BULIMIA NERVOSA: A PLACEBO CONTROLLED DOUBLE-BLIND THERAPEUTIC TRIAL OF MIANSERIN

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Introduction

Anorexia nervosa is a disorder which is reported as increasing in prevalence (Duddle, 1973; Kendell *et al.*, 1973; Crisp *et al.*, 1976; Jones *et al.*, 1980), a finding that could represent a true increase in prevalence or be due merely to increased recognition and seeking of help. At the same time eating problems, allied to, but not typical of anorexia, are being referred to hospital (Palmer, 1979). One such allied eating disorder is compulsive binge eating or bulimia, often accompanied by vomiting or purging. The relationship of bulimia to anorexia nervosa is not yet agreed. In a review of 11 studies of anorexia nervosa followed-up for a minimum of 2½ years, bulimia was present in 14–50% (Hsu, 1980). However, two recent studies have indicated that there are characteristics which distinguish anorexia patients who develop bulimia from those who do not (Casper *et al.*, 1980; Garfinkel *et al.*, 1980). These authors suggested that the presence of bulimia constitutes a distinct subgroup, not just an 'end-stage' of chronic anorexia nervosa. Indeed cases have been described of bulimia, combined with a morbid fear of fatness, occurring without any history of anorexia (Russell, 1979; Fairburn, 1980).

Furthermore it is now evident that binge eating and vomiting behaviour occur in normal weight and even overweight people and this has led to the classification of bulimia as a disorder distinct from anorexia nervosa in the 3rd edition of the *Diagnostic and Statistical Manual* of the American Psychiatric Association (DSM-III, 1980).

Moreover a recent survey of a college population has suggested a prevalence for bulimia of 13%, indicating that binge eating may represent a very serious and growing public health problem (Halmi *et al.*, 1981).

The underlying causes of anorexia nervosa and allied disorders remain unclear. Investigation of the psychopathology in several studies has revealed a strong relationship between anorexia nervosa and affective disorder (Kay & Leigh, 1954; Warren, 1968; Cantwell *et al.*, 1977) and two of these studies noted a high rate of affective disorder in families of the study sample (Cantwell *et al.* and Warren). Cantwell stated, 'data suggest a hypothesis that at least some cases of anorexia nervosa may be a variant of affective disorder'.

The bulimia subgroup has been claimed to be especially associated with affective disorder. Casper *et al.* (1980) reported in her study of anorexia nervosa that bulimic patients manifested greater anxiety, depression and guilt and had more somatic complaints than non-bulimic patients. Accompanying depression was also reported by Russell (1979), who described a syndrome of 'bulimia nervosa' with the core features of: (1) powerful and intractable urges to overeat, (2) induced vomiting or purging or both, (3) morbid fear of fatness. He noted that 'next to preoccupations directly concerned with eating and weight, depressive symptoms were the most prominent feature of the patient's mental state'. Moreover depressed mood and self-deprecating thoughts following eating binges constitute diagnostic criteria for bulimia in DSM-III.

In view of this claimed association of affective disorder with anorexia nervosa and allied eating disorders, the role of antidepressant therapy would seem worthy of investigation. Tricyclic antidepressants have been suggested to be beneficial in the management of anorexia nervosa (Needleman & Waber, 1977). Further advantage might accrue from treatment by mianserin hydrochloride, a tetracyclic piperazino-azepine of proven efficacy in the treatment of depression (Brogden *et al.*, 1978), which has the advantage over tricyclic antidepressants of less anticholinergic effect (Kopera, 1978), lack of cardiotoxicity and established safety in overdose (Crome & Newman, 1977).

Russell (1979) did not believe that a primary depressive illness could account for the disorder of bulimia nervosa. He asserted that while antidepressant therapy should be tried when depressive symptoms were severe, such treatment usually does not influence the eating disorder itself. Nevertheless as depression is prominent in bulimic patients it was decided to test Russell's hypothesis by means of a controlled trial of mianserin in bulimic patients.

Method

Patients

Fifty female patients referred to the Academic

Department of Psychiatry at the Royal Free Hospital were selected for this study. The patients were required to meet the selection criteria and exclusion criteria listed below.

