Imipramine in the Treatment of Bulimia: A Double-blind Controlled Study

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There were 22 bulimic women who participated in a double-blind placebo-controlled study of the effects of imipramine hydrochloride in the treatment of bulimia over a 16 week period. Participants receiving the active drug demonstrated a significantly greater reduction in purging (frequency of self-induced vomiting plus the use of laxatives) at both the 6 and 16 week assessment periods. Depression was reduced to a significantly greater extent in those receiving the active drug at 6 weeks but not at the 16 week assessment. These findings, from the longest duration medication study in this condition, suggest that imipramine is an effective treatment for bulimia. However, only one-third of the participants receiving imipramine had stopped purging by the end of the study. Thus, clinicians may need to add other approaches, such as cognitive-behavioral treatment, to the management of this condition.

Bulimia, a disorder characterized by episodic binge eating and often accompanied by self-induced vomiting and excessive laxative use, ap-

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pears to be a widespread and perhaps increasingly prevalent disorder. Estimates of the prevalence of bulimia in young women using DSM-111 criteria range from 1.0 to 5.9% (e.g., Cooper & Fairburn, 1983; Halmi, Falk, & Schwartz, 1981; Pyle, Mitchell, Eckert, Halvorson, Newman, & Gobb, 1983; Stangler & Printz, 1980). The complications of this disorder include menstrual disturbances, dental problems, potassium depletion, and often severe mood disturbances. The rapid rise in the number of young women seeking treatment for bulimic symptoms, and the paucity of controlled treatment studies, necessitates an intensive effort to test effective approaches to the treatment of this chronic and often disabling condition.

Two major approaches to treatment are emerging, the use of antidepressant therapy (Mitchell & Groat, 1984; Pope, Hudson, Jonas, & Yurgelun-Todd, 1983; Sabine, Yonace, Farrington, Barrat, & Wakeling, 1983; Walsh, Stewart, Roose, Gladis, & Glassman, 1984) and cognitive behavioral treatment (Fairburn, 1981; Kirkley, Schneider, Agras, & Bachman, 1985; Lacey, 1983). The use of antidepressants was sparked by the observation that dysphoria is frequently found in bulimia (e.g., Weiss & Ebert, 1983), and that major affective disorder occurs with an unexpectedly high frequency in the first degree relatives of bulimics (Hudson, Pope, Jonas, & Yurgelun-Todd, 1983). These observations suggested that bulimia may be a form of affective disorder, or that, alternatively, antidepressants reduce the urge to binge by reducing anxiety and depression. In one short-term controlled study of the use of imipramine, those receiving the active drug reduced binging by 70% after 6 weeks, whereas the placebo group showed little change (Pope et al., 1983). Changes in the Hamilton Depression Ratings were correlated with improvement in binge eating (r = .65).

In an 8 week controlled trial of the monoamine-oxidase inhibitor phenelzine, binge eating was reduced by 75% for those receiving the active medication as compared with 5% for those receiving placebo (Walsh et al., 1984). The authors note that patients who showed no signs of depression responded as well as those who were depressed or had a past history of major depression. Two further trials, however, raised questions about the efficacy of antidepressant treatment in bulimia. In one of these studies, patients treated with mianserin showed no greater improvement in depression, eating attitudes, or frequency of binge eating than patients treated with placebo (Sabine et al., 1983). In the second study, no advantage for a group receiving amitriptyline was found, although both medication and placebo groups showed substantial improvement over the 10 week duration of the study (Michell & Groat, 1984). The improvement in both groups may have resulted from the adjunctive use of self-monitoring and reinforcement for improvement. Although not statistically significant, those receiving the active drug showed a greater improvement on all the measures of eat-

ing behavior, and those with more severe depression improved less than those not showing depression.

The effectiveness of relatively simple behavior change procedures in the treatment of bulimia was recently delineated in a controlled study of cognitive behavioral treatment (Kirkley et al., 1985). While the group receiving the full treatment package showed significantly more improvement than the control group, the latter group that received self-monitoring and reinforcement for progress showed a very substantial change. Comparable results were found in another controlled group therapy study using similar procedures (Lacey, 1983). These results point to the need to carefully control interventions that may be therapeutic in pharmacologic studies of bulimia.

In the present study, therefore, participants were randomly allocated to either imipramine or placebo treatment in a double-blind design, while the interaction between therapist and patient was carefully controlled to exclude all other therapeutic intervention. Thus, the study was designed to delineate the specific effects of imipramine. Patients in both groups were treated for 16 weeks, thus substantially extending the length of active treatment for a controlled drug study of bulimia.

