, (6) had received interpersonal, cognitive-behavioral or dialectal behavioral therapy for BED within 3 months of entry into the study, (7) had a clinically unstable medical illness, (8) had a history of seizures, (9) had clinically significant laboratory abnormalities, (10) had received monoamine oxidase inhibitors (MAOIs) within 4 weeks of randomization, (11) had received other psychotropic medication within 2 weeks of randomization, (12) had received investigational medications or depot antipsychotics within 3 months of randomization, (13) had previously been treated with escitalopram or (14) had <2 binge days in the week before randomization. Females were excluded if they were pregnant, lactating or if fertile, not practicing a medically accepted form of contraception.

The Institutional Review Board at the University of Cincinnati Medical Center approved the protocol and all subjects provided written informed consent before administration of any study procedures.

Study design

The study was a single-center, parallel-group, randomized, placebo-controlled, double-blind, flexible-dose study. After 1 week of open evaluation, subjects were randomly assigned to therapy with escitalopram or placebo for a 12-week treatment period. All study medication was dispensed in identical tablets (10 mg of escitalopram or placebo). Subjects began randomized treatment with 10 mg/day for the first 7 days. The dosage was then increased, as tolerated, to 20 mg/day for 7 days and then 30 mg/day, as tolerated, for the remainder of the study. Study medication could be reduced to a minimum of 10 mg/day because of intolerable side effects at any time during the 12-week treatment period.

All subjects underwent a screening evaluation that included an interview for demographic information and medical, psychiatric and family histories; the Structured Clinical Interview for DSM-IV (SCID) (First et al., 2002) (to establish the diagnosis of BED and determine comorbid Axis I diagnoses); a physical examination, vital signs, height and weight measurements to determine BMI, routine blood chemical and hematological tests and fasting leptin and ghrelin plasma levels. At this evaluation and each of the following visits, subjects were given take-home diaries in which to record any binge episodes and, once medication was initiated, the number of capsules taken. Subjects were seen weekly during the first 6 weeks of the double-blind treatment period and bi-weekly during the second 6 weeks.

At each visit following the screen visit, subjects were assessed for number of binge episodes experienced since the last visit, other outcome measures (except for the 17-item Hamilton Depression Rating Scale [HAM-D] (Hamilton, 1967) which was administered at baseline and weeks 2, 4, 6, 8, 10 and 12; see below), medication dose, medication compliance ascertained by capsule count, adverse events, use of non-study medications, vital signs and weight.

Subjects were randomized to receive escitalopram or placebo in a 1:1 ratio according to computer-generated coding. Randomization was balanced by use of permuted blocks. Allocation concealment was achieved by having the research pharmacy perform the randomization, package the study medication and maintain the integrity of the blinded information throughout the trial.

Outcome measures

The primary outcome measure was the weekly frequency of binge-eating episodes (binge frequency). A binge episode was defined using DSM-IV criteria (APA, 1994). As in other studies of SSRIs (Arnold et al., 2002; Hudson et al., 1998; McElroy et al., 2000, 2003), anticonvulsants (McElroy et al., 2004, 2006, 2007b) and selective norepinephrine reuptake inhibitors (McElroy et al., 2007a) in BED, binge episodes were assessed via clinical interview and review of take-home diaries, upon which subjects recorded number and duration of binge episodes and food consumed during binges (so that binges could be confirmed by the investigator). Secondary outcome measures were weekly frequency of binge days (days during which there were one or more binges), weight (kg), BMI (body weight in kg divided by height in m²); Yale-Brown Obsessive-Compulsive Scale (Goodman et al., 1989) modified for Binge Eating (YBOCS-BE) scores; Clinical Global Impression-severity (CGI severity) and improvement (CGI-Improvement Scale) (Guy, 1976) scores and HAM-D (Hamilton, 1967).
total scores. Other secondary efficacy measures included response categories based on percentage decrease in frequency of binges from baseline to endpoint and defined as follows: remission = cessation of binges, marked = 75–99% decrease, moderate = 50–74% decrease and none = less than 50% decrease.

