Effectiveness of Fluoxetine Therapy in Bulimia Nervosa Regardless of Comorbid Depression

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Abstract: **Objective:** *To evaluate fluoxetine efficacy in the treatment of bulimia nervosa patients with or without comorbid depression.* **Method:** *Two parallel, multicenter, double-blind, randomized, placebo-controlled fluoxetine clinical trials were retrospectively analyzed to determine the effect of comorbid depression on bulimia treatment response. Patients were stratified by their 21-item Hamilton Rating Scale for Depression ($HAMD_{21}$) scores at baseline and by the presence or absence of historical or current depression. Change from baseline to endpoint in the number of binge eating and vomiting episodes was used to assess efficacy.* **Results:** *Fluoxetine 60 mg treatment statistically significantly reduced* ($p < .05$) *the median number of binge eating and vomiting episodes. These improvements were independent of baseline $HAMD_{21}$ score and of historical or current comorbid depression diagnosis.* **Discussion:** *Fluoxetine 60 mg was effective in treating bulimia nervosa, regardless of the presence or absence of comorbid depression. Fluoxetine's efficacy in treating bulimia nervosa is not simply a secondary effect of its antidepressant properties. © 1999 by John Wiley & Sons, Inc.* Int J Eat Disord 25: 19–27, 1999.

Key words: *eating disorder; binging; vomiting; SSRI*

INTRODUCTION

Bulimia nervosa affects 1.3% to 10.1% of women (Pope, Hudson, & Yurgelun-Todd, 1984; Pope, Champoux, & Hudson, 1987; Shotte & Stunkard, 1987; Thelan, McLaughlin, Pruitt, & Smith, 1987). It is manifested by binge eating associated with loss of control and

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by purging activities, primarily vomiting. Medical complications of purging include electrolyte abnormalities, potential cardiac arrhythmia, and esophageal erosion. In addition to these medical complications, there is a high frequency of psychiatric comorbidity among bulimia patients. Major depressive disorder (MDD) is present in 60% to 80% of patients with bulimia (Mitchell, Soll, Eckert, Pyle, & Hatsukani, 1989; Zerbe, 1992) and may lead to suicidality (Mitchell, Seim, Colon, & Pomeroy, 1987).

As the incidence of bulimia nervosa increases (Mitchell et al., 1987), new treatments are being investigated to improve outcomes. Currently available nonpharmacological approaches consist of cognitive, behavioral, and other forms of counseling. Other potential therapies, including pharmacotherapy with antidepressants, have also been explored (Walsh, 1991). Many antidepressants, including fluoxetine, have been evaluated for the treatment of patients with bulimia nervosa (Pope, Hudson, Jonas, & Yurgelun-Todd, 1983; Hughes, Wells, Cunningham, & Ilstrup, 1986; Agras, Dorian, Kirkley, Arnow, & Bachman, 1987; Levine & the Fluoxetine Bulimia Nervosa Collaborative Study Group, 1992). Most of these studies have demonstrated improvements in binge eating and vomiting (Price & Babai, 1987), as well as in cognitive function (Goldbloom & Olmsted, 1993). Whether the effectiveness of antidepressant therapy is a direct effect on the bulimia nervosa itself, or is a secondary consequence of improving comorbid depression, has been questioned.

Fluoxetine therapy was presumed to be effective in patients without comorbid depression due to a direct treatment effect on bulimia nervosa (Levine & the Fluoxetine Bulimia Nervosa Collaborative Study Group, 1992; Goldstein et al., 1995). To assess the effects of fluoxetine therapy in bulimia patients with or without comorbid depression, data from two large, multicenter studies were retrospectively analyzed. To investigate the influence of comorbid depression on treatment, two surrogates were used. Patients were grouped by their baseline score on the 21-item Hamilton Rating Scale for Depression ($HAMD_{21}$) and by the presence of a current diagnosis or absence of a current or historical diagnosis of depression.