METHODS

Subjects

The participants in this study were recruited from female patients presenting at the Stanford Eating Disorders Clinic and from persons responding to advertisements describing the study. The nature of the study was explained to each potential participant, and their consent to participate was obtained. Potential participants were then interviewed clinically to ensure that they met DSM-III criteria for bulimia. Exclusion criteria included (1) a diagnosis of concurrent anorexia nervosa, alcoholism, drug addiction, or psychosis; (2) significant suicidal ideation; (3) a previous history of the use of antidepressants for bulimia; (4) age below 18 years. Those meeting the initial entry criteria were asked to monitor their eating behavior, self-induced vomiting, and each episode of the use of laxatives for 1 week using a standard diary. If subjects reported two or more episodes of binge eating followed by self-induced vomiting or laxative use during this week, they were entered into the study.

Experimental Design

Following completion of the baseline procedures, participants were randomly allocated to receive either imipramine or placebo. There were

22 participants entered into the study, 2 being replacements for dropouts from the placebo group. Of those remaining in the study and completing 16 weeks of treatment, 10 received imipramine, and 10 received placebo.

Procedures

Once entered into the study, participants were followed by 1 of 2 physicians for 16 weeks. Neither the physician nor the patient knew whether the active drug or placebo was being prescribed. Visits were held weekly for the first 4 weeks of participation in the study and thereafter at 2 week intervals for a total of 10 visits. Medication was prescribed according to the following maximum dose schedule: One pill (50 mg) for the first 3 days, 2 pills for the next 4 days, 3 pills for the second week, 4 pills for the third week, 5 pills for the fourth week, and 6 pills (300 mg), the maximum dose, for the remainder of the study. Participants were asked to take the medication in a single dose at bedtime. Adjustments to the maximum dose schedule were made according to the therapeutic and side effects reported by the patient, occurrence of intercurrent illness, and reported compliance.

A standard interview protocol was followed at each visit in order to preclude the use of behavior change procedures, such as self-monitoring or reinforcement. The physician questioned the patient about compliance with the medication regimen, side effects to the medication, the amount of binge eating and purging during the past week, life style changes, depression, intercurrent illness and visits to a physician, and the taking of other medication. Advice was given only about medication dosage and methods to improve compliance and ameliorate the side-effects of medication. Each interview lasted some 15 min.

Measures

The main measures of outcome were the participants monitoring of binge eating, self-induced vomiting, and laxative use. Incidents of self-induced vomiting and laxative use were summed to obtain a measure of purging. The self-monitoring diary was completed for 7 days during baseline and during the sixth and sixteenth study weeks. The 6 week measurement was used to allow comparability with the Pope et al. (1983) study previously discussed. To ensure as unbiased a self-report as possible, the participant completed the diary and sealed it in an envelope that was opened only by the measurement team. The participant was told that the prescribing physician would not be aware of the results of this measure. In addition, the Beck Depression Inventory (BDI) (Beck, Ward, Mendelsohn, Mock, & Erbaugh, 1961) and the Eating Attitudes Test (Garner & Garfinkel, 1979) were administered at the

same time intervals. As noted earlier, participants were also asked to recall the number of episodes of binge eating and self-induced vomiting during the past week at each visit. This self-recall was used to study the process of change over the course of the study.

RESULTS

The major baseline variables for each participant, listed by group, are shown in Table 1. The participants in this study, all women, had a mean age of 30.9 years (range 21–48 years), a mean duration of bulimia of 8.7 years (range 1–32 years), and a mean Beck Depression score of 17.8 (range 1–41). They purged on the average 11.8 times per week (range 2–25). There were no significant differences between the groups on any of the baseline measures. There were two drop-outs from the study, both from the placebo group. Both of these participants complained of intolerable side effects from the medication. As noted previously these two subjects were replaced.

Table 1. Characteristics and treatment response for participants receiving imipramine or placebo.