Leptin and ghrelin were measured on fasting plasma samples using commercial radioimmunoassay kits (Linco, Inc, St. Louis, MO) obtained from the screening and week 12 visits (or the last treatment visit if the subject prematurely terminated the trial). Assays were performed according to the manufacturer’s recommended protocol and results of standards and controls were within the range of expected values.

Adverse events, physical examination findings, clinical laboratory data and vital signs were assessed as safety measures. Adverse events were obtained through spontaneous subject reporting and by open-ended investigator questioning. Reportable adverse events were new symptoms or illnesses that occurred during the treatment phase and those that increased in severity compared with baseline.

Statistical methods
Our data analysis was similar to that used in a number of other BED pharmacotherapy trials (Arnold et al., 2002; Hudson et al., 1998; McElroy et al., 2003, 2006, 2007a). Pretreatment comparisons between assignment groups were made using Fisher’s exact test for categorical variables and independent sample t-tests for continuous variables.

The primary efficacy analysis was a longitudinal analysis comparing the rate of change of binge episode frequency, binge day frequency, weight, BMI and rating scale scores during the treatment period between the two groups. The difference in rate of change was estimated by random regression methods (Fitzmaurice et al., 2004; Gibbons et al., 1993). We used a model for the mean of the outcome variable that included terms for treatment, time and treatment-by-time interaction. Time was modeled as a continuous variable, expressed as the square root of days since randomization (baseline). For the analyses of binge frequency and binge day frequency, we used the logarithmic transformations log (binges/week) + 1) and log ((binge days/week +1)), respectively, to normalize the data and stabilize the variance. To simultaneously account for individual differences in initial level of the outcome, rate of change over time and serial autocorrelation (i.e., the tendency for correlation among observations to decrease as a function of the amount of time between them), we used the SAS procedure MIXED, with random intercept and slope terms and a first-order antedependence structure for the residual correlation matrix. The longitudinal analyses were intent-to-treat, using all available observations from all time points from all subjects who completed a baseline evaluation.

Several secondary analyses were performed. Using the last observation carried forward (LOCF), baseline to endpoint change scores were computed for each measure (on the logarithmic scale for the binge-eating measures) and independent-samples t-tests were used to compare these changes between the treatment groups. The Cochrane-Armitage exact trend test for 2-by-k ordered tables in SAS (PROC FREQ) was used to analyze categorical response to treatment (as defined above) for the intent-to-treat and completer groups. Time to recovery (defined as the first four consecutive binge-free weeks after baseline) was analyzed with a Cox proportional-hazards model for the intent-to-treat population. The correlation between percentage change in binge frequency and change in weight was calculated using rank-transformed data (Spearman rank correlation).

For laboratory measures, including weight, leptin and ghrelin, the mean difference between endpoint and baseline measure was computed for each treatment group and then compared using the t-test.

All statistical tests and confidence intervals were two-sided, \( \alpha = 0.05 \).

RESULTS
Forty-four subjects were enrolled in the study from January 2003 through July 2003 and received randomized treatment: 21 subjects received escitalopram and 23 received placebo. An additional 12 subjects were screened but not enrolled because they: failed to meet DSM-IV criteria for BED \((N = 1)\), had an exclusionary psychiatric diagnosis, bipolar disorder \((N = 5)\), had unstable medical conditions \((N = 3)\), withdrew consent to participate \((N = 1)\) or had <2 binge days in the week before randomization \((N = 2)\). At baseline, subjects in the two treatment groups were comparable with respect to age, sex, race, rates of current and lifetime major depressive disorder and baseline values of all outcome measures (Table 1). Depressive disorders were the most common co-occurring psychiatric disorders, occurring in 34 (77.3%) subjects as lifetime diagnoses and currently in 10 (22.7%) subjects.

Forty-three subjects (20 receiving escitalopram and 23 receiving placebo) had at least one postrandomization efficacy measure. Five of 20 (25%) escitalopram
subjects and 4 of 23 (17.3%) placebo subjects did not complete all 12 weeks of treatment. Five subjects withdrew prematurely because of non-adherence to study protocol procedures (N = 4 escitalopram, N = 1 placebo), three subjects withdrew because of adverse events (N = 1 escitalopram and N = 2 placebo) and one subject withdrew because of lack of weight loss (N = 1 placebo). The remaining 34 subjects (15 escitalopram, 19 placebo) completed the 12 weeks of treatment. The mean daily dose at endpoint evaluation for escitalopram-treated subjects was 26.5 mg/day (range 10–30 mg); the corresponding placebo ‘dose’ was 29.1 mg/day.