METHODS

Description of Clinical Trials

Data from two parallel, multicenter, double-blind, randomized, placebo-controlled, clinical trials were retrospectively analyzed. The first was a 13-site, 8-week trial ($N = 383$) comparing fluoxetine 60 mg ($n = 127$) or 20 mg ($n = 128$) treatment with placebo ($n = 128$) treatment for the management of bulimia nervosa (Levine & the Fluoxetine Bulimia Nervosa Collaborative Study Group, 1992). The second site was a 15-site, 16-week trial ($N = 390$) comparing fluoxetine 60 mg ($n = 290$) treatment with placebo ($n = 100$) treatment in long-term management of bulimia nervosa (Goldstein et al., 1995).

Description of Patients and Subgroups

Baseline characteristics of the patients in the two trials are presented in Table 1. The 382 female patients in the 8-week trial were 97% ($n = 370$) Caucasian with a mean age of 25 years and a mean body mass index (BMI) of 22 kg/m^2 at baseline. The 390 patients in the 16-week trial were 97% ($n = 378$) female, 97% ($n = 378$) Caucasian with a mean age of 27 years and a mean BMI of 21 kg/m^2 at baseline. Median baseline number of episodes per week in the 8- and 16-week trials was eight and nine for binge eating and seven and nine for vomiting, respectively.

$HAMD_{21}$ scores and reports of historical and current illnesses were recorded at baseline. The baseline median $HAMD_{21}$ of 12 for both trials was used to stratify patients by the severity of depressive symptomatology into ''high-score'' ($HAMD_{21}$ score $\geq$12) and ''low-score'' ($HAMD_{21}$ score <12) subgroups. Current and historical depression, as recorded on the clinical report form at baseline, was also used to stratify patients into (a) those who reported current depression; (b) those who reported no current or historical depression; and (c) those who reported historical depression but not current depression.

The correspondence between the two stratifications, that is, the $HAMD_{21}$ subgroups and the baseline diagnostic subgroups, was evaluated. Of the total of 193 patients (125 in the 8-week trial and 68 in the 16-week trial) in the diagnostic subgroup with current depression, 141 (73.1%) had a $HAMD_{21}$ total score $\geq$12 at baseline, consistent with an expected score for patients with active depressive symptoms. Of the total of 527 patients (234 in the 8-week and 293 in the 16-week trials) in the diagnostic subgroup with no current or historical depression, 329 (62.4%) had a $HAMD_{21}$ total score <12 at baseline, consistent with an expected score for patients never diagnosed with depression. In contrast, of the total of 52 patients (23 in the 8-week and 29 in the 16-week trials) in the diagnostic subgroup with historical depression but not current depression, only 14 (26.9%) patients had a $HAMD_{21}$ total score $\geq$12 at baseline. Because depression recurrence is common, more patients in this diagnostic subgroup were expected to have a $HAMD_{21}$ total score $\geq$12 at baseline, indicating relatively low correspondence between these strata. Due to this low correspondence as well as to the small sample size per treatment (in the 8-week trial, $n = 6$, $n = 10$, and $n = 7$ patients in the fluoxetine 20 mg, fluoxetine 60 mg, and placebo treatments, respectively; in the 16-week trial, $n = 24$ and $n = 5$ patients in the fluoxetine 60 mg and placebo treatments, respectively), this subgroup of patients was excluded from statistical analysis and further discussion.

Statistical Methods

To assess the effects of severity of depressive symptomatology and comorbid depression on fluoxetine efficacy in the treatment of bulimia nervosa, reductions in the number of binge eating and vomiting episodes from baseline to endpoint were used as measures of efficacy in the two trials. Due to the nonnormal distribution of binge eating and vomiting data, statistical analyses were conducted on rank-transformed data instead of the original scale (Conover & Iman, 1981) and medians were used instead of means as summary measures.