Selection criteria

- 1) Female outpatients (who, if previously inpatients must have been discharged at least one month previously).
- 2) Aged 16–65 years.
- 3) Subjects show features of bulimia nervosa:
 - a) Abnormal mental state—characterized by preoccupation with food and ideas suggesting (i) fear of fatness or (ii) fear of weight or (iii) pursuit of thinness.
 - b) Abnormal behaviour—(i) binge eating: an excessive ingestion of large quantities of food (as assessed by investigator in comparison with standard diet) resulting from 'powerful and intractable urges to overeat' (Russell, 1979) over which control cannot be exerted; and/or (ii) vomiting—voluntary action resulting in vomiting on average one or more times a week; and/or (iii) purging—consumption of at least twice recommended daily dose of laxatives.

The study therefore selects those patients whose abnormal behaviour of binge eating and/or vomiting is associated with an abnormal attitude towards food, eating and body-shape. Those patients (if any) with the relevant abnormal behaviour but without the abnormal attitude described are not included.

Exclusion criteria

- 1) Any major progressive medical condition.
- 2) Other severe, major psychiatric illness.
- 3) Patients on court order.
- 4) Risk of pregnancy or lactation.
- 5) Current alcohol or drug abuse (other than abuse of laxatives).
- 6) Evidence of renal or hepatic failure.
- 7) Active treatment with antidepressant medication.
- 8) Concurrent psychological treatment from another source.
- 9) Excessively low weight (i.e., less than 25% of original weight or 75% of average weight for height of general population).

Clinical assessments

Questionnaires and ratings

At the start of the study:

- 1) Personal Data Inventory (PDI).
- 2) Eating Attitudes Test (EAT) (Garner & Garfinkel, 1979). This is a 40 item self-rating scale designed to evaluate a broad range of behaviour and attitudes characteristic of anorexia nervosa.
- 3) Bulimia Rating Scale (BRS). This is an unpublished self-administered questionnaire with 23 items designed to evaluate target behaviour and attitudes characteristic of bulimia nervosa.
- 4) Hamilton Rating Scale for Depression (HRSD), (Hamilton, 1960).
- 5) Hamilton Rating Scale for Anxiety (HRSA), (Hamilton, 1959).
- 6) Multiple Affect Adjective Check List (MAACL), (Zuckerman *et al.*, 1964). This self-administered scale gives scores for three affective dimensions; anxiety, hostility and depression.
- 7) Feeding Disorder Check List.
- 8) Clinical Global Impression (CGI). Rated on a four point scale.
- 9) Treatment Emergent Symptom Scale Check List (TESS).

Investigations

- 1) General physical examination.
- 2) Blood pressure (BP) and pulse rate (PR).
- 3) Full blood picture (FBP) including differential white cell count.
- 4) Body weight.

Assessments made throughout the study

- 1) Observer ratings: HRSD, HRSA, CGI, TESS, every two weeks. The same investigator made these ratings at a similar time each day.
- 2) EAT and BRS were also completed fortnightly by the subject.
- 3) Feeding Disorder Check List and MAACL were completed by the patient daily at the end of each day.
- 4) Body weight was recorded every two weeks.
- 5) BP/PR were recorded at monthly intervals.
- 6) General physical examination (when needed).

Medication

Patients were randomly allocated to treatment with mianserin or with placebo. The allocation was made by persons unconnected with the clinical care of the patient. The drugs were taken at night to minimize the recognition of drowsiness due to mianserin (in contrast with placebo). A dose of

30 mg daily of mianserin to be increased to 60 mg daily after one week was prescribed. The trial lasted for eight weeks.

Ethical considerations

All patients gave an informed consent. The manifestation of affective disorder in bulimic patients is usually mild (Garfinkel *et al.*, 1980) and not typical of the depressive disorder for which antidepressant therapy and/or ECT has been shown to be the treatment of choice. The use of a placebo as a control preparation was considered acceptable, particularly in view of the short duration and close supervision of the trial. Action would have been taken to break the code and review treatment if significant or sustained deterioration of mood occurred or if suicidal thoughts became a serious preoccupation.

Statistical analysis

The two groups (active drug and placebo treated) were compared at two weekly intervals for mean scores HRSD, HRSA, CGI, BRS, EAT and weight. Drop-outs from the trial were compared with those completing eight weeks and a reverse cohort analysis was carried out to compare only those who completed eight weeks on each regime. Non-parametric statistics were used to compare the scores of the two groups.

