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Long-Term Fluoxetine Treatment of Bulimia Nervosa

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Background. A large collaborative 8-week study has shown fluoxetine to be effective and safe in treating patients with bulimia nervosa. The present study evaluated fluoxetine over 16 weeks.

Method. Fifteen US out-patient psychiatry clinics conducted a double-blind parallel study in men and women with DSM–III–R bulimia nervosa (483 patients entered, 398 randomised [3:1 ratio, fluoxetine 60 mg/day or placebo], 225 completed). Outcome measures included change in vomiting and binge-eating episodes per week, Eating Disorder Inventory, Clinical Global Impressions and Patient's Global Impression.

Results. Compared with placebo, fluoxetine treatment resulted in significantly greater reductions in vomiting ($F[1,360] = 14.73$, $P<0.0001$) and binge-eating ($F[1,360] = 14.39$, $P=0.0002$) episodes per week at endpoint and improvement in other outcome measures. Adverse event, vital sign and laboratory analyses indicated that fluoxetine was safe.

Conclusion. Fluoxetine appeared to be safe and effective in patients with bulimia nervosa for up to 16 weeks.

Bulimia nervosa is a public health problem estimated to affect at least 1.3% of American women (Mitchell *et al*, 1987) of all socio-economic classes (Pope *et al*, 1987). Characterised by uncontrolled binge-eating and self-induced purging by vomiting or laxative abuse, or other patterns of behaviour to prevent weight gain (DSM–III–R; American Psychiatric Assocation, 1987), untreated bulimia nervosa is associated with increased morbidity and, occasionally, mortality (Patton, 1988).

Antidepressant treatment has been shown to reduce the frequency of binge-eating and purging in bulimia nervosa (Mitchell *et al*, 1993). The effectiveness of fluoxetine hydrochloride, a serotonin uptake inhibitor, in the treatment of bulimia nervosa has previously been reported in two 8-week double-blind trials (Fichter *et al*, 1991; Fluoxetine Bulimia Nervosa Collaborative Study Group, 1992). Less is known about its use for longer periods. The present study compared fluoxetine with placebo in the treatment of patients with bulimia nervosa to assess the safety and effectiveness of fluoxetine (60 mg) over a 16-week double-blind treatment period.

Method

Study design

This multicentre study, conducted at 15 sites in the US, began with a 1-week drug-free prescreening period followed by a 2-week single-blind placebo lead-in. Placebo responders (i.e. patients who had a 75% decrease in the number of vomiting episodes or less than three vomiting episodes per week during the placebo lead-in) were excluded. Patients were randomly assigned to 16 weeks of double-blind therapy with fluoxetine (60 mg/day) or placebo in a 3:1 ratio. The protocol was approved by each investigator's institutional review board, and all patients gave written informed consent prior to enrolment.

The sample size and allocation ratio were selected such that an estimated 100 fluoxetine-treated patients would complete the 16-week study. The effective sample size was 150, based on the harmonic mean (Cohn, 1977). For safety, this sample size would give the study at least 80% power to detect a treatment difference of $\geqslant$15% in adverse events commonly reported in fluoxetine clinical trials. For efficacy, this sample size would give the study 74% and 93% power to detect a treatment difference of three and four vomiting episodes per week, respectively, in the analysis of baseline-to-endpoint change. Weekly analyses would have similar power characteristics.

Study population

The study population included male and female out-patients, at least 18 years old, who met DSM–III–R criteria for bulimia nervosa with at least three vomiting episodes per week after binge-eating and a history of bulimia nervosa of at least six months rather than three months. Patients were excluded if they had participated in a prior fluoxetine study, had taken any fluoxetine within the five weeks before enrolment or had taken a cumulative lifetime fluoxetine

dose of more than 140 mg. Patients were also excluded if they had psychosis; acute suicidality; organic brain disease; a history of seizures; a diagnosis of anorexia nervosa; a medically unstable condition; allergy to fluoxetine or a history of severe allergies or multiple adverse drug reactions; or hypertension treated with guanethidine, reserpine, clonidine or methyldopa. Patients who had used a monoamine oxidase inhibitor within two weeks of enrolment or had an anticipated need within five weeks of study completion were excluded, as were those who had used psychoactive medications including lithium and tryptophan in the week before enrolment. Women who were pregnant, lactating or not using medically accepted contraception were excluded. Patients were excluded if they had used any other method of bulimic therapy within one month of entry (Visit 1). Patients were not allowed seizure medications during the trial.