An analysis of variance (ANOVA) model including parameters for treatment, investigator, and their interaction was fitted to rank-transformed percent change in the number of binge eating and vomiting episodes from baseline to endpoint, for each subgroup of patients (i.e., high-score $HAMD_{21}$, low-score $HAMD_{21}$, presence of current diagnosis of depression, and absence of current or historical diagnosis of depression) for each trial. A reduced model, with parameters for treatment and investigator effects only, was fitted to the data in cases where the treatment-by-investigator interaction was shown to be nonsignificant ($p \geq .10$). All patients with baseline and at least one postbaseline measurement were included in the analysis.

Subsequent to the ANOVA, pairwise comparisons were conducted to compare treatments in each subgroup for the 8-week trial.

All tests of significance (except for interaction) were carried out at the two-sided probability level of .05.

Table 1. Baseline characteristics of patients in the 8- and 16-week bulimia nervosa trials

	Study 1 8-Week Trial	Study 2 16-Week Trial
Number of patients	382	390
Caucasian (%)	97	97
Female (%)	100	97
Age (mean years)	25	27
Body mass index (mean kg/m^2)	22	21
Binge eating episodes/week (median)	8	9
Vomiting episodes/week (median)	7	9
$HAMD_{21}$ score (median)	12	12

Note: $HAMD_{21}$ = 21-item Hamilton Rating Scale for Depression.

RESULTS

Data stratified by $HAMD_{21}$ at baseline showed that fluoxetine 60 mg treatment, compared with placebo treatment, significantly reduced binge eating and vomiting episodes in the low-score ($p = .024$ and $p = .003$, respectively) and high-score ($p = .032$ and $p = .002$, respectively) subgroups in the 8-week trial (Figure 1). Similarly, for the 16-week trial, fluoxetine 60 mg treatment, compared with placebo treatment, significantly reduced binge eating and vomiting episodes in the low-score ($p = .002$ and $p = .002$, respectively) and high-score ($p = .042$ and $p = .027$, respectively) subgroups (Figure 2).

In the 8-week trial, fluoxetine 20 mg treatment statistically significantly reduced vomiting episodes ($p = .014$) and tended to reduce binge eating episodes ($p = .120$) in the low-score subgroup. Fluoxetine 20 mg treatment did not statistically significantly reduce binge eating ($p = .476$) or vomiting ($p = .532$) in the high-score subgroup of this trial (Figure 1).

Pairwise comparison of the two fluoxetine dosages in the 8-week trial showed no significant differences between fluoxetine 60 and 20 mg treatments in reducing the median number of binge eating and vomiting episodes ($p > .05$) in the low-score subgroup. In the high-score subgroup in the same trial, fluoxetine 60 mg treatment resulted in significantly higher reduction in binge eating ($p = .004$) and vomiting ($p = .011$) episodes than the 20 mg treatment group (Figure 1).

The same analyses were performed for bulimia stratified by the presence of current depression or absence of current or historical depression for each trial. In both trials, fluoxetine 60 mg treatment compared to placebo treatment significantly reduced binge eating episodes in the current depression and in no current or historical depression diagnostic subgroups ($p = .044$ and $p = .005$, respectively, for the 8-week trial and $p = .005$ and $p = .011$, respectively, for the 16-week trial). Fluoxetine 60 mg treatment also statistically significantly reduced vomiting episodes in both diagnostic subgroups ($p = .005$ and $p = .0004$, respectively, for the 8-week trial and $p = .001$ and $p = .005$, respectively, for the 16-week trial; Figure 3 and Figure 4).

In the 8-week trial, fluoxetine 20 mg treatment showed no significant difference from placebo treatment in reducing binge eating ($p = .742$) and vomiting ($p = .353$) episodes in patients reporting current depression (Figure 3). Fluoxetine 20 mg treatment also showed no significant difference from placebo treatment in reducing binge-eating ($p = .461$) and vomiting ($p = .093$) episodes in patients reporting no current or historical depression at baseline (Figure 3).