			Baseline		16 Weeks	
Subject	Age (yrs)	Duration Bulimia (yrs)	BDI	Purges Per Week	BDI	Purges Per Week
Imipramine Group						
1	44	32	1	14	0	13
2	42	22	16	22	4	0
3	21	3	5	8	0	0
4	35	21	28	3	15	1
5	24	5	6	9	2	2
6	24	5	32	17	22	2
7	30	12	16	4	7	1
8	35	3	29	10	11	0
9	25	5	11	7	13	7
10	23	4	24	13	9	4
$\bar{X}$	30.3	9.6	16.8	10.7	8.3	3.0
Placebo Group						
1	26	1	27	12	29	3
2	31	7	13	13	29	3
3	27	6	4	8	2	5
4	27	8	4	2	2	2
5	26	3	17	25	10	19
6	33	3	33	10	7	0
7	25	5	20	7	13	4
8	38	14	20	13	19	7
9	34	8	9	22	0	14
10	48	25	41	17	30	25
$\bar{X}$	31.5	7.8	18.8	12.6	14.2	8.2

The baseline, 6 week, and 16 week measures for both groups are shown in Table 2, and the posttreatment depression scores and purging rates for each individual are shown in Table 1. The mean dose of medication in the imipramine group was 186 mg at 6 weeks, and 167 mg at 16 weeks; in the placebo group the dosage was 281 mg at 6 weeks and 300 at 16 weeks. The participants receiving imipramine decreased their purging by 44% at 6 weeks, and by 72% at 16 weeks compared to decreases in the placebo group of 12 and 35%, respectively. A comparison of the percentage change in purging, using the Students *t*-test (one-tailed), revealed that at both 6 weeks and 16 weeks the difference between the groups was significant ($t = 2.04$, $p < .02$ and $t = 1.78$, $p < .05$). Within-group analyses revealed that the rate of purging in the placebo group was not significantly different from baseline at 6 weeks, but that at 16 weeks the improvement was statistically significant ($t = 2.4$ $p < .04$). Three individuals in the imipramine group were free of purging at the 16 week assessment, as compared with one person in the placebo group.

The changes in binge eating paralleled those for purging. Those receiving imipramine improved significantly more than those in the placebo group at both 6 weeks ($t = 1.91$, $p < .04$) and at sixteen weeks ($t = 1.76$, $p < .05$). Within-group analysis revealed that the changes in the placebo group were not significant at 6 weeks, but that they were at 16 weeks ($t = 2.37$, $p < .04$). The participants receiving imipramine showing a decline in depression, as measured by the BDI of 46% at 6 weeks and 51% at 16 weeks; whereas those receiving placebo showed declines of 24 and 25%, respectively. These differences are significant between the groups at 6 weeks ($t = 1.77$, $p < .05$) but not at 16 weeks

Table 2. Baseline and 6 week and 16 week posttreatment measures for women receiving either imipramine or placebo (standard deviations in brackets).

	Baseline	6 Weeks	16 Weeks
Imipramine Group ($n = 10$)			
Binge Eating (rate/week)	11.6 (6.35)	7.1 (7.8)	3.2 (2.51)
Purging (rate/week)	10.7 (5.89)	6.0 (7.26)	3.0 (4.14)
Beck Depression Scale	16.8 (11.04)	9.1 (7.11)	8.3 (7.15)
Eating Attitudes Scale	29.5 (12.7)	25.2 (13.5)	22.0 (12.9)
Medication Dosage (mg)	0	186	167
Placebo Group ($n = 10$)			
Binge Eating (rate/week)	13.0 (8.4)	10.2 (6.83)	7.4 (7.2)
Purging (rate/week)	12.6 (7.23)	11.1 (6.23)	8.2 (8.31)
Beck Depression Scale	18.8 (12.18)	14.2 (8.36)	14.1 (11.9)
Eating Attitudes Scale	39.2 (8.9)	33.5 (14.4)	30.8 (15.5)
Medication Dosage (mg)	0	281	300

($t = 1.46$, $p < .08$). Within-group analysis revealed that the changes in the placebo group were not significant at either 6 or 16 weeks, but that the changes in those receiving medication were significant at both 6 ($t = 3.56$, $p < .006$) and 16 weeks ($t = 4.21$, $p < .003$). To examine the question whether there was a relationship between level of depression and outcome, correlations between the initial scores on the Beck Depression Inventory, and outcome in terms of changes in binge eating and in purging, were examined within each group and for both groups combined. No significant association was found.

Changes in the Eating Attitudes Test were not significantly different between the groups at either 6 or 16 weeks. Within group analysis revealed no significant difference at either 6 or 16 weeks for those in the placebo group and a significant difference only at 16 weeks for those receiving imipramine ($t = 1.82$, $p < .05$).

Turning to a consideration of the process of change, the cumulative number of weeks in which subjects were free of self-induced vomiting, an indication of increasing self-control over the binge-purge cycle is shown in Figure 1. As can be seen, there is a considerable advantage for those receiving imipramine, with the curves beginning to separate after 3 weeks of treatment. A chi-square comparison of the proportion of vomiting-free weeks in each group revealed a significant advantage for those receiving imipramine (chi-square = 7.47, $p < .01$).