Study procedures

During the placebo lead-in period, patients had a weekly clinic visit with the physician and one interim visit with the physician or study coordinator or both. During the 16-week, double-blind therapy period, patients had clinic visits with the physician every other week for the first four weeks of randomised treatment, then monthly until completion of the study. They had interim visits with the physician or study coordinator or both between each clinic visit.

Efficacy was measured by the change in the number of vomiting and binge-eating episodes per week and ratings on the Eating Disorder Inventory (EDI) (Garner *et al*, 1983), Clinical Global Impressions (CGI) – Severity and Improvement (Guy, 1976), Patient's Global Impression (PGI; Guy, 1976), and 21-item Hamilton Rating Scale for Depression ($HRSD_{21}$) (Hamilton, 1967). The $HRSD_{21}$ was used to measure the presence and severity of depression. Information about bulimic patterns of behaviour was obtained using a preprinted bulimic activity diary given to the patient at each visit. The primary efficacy measure was the change in the number of vomiting episodes per week.

Safety was assessed by evaluation of adverse events that first occurred or worsened during double-blind therapy, vital signs and laboratory tests.

Statistical analyses

Absolute change (endpoint value minus baseline value) and percentage change in vomiting and binge-eating episodes per week from baseline (randomisation, Visit 2) were evaluated by both weekly and endpoint analyses. The weekly analysis included data from all patients active in the study at a given visit. The endpoint analysis included data from all patients with a baseline and at least one post-baseline measurement, with the last observation recorded during double-blind therapy carried forward to endpoint. If data were missing at Visit 2, the measurement recorded at Visit 1 (study entry) was used. For the analysis of percentage change, when the baseline and endpoint values were both zero, endpoint percentage change was defined as zero. When the baseline value was zero and the endpoint value was greater than zero, endpoint percentage change was defined as 1000% increase. The median change was used as the summary statistic of location for these variables.

For continuous efficacy variables, both ranked and unranked data were analysed using analysis of variance with treatment, investigator and treatment-by-investigator interaction as independent variables in the model. Because of the non-normality or skewness of data for most of the variables, only the rank-transformed analyses are presented. If the test for treatment-by-investigator interaction was statistically significant ($P<0.15$), further evaluation of the treatment contrasts among investigators was performed.

A stage-wise rejective modified Bonferroni test was used to control the overall type I error rate when performing weekly analyses of repeated measurements (Hommel, 1988).

A response to therapy was defined as a 50% reduction in bulimic episodes (vomiting, binge-eating) from baseline to the patients' last visit after randomisation. Data were analysed for each response category (remission [100% decrease in number of bulimic episodes], marked response [75–99% decrease], moderate response [50–74% decrease], no response [<50% improvement] and for all responders [≥50% improvement] v. non-responders [<50% improvement]) using Pearson's χ^2 test with 3 d.f. and the Mantel–Haenszel χ^2 test of linear association (Mantel & Haenszel, 1959). Odds ratios were estimated as standard cross-product ratios. The confidence intervals around the odds ratios were computed using Woolf's method (Woolf, 1955).

Reasons for withdrawing from the study, adverse events and categorical change with respect to the reference ranges for clinical laboratory variables were compared between treatment groups using Pearson's χ^2 test with 1 d.f. Ranked and unranked vital sign and continuous clinical laboratory test data and change from baseline to maximum and minimum values were analysed as described above for continuous efficacy variables. Data were analysed from all randomised patients with at least one post-baseline measurement.

Tests of hypotheses were carried out at a two-sided $\alpha = 0.05$ level. All analyses were performed using SAS procedures (SAS Institute, 1985).