A comparison of the two fluoxetine dosages in the 8-week trial showed a treatment

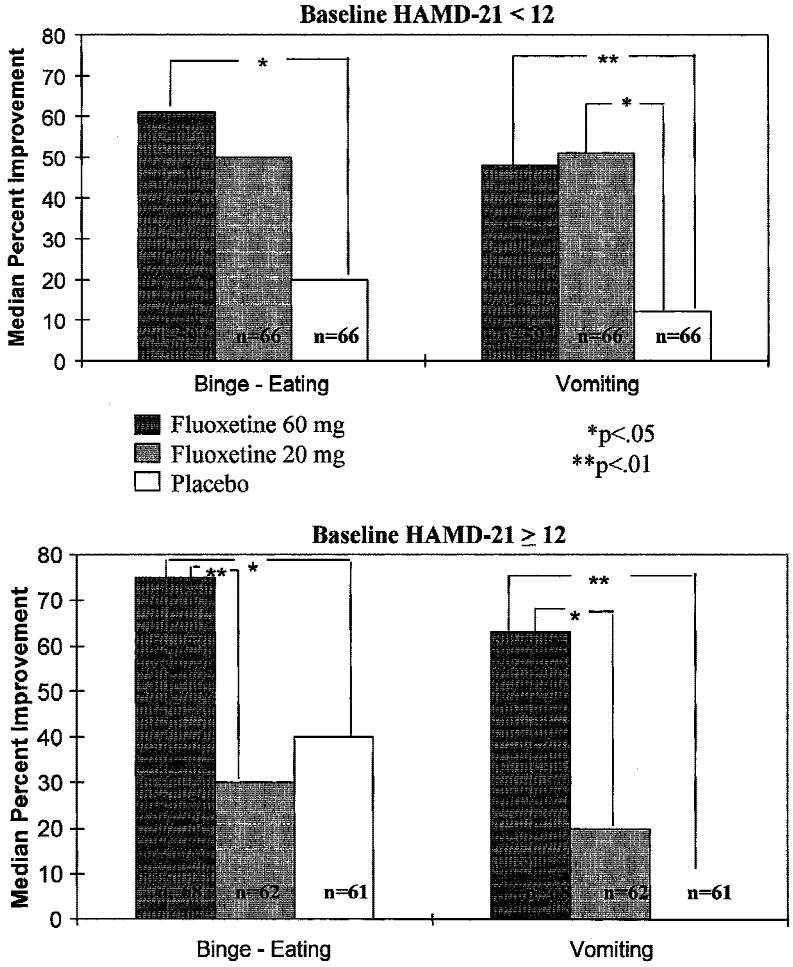

Figure 1. Comparison of the treatment effects of fluoxetine 60 mg, fluoxetine 20 mg, and placebo on the median percent improvement in binge eating and vomiting episodes for the 8-week trial by baseline $HAMD_{21}$ category of scores <12 and ⩾12.

advantage of fluoxetine 60 mg over fluoxetine 20 mg in reducing binge eating (p = .028) and vomiting (p = .043) episodes in patients who reported no current or historical depression at baseline (Figure 3). Similarly, in bulimia patients who reported current depression at baseline, fluoxetine 60 mg treatment produced significantly higher reduction than fluoxetine 20 mg treatment in binge eating episodes (p = .023). Fluoxetine 60 mg treatment also produced higher reduction than fluoxetine 20 mg treatment in vomiting episodes in this subgroup, although in this case the reduction approached, but did not reach, borderline significance (p = .069; Figure 3).