The mean frequency of binge-eating episodes decreased over the study period in both treatment groups (Figure 1). Mean body weight decreased over the study period in the escitalopram group, but not in the placebo group (Figure 2).

The primary efficacy analysis using random regression showed that subjects receiving escitalopram and those receiving placebo had similar rates of reduction in binge-eating episodes and binge eating days per week (Table 2). There was also no difference in the rate of change in reduction in the Y-BOCS-BE total or subscale scores, or in the HAM-D scores between the treatment groups (Table 2). By contrast, escitalopram was associated with a significantly greater rate of improvement than placebo for body weight, BMI and CGI-Severity Scale scores.

In the secondary analysis of baseline-to-endpoint change scores using LOCF, escitalopram was associated with significant decreases in binge-eating episodes per week, binge days per week, weight, BMI and scores on the CGI-Severity Scale compared with placebo (Table 2). Marginally non-significant changes were obtained for the Y-BOCS-BE total and compulsion subscale scores. There were no significant differences between groups in the change in scores on the Y-BOCS-BE obsession or HAM-D scales.

Regarding global response, the mean final CGI-Improvement Scale at endpoint was rated much or very much improved in 17 (85%) of escitalopram-treated subjects as compared with 9 (39.1%) of placebo-treated subjects (p = 0.029). In the categorical response analyses, there were higher levels of response for subjects receiving escitalopram in both the intent-to-treat and completer groups, but neither were statistically significant (Table 3). Thus, in the intent-to-treat population, remission of binge-eating episodes was attained by 50% of escitalopram-treated subjects at endpoint compared with 26% of placebo-treated subjects (p = 0.088). High dose escitalopram

### Table 1. Baseline characteristics of 44 subjects with binge-eating disorder and obesity receiving escitalopram or placebo

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Escitalopram (N = 21)</th>
<th>Placebo (N = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>36.9 (10.0)</td>
<td>41.0 (10.7)</td>
</tr>
<tr>
<td>Female, N (%)</td>
<td>21 (95.5)</td>
<td>22 (95.7)</td>
</tr>
<tr>
<td>Caucasian, N (%)</td>
<td>16 (72.7)</td>
<td>17 (73.9)</td>
</tr>
<tr>
<td>Current major depressive disorder, N (%)</td>
<td>6 (27.3)</td>
<td>4 (17.4)</td>
</tr>
<tr>
<td>Lifetime major depressive disorder, N (%)</td>
<td>16 (72.7)</td>
<td>18 (78.3)</td>
</tr>
<tr>
<td>Lifetime alcohol use disorder, N (%)</td>
<td>2 (9.5)</td>
<td>3 (13.0)</td>
</tr>
<tr>
<td>Lifetime anxiety disorder, N (%)</td>
<td>3 (14.3)</td>
<td>7 (30.4)</td>
</tr>
<tr>
<td>Measure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Binges/wk</td>
<td>4.9 (2.6)</td>
<td>5.1 (2.3)</td>
</tr>
<tr>
<td>Binge days/wk</td>
<td>4.0 (1.7)</td>
<td>4.1 (1.5)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>40.1 (6.8)</td>
<td>40.3 (4.8)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>113.0 (20.0)</td>
<td>109.2 (17.2)</td>
</tr>
<tr>
<td>Waist Circumference, cm</td>
<td>111.8 (13.2)</td>
<td>111.2 (11.8)</td>
</tr>
<tr>
<td>Clinical Global Impression-Severity</td>
<td>4.8 (0.7)</td>
<td>4.7 (0.7)</td>
</tr>
<tr>
<td>YBOCS-BE² total</td>
<td>19.1 (5.3)</td>
<td>19.0 (3.6)</td>
</tr>
<tr>
<td>Obsessions</td>
<td>9.2 (2.8)</td>
<td>9.0 (2.2)</td>
</tr>
<tr>
<td>Compulsions</td>
<td>9.9 (3.2)</td>
<td>10.0 (1.8)</td>
</tr>
<tr>
<td>Hamilton Depression Rating Scale</td>
<td>4.6 (3.75)</td>
<td>5.7 (4.5)</td>
</tr>
<tr>
<td>Leptin, ng/ml²</td>
<td>43.1 (16.1)</td>
<td>42.9 (18.3)</td>
</tr>
<tr>
<td>Ghrelin, ng/L²</td>
<td>818.6 (369.5)</td>
<td>821.9 (343.8)</td>
</tr>
</tbody>
</table>