Results

Demographics

Of the 483 patients who entered the study, 85 did not meet entry criteria and were excluded from random treatment assignment. Baseline characteristics of the 398 patients randomly assigned to double-blind therapy are given in Table 1. At baseline, the treatment groups were comparable with respect to age, race, weight, bulimic patterns of behaviour and CGI scores. The majority of the patients were women (96.2%) and white (96.7%).

Weekly analysis of change in bulimic episodes

As shown in Fig. 1, compared with placebo-treated patients, fluoxetine-treated patients experienced significantly greater median percentage decreases in number of weekly vomiting episodes through week 10

Table 1
Patient baseline demographic characteristics

Variable	Treatment group	
	Fluoxetine[1]	Placebo[2]
Number randomly assigned	296	102
Women (%)	95.3	99.0
Caucasian (%)	96.6	97.1
Bulimic-type behaviour (%)		
binge-eating	99.0[1]	100.0
vomiting	100.0	99.0[2]
laxative use	16.6	11.8
diuretic use	7.4	6.9
fasting	17.9	14.7
>1 purging behaviour	32.8	27.5
Age (years)[3]	27 (17,63)	26 (17,61)
Weight (kg)[3]	58 (39,132)	58 (43,96)
Bulimic-type behaviour (no.)		
vomiting (episodes/week)[3]	9 (1,94)	9 (0,225)
binge-eating (episodes/week)[1,3]	9 (0,68)	9.5 (1,150)
binge-eating (median days/week)[1,3]	6 (0,15)	6 (1,12)
vomiting (median days/week)[3]	6 (0,15)	5.5 (0,12)
fasting (days/week)[3]	0 (0,7)	0 (0,7)
diuretic abuse (median days/week)[3]	0 (0,14)	0 (0,8)
laxative abuse (median days/week)[3]	0 (0,14)	0 (0,9)
Clinical Global Impression score[3]	5 (3,7)	5 (3,7)

1. Three randomly assigned patients in the fluoxetine group did not exhibit binge-eating behaviour at baseline, but had done so during the placebo lead-in period.
2. One patient in the placebo group did not exhibit vomiting behaviour at baseline, but had done so during the placebo lead-in period.
3. Values are median (minimum, maximum).

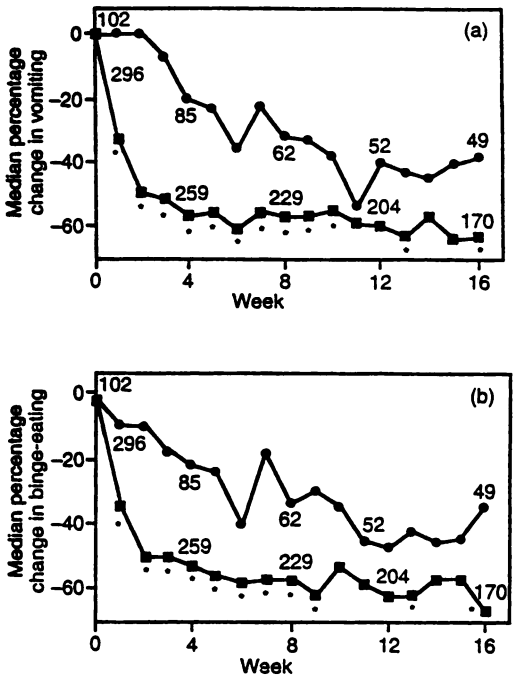

Fig. 1 Median percentage change in the number of vomiting (a) and binge-eating (b) episodes at each week of double-blind therapy. The numbers shown on the graph represent the number of patients remaining in the study at each month. The asterisks denote a statistically significant difference between treatment groups (vomiting, modified Bonferroni $P<0.0167$; binge-eating, modified Bonferroni $P<0.01$). ■, fluoxetine; ●, placebo.

and for weeks 13 and 16 (modified Bonferroni, $P<0.0167$) and significantly greater median percentage decreases in the number of weekly binge-eating episodes through week 9 and for weeks 13 and 16 (modified Bonferroni, $P<0.01$). Fluoxetine appeared to be more effective than placebo in reducing the number of weekly vomiting and binge-eating episodes during the 16 weeks of the study.