DISCUSSION

The results from the two trials showed that treatment with fluoxetine 60 mg was effective in reducing binge eating and vomiting episodes in bulimia nervosa patients,

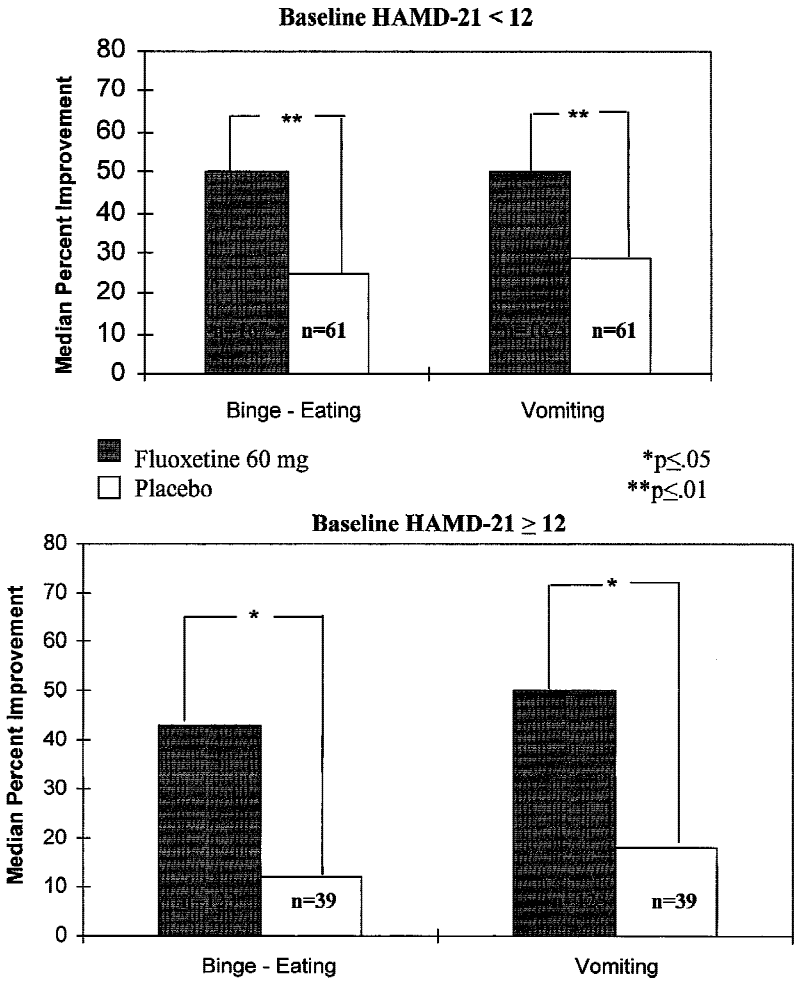

Figure 2. Comparison of the treatment effects of fluoxetine 60 mg versus placebo on the median percent improvement in binge eating and vomiting episodes for the 16-week trial by baseline $HAMD_{21}$ category of scores <12 and ⩾12.

independent of the presence or absence of depressive symptomatology (as measured by $HAMD_{21}$ at baseline) and also independent of baseline depression diagnosis. That is, fluoxetine 60 mg is effective in treating bulimia nervosa regardless of the presence or absence of comorbid depression. In contrast, treatment with fluoxetine 20 mg was statistically significantly effective in reducing vomiting episodes and tended to reduce the number of binge eating episodes in patients with low $HAMD_{21}$ scores only. These results indicate that though depression might serve as a marker of more severe bulimia nervosa (American Psychiatric Association [APA], 1994), fluoxetine's therapeutic effect is not simply a secondary outcome of its antidepressant properties.