¹Differences between groups on all characteristics were not significant.
²Yale-Brown Obsessive-Compulsive Scale modified for binge eating.
³N = 19 for escitalopram group.
was not associated with shortened time to recovery of binge eating in the intent-to-treat group (hazard ratio for recovery = 1.5 [95% CI: 0.2–2.3], $\chi^2 = 0.45$, $p = 0.50$).

Subjects given escitalopram experienced a mean (SD) weight loss of 1.0 (2.6) kg from baseline to endpoint, whereas those given placebo experienced a mean (SD) weight gain of 0.6 (2.4) kg ($p = 0.002$).
Among subjects who completed the 12 weeks of treatment, the escitalopram group lost 1.1 (2.9) kg and the placebo group gained 0.7 (2.5) kg ($p = 0.037$). Weight loss since baseline showed a marginally significant correlation with percentage reduction in binge frequency at week 12 in the overall sample (Spearman $r = 0.25$, $p = 0.10$). The correlation among these changes was of a similar magnitude among subjects receiving escitalopram (Spearman $r = 0.23$, $p = 0.30$).

There were no significant differences between subjects receiving escitalopram and those given placebo in mean change from baseline to final visit for the fasting measurements of insulin (−0.2 and 2.3 μU/ml), glucose (−0.3 and −2.3 mg/dl), triglycerides (−6.6 and 3.1 mg/dl), LDL cholesterol (2.8 and 7.6 mg/dl), total cholesterol (4.8 and 10.5 mg/dl), leptin (0.1 and 2.9 ng/ml) and ghrelin (−1.6 and 71.8 ng/L, respectively).

The most common adverse events reported by the escitalopram-treated subjects were dry mouth ($N = 7$) and diarrhea ($N = 5$) (Table 4). There were no significant differences between treatment groups in the incidence of adverse events. Two subjects given escitalopram developed serious adverse medical events. The first subject had a metatarsal fracture in her left foot obtained during a syncopal episode induced by having her blood drawn. The second subject was hospitalized for dehydration due to an acute gastrointestinal viral syndrome. Neither event was thought to be due to study medication.

There were no changes in physical findings, vital signs or clinical laboratory values suggestive of drug-
related toxicity. There was no evidence of withdrawal symptoms in the subjects in whom escitalopram was discontinued.

DISCUSSION

In the primary longitudinal analysis of this 12-week placebo-controlled study of an SSRI in BED with comorbid obesity, high-dose escitalopram (mean dose 26.5 mg/day) was not significantly superior to placebo in reducing rate of binge episode frequency, binge day frequency or obsessive-compulsive features of binge-eating symptoms, but was superior in reducing weight, BMI and global severity of illness. A secondary analysis, estimating change from baseline to endpoint using LOCF, yielded more positive findings, with high-dose escitalopram being associated with significant decreases in binge episode frequency, binge day frequency, weight, BMI and global severity of illness, but not with obsessive-compulsive features of binge eating, compared with placebo. The mean (SD) weight loss in the intent-to-treat group receiving escitalopram was 1 (2.6) kg, as compared with 0.6 (2.4) kg weight gain in the group receiving placebo. Both analyses of binge frequency indicated a directional trend in favor of efficacy and both models produced very similar effect estimates and confidence intervals. Moreover, although the effect size estimates were in the range conventionally termed moderate, the trial as designed did not have sufficient power to detect such effects and therefore, no definitive conclusion about efficacy of high-dose escitalopram with respect to binge eating can be drawn.