As expected in a study with multiple investigators, a statistically significant treatment-by-investigator interaction was observed at some weeks. No treatment contrast within any investigator favoured placebo significantly ($P>0.15$) at any week. The interaction was quantitative only and did not alter the conclusion of a beneficial fluoxetine treatment effect.

The treatment contrast for the weekly analysis was reduced by the differential discontinuation rates for lack of efficacy between fluoxetine (7.8%) and placebo (25.5%) treatments ($\chi^2 = 22.064$, d.f. = 1, $P<0.001$). This contributed to an overall difference in completion rates for the fluoxetine (59.5%) and

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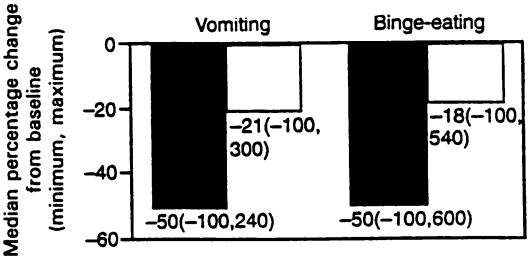

Fig. 2 Median percentage change in vomiting [$F(1,360) = 14.73$, $P < 0.0001$] and binge-eating [$F(1,360) = 14.39$, $P = 0.0002$] episodes per week from baseline to endpoint (last observation carried forward). The numbers shown below the bars reflect the median (minimum, maximum) values. ■, fluoxetine 60 mg, $n = 290$; □, placebo, $n = 100$.

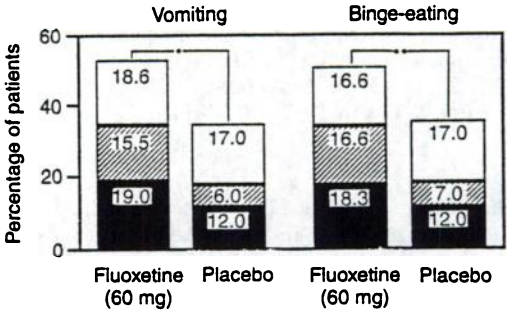

Fig. 3 The percentage who had remission (a 100% reduction) (■), a 75–99% reduction (▨), and a 50–74% reduction (□) in vomiting or binge-eating episodes per week at endpoint. The asterisks denote a statistically significant difference between treatment groups (*$\chi^2 = 9.616$, d.f. = 1, $P = 0.002$; **$\chi^2 = 7.831$, d.f. = 1, $P = 0.005$).

placebo (48.0%) treatment groups ($\chi^2 = 4.026$, d.f. = 1, $P = 0.045$).

Endpoint analysis of change in bulimic episodes

Overall, both treatment groups had similar bulimic activity at baseline (see Table 1). As shown in Fig. 2, compared with placebo-treated patients, fluoxetine-treated patients experienced a significant decrease in median percentage change in vomiting episodes per week (fluoxetine, −50; placebo, −21 [$F(1,360) = 14.73$, $P < 0.0001$]) and in binge-eating episodes per week (fluoxetine, −50; placebo, −18 [$F(1,360) = 14.39$, $P = 0.0002$]).

The 290 fluoxetine-treated and 100 placebo-treated patients who had at least one post-baseline visit had an absolute median change (and range) in number of vomiting episodes per week from baseline to endpoint of −4 (−64, 34) and −2 (−55, 58) [$F(1,360) = 12.47$, $P < 0.0005$] and of binge-eating episodes per week of −4 (−59,30) and −2 (−143, 40) [$F(1,360) = 13.54$, $P = 0.0003$].

Response rates

Fluoxetine-treated patients experienced a significantly greater rate of improvement for both vomiting ($\chi^2 = 9.616$, d.f. = 1, $P = 0.002$) and binge-eating ($\chi^2 = 7.831$, d.f. = 1, $P = 0.005$) episodes per week than placebo-treated patients (Fig. 3). A greater percentage of fluoxetine-treated (19.0%) than placebo-treated patients (12.0%) experienced remission of vomiting.