A potential weakness of this study is that baseline diagnosis was assessed by patient history and not by a clinician-rated tool such as the Structured Clinical Interview for Depression (SCID). However, the relatively high correspondence between patient's reported diagnosis and $HAMD_{21}$ total scores at baseline in the two subgroups of patients,

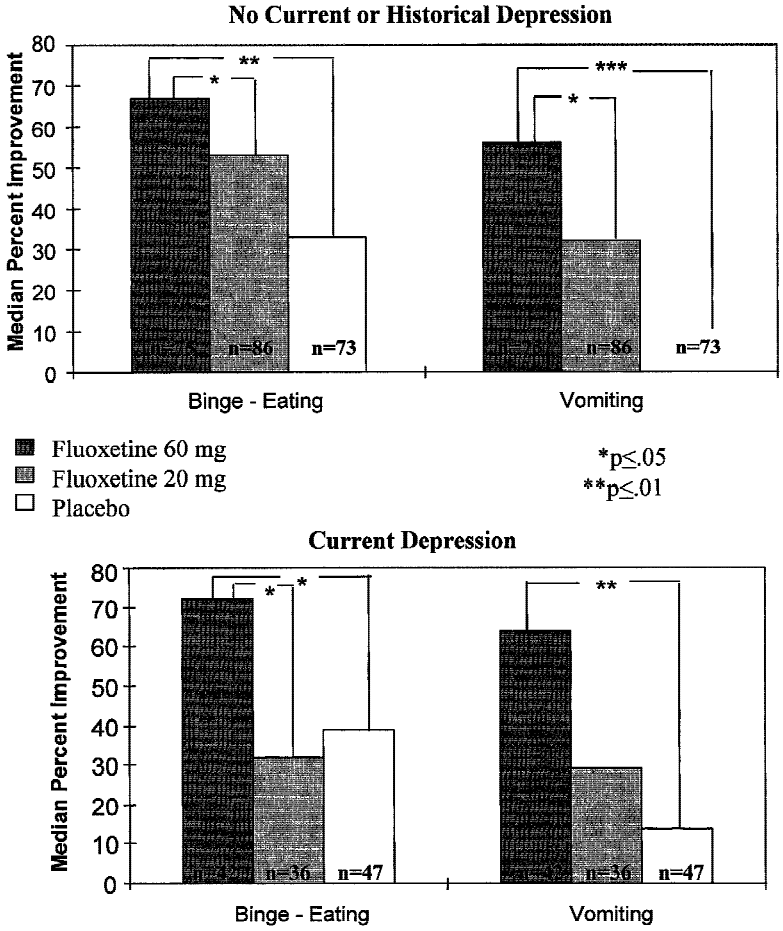

Figure 3. Comparison of the treatment effects of fluoxetine 60 mg, fluoxetine 20 mg, and placebo on the median percent improvement in binge eating and vomiting episodes for the 8-week trial by baseline report of the presence of depression or absence of current or historical depression.

that is, those who reported current depression and those who reported no current or historical depression at baseline, suggests that either of these assessments could serve as a weak surrogate for a more precise diagnostic measure.

Several hypotheses have been proposed explaining fluoxetine's direct effect in treating bulimia nervosa. The two most prominent relate to fluoxetine's effect on satiety. It has been suggested that the satiety-enhancing effects of fluoxetine may help to enhance restraint (Leibowitz, 1990). Because this effect appears to be dose related (Levine et al., 1989), it may be that patients with more severe bulimia nervosa require the higher dose to produce adequate restraint. Interestingly, the placebo response rate appears to be consistently lower in the depressed patients in the longer trial (Figures 2 and 4). This difference may reflect the fact that patients with comorbid mood disorders are more resistant to treatment (APA, 1994). This would also explain why patients with higher $HAMD_{21}$ scores and those reporting comorbid depression required higher doses of fluoxetine.

Alternatively, it has been proposed that the abnormal satiety response in patients with