High-dose escitalopram was not associated with a significantly higher level of categorical response in both the endpoint and completer analyses, and was not associated with a shortened time to recovery of binge eating. However, it was associated with a significantly higher rate of global response as assessed by the CGI Improvement scale. There were no significant changes in HAM-D scores, but mean HAM-D scores were low at baseline. These findings provide preliminary evidence for the efficacy of high-dose escitalopram monotherapy for reducing overall severity of illness and for weight loss in BED associated with obesity. The reduced severity of illness and the small, but statistically significant, weight loss associated with escitalopram in this trial are consistent with the four previous controlled monotherapy trials of other SSRIs in BED (Arnold et al., 2002; Hudson et al., 1998; McElroy et al., 2000, 2003) and with a meta-analysis of these trials (Carter et al., 2003). This study is the first placebo-controlled study assessing the effects of an SSRI on BED associated with obesity. It is also the longest placebo-controlled monotherapy study (12 weeks) of an SSRI in BED. Thus, although comparing the results of this trial with the results of other studies of SSRIs is not entirely valid, the weight loss on high-dose escitalopram (1 kg, 12 weeks) was comparable with that seen in the 9-week study of fluvoxamine (1.2 kg) (Hudson et al., 1998), but less than that seen in the shorter studies of sertraline (5.6 kg, 6 weeks) (McElroy et al., 2000), fluoxetine (2.4 kg, 6 weeks) (Arnold et al., 2002) and citalopram (2.4 kg, 6 weeks) (McElroy et al., 2003). At this time it is unknown if this apparent diminishing degree of weight loss with increasing trial duration represents a methodological artifact, pharmacodynamic differences across individual SSRIs [e.g., sertraline also has some dopamine reuptake blocking properties (Nemeroff and Owens, 2004)] or characteristics of SSRIs as a class in patients with BED that they may share with patients with obesity without psychopathology.

The mechanism of action of escitalopram for reduced illness severity and weight loss in the short-term treatment of BED is unknown. Serotonin is involved in the regulation of feeding behavior (Hainer et al., 2006) and serotonergic dysfunction has been hypothesized to be involved in the pathophysiology of BED (Gorwood, 2004; Kuikka et al., 2001; Tammela et al., 2003). Escitalopram may exert its therapeutic effects in BED by correcting an abnormality of serotonin neurotransmission.

Table 4. Adverse events reported by ≥5% of 44 subjects

<table>
<thead>
<tr>
<th>Event</th>
<th>Escitalopram (N = 21) N (%)</th>
<th>Placebo (N = 23) N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>7 (33)</td>
<td>6 (27)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (24)</td>
<td>5 (22)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (14)</td>
<td>5 (22)</td>
</tr>
<tr>
<td>Increased urinary freq</td>
<td>3 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (14)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3 (14)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Gastrointestinal flu</td>
<td>3 (14)</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Sweating</td>
<td>3 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>3 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Yawning</td>
<td>3 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Nervousness</td>
<td>2 (10)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Upper respiratory inf</td>
<td>2 (10)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Cold/pharyngitis</td>
<td>1 (5)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Edema</td>
<td>1 (5)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (5)</td>
<td>3 (13)</td>
</tr>
</tbody>
</table>

*aAll differences between groups were non-significant.*
Unlike earlier studies of SSRIs in BED, the effects of high dose escitalopram on weight loss appeared to be somewhat more pronounced relative to its effects on binge eating. This observation could be due to methodological limitations, including the possibility that changes in binge-eating behavior may be more difficult to measure and differentiate between an active drug and placebo than changes in weight. It could also be due to differences in subject populations. Subjects in this study were required to be obese and to have at least two binge eating episodes in the week prior to study entry. In most of the other SSRI studies, patients were not required to be obese, but were required to have at least three binge eating episodes in the week prior to randomization. There may be important differences between individuals with BED who have different binge-eating frequencies and different body weights, and SSRIs may have differential effects in those subgroups. Another possibility is that high-dose escitalopram may have therapeutic effects in BED with obesity that do not involve reduction of binge eating. For example, it might decrease other forms of overeating in BED that might contribute to obesity. Such forms have been identified as night eating (Grilo and Masheb, 2004), subjective overeating (Grilo et al., 2001), emotional overeating (Masheb and Grilo, 2006) and grazing (Saunders, 2004).