When patients were classified as responders and non-responders, the proportion experiencing at least a 50% improvement in number of vomiting (53.1 v. 35.0%, $\chi^2 = 9.737$, d.f. = 1, $P = 0.002$) and binge-eating (51.4 v. 36.0%, $\chi^2 = 7.054$, d.f. = 1, $P = 0.008$) episodes per week was nearly twice as great for fluoxetine-treated as for placebo-treated patients.

The odds ratio (95% confidence interval, logit) for response to fluoxetine v. placebo was 2.10 (1.31, 3.37) for vomiting and 1.88 (1.18, 3.00) for binge-eating. Both analyses of response rate support the conclusion that fluoxetine-treated patients experienced greater improvement in the number of weekly vomiting and binge-eating episodes than placebo-treated patients.

Other measures

EDI

A significant [$F(1,239) = 7.74$, $P = 0.006$] treatment benefit was observed in median change from baseline to endpoint on the EDI total score for fluoxetine (−21) compared with placebo (−12). Significant treatment benefits observed on the bulimia (fluoxetine, −6; placebo, −3 [$F(1,267) = 8.85$, $P = 0.003$]) and drive for thinness (fluoxetine, −3; placebo, −1 [$F(1,265) = 4.25$, $P = 0.040$]) subscales indicated a greater reduction in the tendency toward episodes of binge-eating and a greater reduction in concern with an extreme pursuit of thinness among fluoxetine-treated than among placebo-treated patients. No statistically significant differences were observed for the body dissatisfaction [$F(1,262) = 1.18$, $P = 0.279$], ineffectiveness [$F(1,263) = 3.40$, $P = 0.066$], perfectionism [$F(1,264) < 0.01$, $P = 0.993$], interpersonal distrust [$F(1,270) = 1.65$, $P = 0.200$], interoceptive awareness [$F(1,264) = 0.45$, $P = 0.502$], and maturity fears [$F(1,266) = 2.41$, $P = 0.122$] subscales.

CGI and PGI

The greater therapeutic benefit in the fluoxetine group compared with the placebo group was further confirmed by statistically significantly lower median

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(minimum, maximum) CGI and PGI scores in the fluoxetine-treated patients than the placebo-treated patients at endpoint: CGI 2 (1, 6) v. 3 (1, 6) [$F(1,283) = 15.40$, $P < 0.0001$]; PGI 2 (1, 6) v. 3 (1, 5) [$F(1,283) = 16.47$, $P < 0.0001$].

$HRSD_{21}$

The median baseline $HRSD_{21}$ scores were in the non-depressed range in both treatment groups (10 for fluoxetine-treated and 8.5 for placebo-treated patients). Evaluation of change in $HRSD_{21}$ scores from baseline (randomisation) to endpoint indicated that patients in both treatment groups had decreased total scores at endpoint (median of 5 for both fluoxetine-treated and placebo-treated patients). Numerically, fluoxetine-treated patients had a greater median decrease in the total score than the placebo-treated patients, but the median differences (minimum, maximum) between the treatment groups were not statistically significant (fluoxetine, −4 (−21, 20) v. placebo, −3 (−27, 9) [$F(1,275) = 1.85$, $P = 0.175$]).

Safety

Adverse events

Adverse events that first occurred or worsened during therapy with a statistically significant ($\chi^2 < 3.8$, d.f. = 1, $P \leqslant 0.05$) difference in frequency between groups are shown in Table 2 along with corresponding discontinuation rates. Adverse events reported statistically significantly more frequently with fluoxetine than placebo were insomnia, nausea, asthenia, anxiety, tremor, dizziness, yawning, sweating and decreased libido. Adverse events reported statistically significantly more frequently with placebo than fluoxetine were depression, myalgia, emotional lability and conjunctivitis. No patients experienced convulsions. Discontinuations for any adverse event were similar ($\chi^2 = 2.134$, d.f. = 1, $P = 0.144$) with fluoxetine (10.8%) and placebo (5.9%).