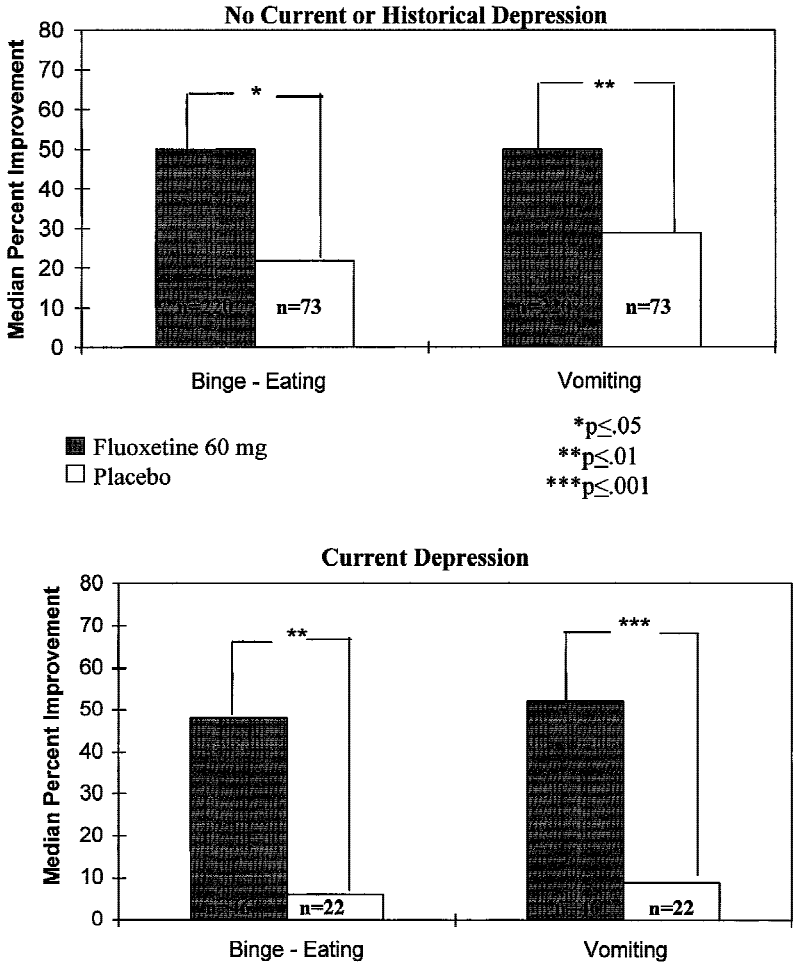

Figure 4. Comparison of the treatment effects of fluoxetine 60 mg versus placebo on the median percent improvement in binge eating and vomiting episodes for the 16-week trial by baseline report of the presence or absence of current or historical depression.

bulimia nervosa may be related to abnormal vagal tone (Pyle, Mitchell, & Eckert, 1981; Kennedy & Heslegrave, 1989). Fluoxetine may help to restore normal vagal tone in bulimia patients, improving peripheral gastrointestinal signals. Once these signals are restored, patients may have a reduced urge to binge, thus breaking the binge eating and purging cycle that characterizes this disorder. Regardless of the mechanism of action, these trials establish that fluoxetine 60 mg is effective in treating moderate to severe bulimia nervosa outpatients even in the absence of comorbid depression.

Furthermore, the efficacy of fluoxetine 20 mg in reducing vomiting episodes in patients with low $HAMD_{21}$ scores suggests that the initiation of treatment of bulimia with fluoxetine 20 mg may be beneficial for certain patients with low $HAMD_{21}$ scores. Because patients in bulimia trials, on average, begin to show improvement after 1 week of fluoxetine therapy (Levine & the Fluoxetine Bulimia Nervosa Collaborative Study Group, 1992; Goldstein et al., 1995), this dosage should be increased to 60 mg after 1 week if no response is observed.

It is not known whether fluoxetine's efficacy in the treatment of bulimia nervosa with or without comorbid depression is a unique or a more general effect. Since 20 mg was effective in patients with low baseline depression symptoms but not those with high baseline depression symptoms, and because 60 mg was effective in patients with both high and low baseline depression symptoms, the antidepressant effect of fluoxetine does not appear to be the mechanism for improvement of bulimia nervosa. Our results indicate that fluoxetine's therapeutic effect in bulimia nervosa patients is not simply a secondary result of its antidepressant properties.

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