Results

The groups

The patients had been allocated at random to the two groups and it turned out that 20 patients had been given mianserin and 30 patients placebo. Table 1 shows that there were no significant differences between the two groups in age, social class, marital status and initial weight. The two groups were also closely matched on all the questionnaires (HRSD, HRSA, EAT, BRS, MAACL).

Drop-outs

Fourteen subjects did not complete eight weeks on the trial, six from the mianserin group and eight from the placebo group. Table 2 shows that there were no significant differences as regards age, weight, marital status, social class and initial scores

Table 1 Similarity of mianserin and placebo treated groups at outset

	<i>Mianserin (n = 20)</i>	<i>Placebo (n = 30)</i>
Mean age (years)	22.4	25.0
Mean weight (kg)	63.3	61.0
Marital status		
Single	18	23
Married	1	2
Separated	1	4
Divorced	0	1
Social class		
1	4	7
2	12	18
3	1	1
4	2	2
5	0	2
Other	1	0
Previous history of anorexia nervosa	5	10

Table 2 Comparison of drop-outs with the rest

	<i>Mean value at outset</i>	
	<i>Drop-outs (n = 14)</i>	<i>All other (n = 36)</i>
Age (years)	24.9	23.6
Weight (kg)	64.4	61.0
HRS depression	12.6	14.8
HRS anxiety	11.8	14.1
EAT	50.4	45.8
BRS	22.0	21.5

Table 3 Comparison between mianserin and placebo groups at outset, excluding all drop-outs. Mean score

	<i>Mianserin (n = 14)</i>	<i>Placebo (n = 22)</i>	<i>Mann-Whitney U-test, P value</i>
HRS depression	16.9	13.4	0.33
HRS anxiety	16.3	12.6	0.24
EAT	45.9	45.7	0.88
BRS	22.5	20.9	0.42
Weight (kg)	63.5	59.4	0.33

(HRSA, HRSD, EAT and BRS) between those subjects who dropped out and those who remained in the trial.

Changes during the eight week trial

Fortnightly ratings. A comparison of those who completed eight weeks (14 in drug group, 22 in placebo group) is shown in Tables 3 and 4. Table 3

Table 4 Change over time. *P* values showing significance of difference between scores at onset and at eight weeks for mianserin and placebo groups (Wilcoxon's Matched Pairs Signed Ranks Test)

		Mianserin group (<i>n</i> = 14)		Placebo group (<i>n</i> = 22)
HRS depression		0.003		0.002
HRS anxiety		0.002		0.003
EAT		0.10 (NS)		0.0001
BRS		0.02		0.0001
Mean weight (kg) (<i>t</i> -test)	Onset		Onset	
	63.3	0.59 (NS)	59.6	0.81 (NS)
	8 weeks		8 weeks	
	63.9		59.5	

demonstrates that there were no significant differences between the two groups on HRSD, HRSA, EAT and BRS scores or weight at outset.

Figures 1–3 demonstrate the progress of the two groups over eight weeks. During the course of the trial the scores on each questionnaire fell for both groups and at the end of the trial there were no significant differences between the two groups on HRSD, HRSA, EAT and BRS scores.

Table 4 demonstrates that the fall in the scores on the questionnaires reached significance in four in the placebo group (HRSD, HRSA, EAT and BRS) and in three in the mianserin group (HRSD, HRSA and BRS).

The amount of change over the period of the trial did not differ significantly between the two

Figure 1 Comparison of the mean (a) Hamilton Depression and (b) Anxiety Score in the two treatment groups. --- Mianserin, — placebo. **Figure 2** Comparison of the mean (a) EAT and (b) BRS scores in the two treatment groups. Symbols as in Figure 1.

groups on any of the questionnaires. Both groups therefore showed improvement on these measures throughout the trial, but the improvement was not different whether the subject was receiving mianserin or placebo treatment.

There was no significant change in weight in either group throughout the study.

Daily self-ratings. For each patient a mean daily score was computed for each week for each of the

Figure 3 Comparison of the mean (a) CGI score and (b) weight in the two treatment groups. Symbols as in Figure 1.

three affective dimensions measures on the Daily Self-rating Mood Scale (MAACL). Table 5 shows the mean daily score for each week for the two patient groups throughout the trial. There were no significant differences between the two groups on any of the dimensions at the outset of the trial. There was no significant change on any of the measures for either group during the course of the trial.