Table 2
Incidence of adverse events with a statistically significant difference between treatment groups and corresponding discontinuation rates[1]

Adverse event	Adverse event reports		Discontinuations[2]	
	Fluoxetine $n = 296$ (%)	Placebo $n = 102$ (%)	Fluoxetine $n = 296$ (%)	Placebo $n = 102$ (%)
More common for fluoxetine				
Insomnia	34.5	18.6*	1.7	0
Nausea	30.4	12.7***	0	0
Asthenia	21.3	6.9***	0.7	0
Anxiety	17.6	8.8*	1.0	0
Tremor	14.2	2.0***	0	0
Dizziness	12.5	3.9*	0.3	0
Yawning	12.2	0.0***	0	0
Sweating	9.5	2.0*	0	0
Libido decreased	6.4	1.0*	0	0
More common for placebo				
Depression	10.1	18.6*	1.0	1.0
Myalgia	4.7	11.8*	0	0
Emotional lability	2.7	7.8*	0	0
Conjunctivitis	0.3	2.9*	0	0

1. Ordered by decreasing frequency of fluoxetine 60 mg.
2. None of the treatment differences was statistically significant.
*$P \leqslant 0.05$; ***$P \leqslant 0.001$.

There were no fatal suicidal acts during the trial. Non-fatal suicide attempts were reported in 1.4% (4 of 296) of the fluoxetine-related and 1.0% (1 of 102) of the placebo-treated patients, a non-significant difference ($Z = 0.313$, $P = 0.754$). A comprehensive analysis of suicidality in patients with bulimia nervosa has been reported previously (Wheadon *et al*, 1992).

Vital signs

There were no statistically significant ($P > 0.05$) differences in baseline-to-endpoint change in diastolic or systolic blood pressure, heart rate or temperature. There was a statistically significant [$F(1,355) = 10.77$, $P = 0.001$] difference in baseline-to-endpoint median change in weight for fluoxetine (−0.45 kg) compared with placebo (0.16 kg).

Laboratory evaluations

Although there were statistically significant differences in mean change in certain laboratory analytes from baseline to endpoint (alanine aminotransferase, aspartate aminotransferase, bicarbonate, albumin, serum uric acid, lymphocytes, basophils, platelets), the mean endpoint values were not indicative of drug-related toxicity.

Discussion

Fluoxetine (60 mg/day) was more effective than placebo in reducing the number of bulimic episodes per week, with response rates higher with fluoxetine than with placebo, based on reduction in binge-eating and in vomiting episodes per week. More placebo-treated than fluoxetine-treated patients discontinued the study for lack of efficacy.

Analyses of secondary efficacy measures (EDI, CGI, and PGI) provided further evidence of the beneficial effect of fluoxetine. The changes in EDI scores suggest that patients might have improved quality of life because of enhanced feelings of control

of eating and less preoccupation with thinness, and also that fluoxetine may improve the underlying psychopathology related to obsessive preoccupation with body shape and size, as noted previously (Goldbloom & Olmsted, 1993). CGI and PGI ratings improved significantly more in patients receiving fluoxetine (60 mg) than in those receiving placebo. While no statistically significant treatment differences were observed in $HRSD_{21}$ scores at endpoint, the result was not unexpected since scores were in the non-depressed range in both treatment groups at baseline. Interestingly, more placebo-treated patients than fluoxetine-treated patients reported depression after initiating therapy, suggesting that fluoxetine might have a mood-stabilising effect in patients with bulimia nervosa.

Analyses of adverse event reports and discontinuations, vital signs and clinical laboratory data indicated that fluoxetine was safe and well tolerated over the 16-week period. Discontinuations for an adverse event were similar with fluoxetine and placebo, and $\leqslant 2\%$ of patients discontinued for any individual adverse event. The adverse events reported significantly more frequently with fluoxetine than placebo were similar to those reported previously with fluoxetine over eight weeks (Fluoxetine Bulimia Nervosa Collaborative Study Group, 1992). No patients experienced convulsions, a finding of special note in this patient population. The slight weight loss in fluoxetine-treated patients compared with placebo-treated patients in the present study suggests that there may be a potential advantage of fluoxetine over tricyclic antidepressants, since patients treated with tricyclic antidepressants often gain weight when treated for major depression. The weight-stabilising effect of fluoxetine observed in this study could possibly enhance patient compliance, particularly given this patient population's preoccupation with weight gain.