In an attempt to discover potential predictors of outcome, the correlations between baseline variables such as age, duration of bulimia, baseline scores on the Eating Attitudes Test, lowest reported body mass index (BMI = Wt (kg)/Ht $(m)^2$), and reduction in purging were examined. The only baseline variable associated with reduction in purging in either group at 16 weeks was the lowest reported body

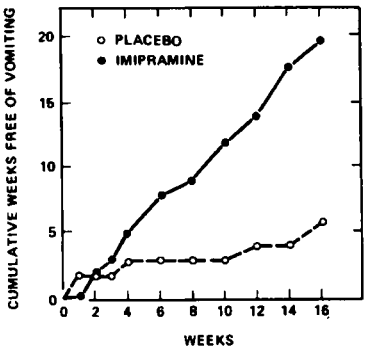

Figure 1. The cumulative number of weeks in which participants reported that they were free of vomiting shown separately for the imipramine and placebo groups.

mass index since the onset of bulimia ($r = 0.69$, $p < .01$). Individuals with lower reported BMI did less well than those with higher BMI's. This variable can be regarded as a measure of the intensity of dietary restriction.

DISCUSSION

This report confirms the findings of Pope et al. (1983) that imipramine is more effective than placebo in the treatment of bulimia after 6 weeks of treatment. In our study binge eating was reduced by 39% in those receiving the active medication as compared with 70% in the Pope et al. (1983) study. This reduction was extended by the sixteenth week of treatment in our study to 72% as compared with a reduction of 43% in the placebo group. There were 30% of the subjects in the treatment group who were abstinent at the end of 16 weeks of treatment, compared with 35% as reported by Pope et al. (1983). These results are also roughly comparable with those found with the use of phenelzine in this condition. The results reported for phenelzine were somewhat more promising in terms of reductions in binging/vomiting, but the dropout rate was higher (Walsh et al., 1984). In addition, bulimics tend to violate the dietary restrictions required for safe administration of the monomine-oxidase inhibitors, making the use of these drugs problematic (Walsh et al., 1984). The strong association between the lowest reported body mass index and outcome suggests that antidepressant therapy may be less effective with bulimics who have severely restricted their dietary intake.

Although the mechanism of action of antidepressants in controlling bulimia is unclear, the effect does not appear to be due solely to reduction in the degree of depression, since baseline depression scores were unrelated to outcome. Although differing from the conclusions of Pope et al. (1983) in this respect, it should be noted that the findings from that study, namely an association between change in depression levels and reduction in the frequency of binge eating, could be interpreted to mean that depression improves as a consequence of reduction in binge eating and purging. Similar observations were recently made in a study of the cognitive-behavioral treatment of bulimia (Kirkley et al., 1985) where depression scores decreased in parallel with improvement in binge eating and purging. In addition, as noted by Walsh et al. (1984) for phenelzine, a number of participants with no evidence of depression improved markedly upon receiving imipramine in the present study, whereas in the study of amitryptyline the more severely depressed patients showed less improvement in bulimic symptoms (Mitchell & Groats, 1984).

The antidepressant treatment of bulimia appears to have some limi-

tations, particularly when we consider the relatively low proportion of individuals able to gain complete control over binge eating and purging. As suggested by the modest decreases in the Eating Attitudes Test, disturbed eating habits and rigid food rules seem to have persisted and may have led to continued binge eating and purging. Since cognitive behavioral treatment of bulimia may result in greater changes in these areas, with reductions of 96% in two recent controlled studies (Kirkley et al., 1985; Lacey, 1983), it may be that the combination of pharmacological and cognitive behavioral therapy would prove more successful than either treatment alone. At the present time, it is not possible to identify those patients who might improve more with one or another therapy; thus the choice of which treatment to use is at the moment one of trial and error. Larger scale studies are needed to address the issue of therapeutic specificity as well as to delineate the longer term effects of both therapeutic modalities.

Overall, the results of this study confirm that imipramine is useful in the treatment of patients suffering from chronic bulimia, a benefit that, due to the careful controls used in this study to eliminate other therapeutic influences, can be attributed solely to the effects of the antidepressant medication. Although the extent of the reduction in binge eating, self-induced vomiting, and laxative use leaves something to be desired, the medication is likely to be of some benefit to the majority of patients and of great benefit to a few.

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