The above reasons might also explain why, unlike the only other study that assessed the effects of an SSRI (citalopram) on obsessiveness of binge-eating thoughts and compulsiveness of binge-eating behaviors (McElroy et al., 2003) in subjects with BED, high-dose escitalopram did not result in improvement of YBOCS-BE scores. Alternatively, it suggests that binge-eating behavior, including in obese subjects, might be closely related to impulse control disorders (ICDs) than to OCD. Indeed, a number of studies have shown impulse control dysregulation in eating disorders in general (Christenson et al., 1994; Rosval et al., 2006), including in BED patients (Fontenelle et al., 2005; Hudson et al., 2007), as well as in subjects with obesity (Lundstedt et al., 2006; Rodin et al., 1989). For as yet unknown reasons, the response of ICDs in general to SSRIs appears to be more variable than is OCD response (Brown et al., 2005). Like ICDs, the response of BED to SSRIs may be similarly variable, with certain as yet unidentified features or subgroups displaying preferential responses.

Regarding metabolic assessments, the finding that leptin, which usually decreases with even small amounts of weight loss (Goodpaster et al., 1999), did not differ between the two groups was consistent with the results from the only other study that assessed leptin changes with treatment in patients with BED and obesity (McElroy et al., 2006). This study similarly found that leptin levels did not change despite a significantly greater weight loss in study completers receiving zonisamide (8.9 ± 5 kg) versus those receiving placebo (1.2 ± 3.8 kg) over 16 weeks. Although the significance of these findings is unknown, taken together they add support to the notion that leptin function may be dysregulated in BED and obesity.

This study has several important limitations. First, although the longest controlled study of an SSRI as monotherapy in BED completed to date, the duration of treatment was only 12 weeks, and the results may not generalize to longer treatment periods. In the longest open-label study of an SSRI in BED and obesity conducted to date, Leombruni et al. (2006) showed significant reductions in binge frequency and body weight that persisted up to 24 weeks in sertraline-treated subjects, suggesting that some patients with BED and obesity might do well over the long-term with SSRI treatment. Future studies should address the long-term efficacy of escitalopram and other SSRIs in BED with obesity.

A related limitation is that the weight loss in the escitalopram-treated group, although statistically significant, was small and possibly not clinically meaningful. Indeed, weight-loss in long-term studies of SSRIs in obesity without comorbid psychopathology have often found no drug-placebo differences by 6 months of treatment (Ljung et al., 2001; Molinari et al., 2005; Svacina, 2005) However, it should be noted that guidelines for what constitutes clinically significant weight loss in patients with BED and obesity may differ from those for patients with obesity without comorbid psychopathology. Thus, induction and maintenance of even a small weight loss (e.g., 1–4% of baseline body weight), or prevention of further weight gain, in patients with BED and obesity might be clinically significant. Future studies will need to specifically address weight management goals in patients with BED and obesity versus patients with obesity and no psychopathology.

Another limitation is that the size of groups was small and it is thus possible that the lack of effect on binge-eating symptoms of BED were false negative findings due to low power to detect important differences. Indeed, Cohen’s effect size for the longitudinal analysis of weekly binge frequency was 0.54. This value is considered a medium effect (Cohen, 1988) and is at a level that is clinically significant. Yet another limitation is that individuals
with several forms of psychopathology were excluded. Thus, the results may not generalize to BED with certain forms of comorbid psychopathology, such as psychotic and bipolar disorders, substance use disorders or severe personality disorders. Finally, because the majority of subjects were females, it is unknown if these results would extend to males.

In summary, in a 12-week, randomized, double-blind, flexible-dose trial, high-dose escitalopram monotherapy was found to be well tolerated and superior to placebo in reducing weight, BMI and severity of illness, but not in reducing binge-eating behavior or the obsessive-compulsive features of binge-eating symptoms in subjects with BED and obesity. In light of the study’s limitations, however, these findings should be considered preliminary, and in need of replication in larger, longer-term trials with a broader range of subjects with BED and obesity.

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REFERENCES