The results of the present trial are in keeping with those of previously published double-blind controlled fluoxetine studies (Fichter *et al*, 1991; Fluoxetine Bulimia Nervosa Collaborative Study Group, 1992). In a small double-blind trial, Fichter *et al* (1991) compared fluoxetine and placebo in 40 patients with an intensive in-patient behaviour psychotherapy programme over 35 days. Although the results did not demonstrate a statistically significant treatment difference, there was a trend for the fluoxetine-treated patients to have greater improvement on the EDI and in binge-eating than the placebo-treated patients.

The Fluoxetine Bulimia Nervosa Collaborative Study Group (1992) studied 387 bulimic women treated with fluoxetine (20 or 60 mg/day) or placebo for eight weeks in a randomised, double-blind design. Fluoxetine (60 mg) was significantly superior to placebo from the first week of the treatment period. The 60 mg dose was more effective in reducing the number of both vomiting and binge-eating episodes per week than the 20 mg dose, which was more effective than placebo in reducing the number of vomiting episodes per week. The 60 mg treatment group improved by the first week. Adverse event discontinuation rates were generally low (placebo, 8 of 129, 6.2%; fluoxetine 20 mg/day, 4 of 129, 3.1%; fluoxetine 60 mg/day, 11 of 129, 8.5%). Ten adverse events were reported significantly more frequently with fluoxetine than placebo (insomnia, nausea, asthenia, tremor, sweating, urinary frequency, palpitation, yawning, mydriasis, vasodilatation). Few patients discontinued for any single adverse event.

Other antidepressants have also been studied in the treatment of bulimia nervosa and have shown beneficial effects on reduction of binge-eating and purging. In a recent review of controlled trials, Mitchell *et al* (1993) suggested that all antidepressants studied appeared to be similarly effective in the treatment of bulimia nervosa, but that fluoxetine appeared to have fewer side-effects.

Both pharmacological and non-pharmacological therapies have been used for patients with bulimia nervosa (Mitchell *et al*, 1993). Although the effectiveness of these therapies cannot be directly compared because of methodological difficulties and differences in patient populations, both are useful in reducing the symptomatology of bulimia nervosa. Antidepressants may be an effective component of an initial treatment programme for patients with bulimia nervosa. They may be especially beneficial for treating patients who have significant comorbid symptoms of depression, anxiety, obsession or certain impulse disorders, or for patients who have failed prior psychosocial therapy (American Psychiatric Association, 1993).

It is possible that some combination of pharmacological and non-pharmacological therapy may produce even greater benefits than either individually. Mitchell *et al* (1990), Fichter *et al* (1991) and Agras *et al* (1992) studied the combination of antidepressant and non-pharmacological therapy. Mitchell *et al* (1990) and Fichter *et al* (1991) were unable to show greater improvement with pharmacological therapy in combination with counselling than with counselling alone. Agras *et al* (1992) studied 71 patients randomly allocated to treatment with desipramine, cognitive behaviour therapy and the combination. At 16 weeks, cognitive behaviour therapy and combined therapy were superior to medication alone in

reducing binge-eating and purging. The combined therapy given for 24 weeks was the most effective at reducing binge-eating, purging, dietary preoccupation and hunger. Since the earlier two studies (Mitchell *et al*, 1990; Fichter *et al*, 1991) were of shorter duration, Mitchell *et al* (1993) hypothesised that the combination of pharmacological therapy and counselling would be of benefit after longer term therapy.

Since the duration of double-blind therapy in this study was limited to 16 weeks, the results are not generalisable to a longer duration of therapy. It is also not known whether patients would have continued to maintain the level of response or remission of bulimic activity achieved. Blinded studies of the effectiveness of long-term treatment in maintaining response/remission of bulimic activity and of the effect of discontinuation of therapy are needed to further evaluate the benefit of antidepressants in the treatment of bulimia nervosa.

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