Relationship between daily mood ratings and daily ratings of eating behaviour

In addition to the completion of the MAACL at the end of each day, each patient recorded whether or not she had binged or vomited. The number of days per week the subjects reported bingeing and vomiting did not change throughout the eight week period, for either group. For each of the patients

completing the trial the mean daily scores on the MAACL for those days on which the patient either binged or vomited were compared with the mean scores for the non-vomiting and non-bingeing days. Table 6 shows that for both groups there were significantly higher mood scores on the days the subjects binged and vomited.

Discussion

Eating attitudes and behaviour, as assessed by the EAT and Bulimia Rating Scale, and mental state as assessed by the Hamilton Anxiety and Depression Scales for all subjects on the trial improved during the eight week follow-up for both groups. Weight did not alter during this time. There was no indication that medication by mianserin altered this rate of improvement.

The study was adequate on methodological grounds in that the patient group met precise inclusion criteria and the patients randomly allocated to either active or placebo groups. Follow-up was double-blind. However the drop-out rate was high; drop-outs occurring at all stages of the follow-up. Analysis of the data showed that those not completing the follow-up did not differ at the outset from those completing the study period. A reverse cohort analysis only devoted to those completing the study period showed a similar result to that when drop-outs are included as far as possible.

As assessed by the Hamilton Rating Scales the bulimia patients as a population were only mildly depressed. The initial scores on the EAT were high for all the subjects. As this scale cannot distinguish between anorexia and bulimia nervosa the scores were well within the range for patients with anorexia nervosa [cut-off score 30, Garner & Garfinkel (1979)]. At the end of the trial although these scores had fallen most patients still had scores above the cut-off point for anorexia nervosa.

Table 5 Mean daily scores for each week on the three affective dimensions derived from the MAACL daily self-rating scale

		Week							
		1	2	3	4	5	6	7	8
Depression Mean daily score	Drug	23.1	21.9	21.7	22.6	22.6	21.2	21.5	22.4
	Placebo	21.3	21.7	20.9	21.1	21.4	21.0	20.2	20.2
Anxiety Mean daily score	Drug	11.4	10.8	11.2	11.4	11.7	10.4	10.4	11.0
	Placebo	10.3	10.6	10.3	10.6	10.4	10.9	10.2	10.0
Hostility Mean daily score	Drug	13.7	12.1	13.2	13.0	12.7	11.8	12.2	12.1
	Placebo	11.7	11.6	11.6	11.7	11.3	11.6	11.5	11.6

Table 6 Mean daily scores of depression, anxiety, hostility on days when the subjects binged and vomited, and on days when they did not, for drug and placebo groups (standard deviations in brackets)

	Drug group		Placebo group	
	Yes	No	Yes	No
Binge				
Mean depression score	23.9 (4.9)	19.5 $P < 0.05$ (4.8)	23.0 (5.8)	18.2 $P < 0.01$ (6.6)
Mean anxiety score	11.9 (2.7)	9.8 $P < 0.05$ (2.7)	11.3 (3.3)	9.2 $P < 0.01$ (3.5)
Mean hostility score	13.6 (3.3)	11.2 NS (2.8)	12.2 (3.1)	10.8 $P < 0.01$ (3.3)
Vomit				
Mean depression score	23.7 (5.1)	20.5 $P < 0.01$ (4.8)	21.2 (6.7)	19.5 $P < 0.01$ (7.7)
Mean anxiety score	11.9 (2.9)	10.0 $P < 0.01$ (2.7)	10.3 (3.5)	9.3 $P < 0.01$ (3.6)
Mean hostility score	13.6 (3.4)	11.6 $P < 0.05$ (3.0)	11.5 (3.6)	11.0 $P < 0.05$ (3.5)

It is of interest that on the daily self-rated mood scales there was no significant change in either group throughout the course of the trial. Moreover, despite the improvement in both EAT and BRS scores, the number of days per week the subjects reported bingeing, vomiting or purging did not change throughout the eight weeks of the trial for either group. However, on comparing the days each subject reported bingeing and vomiting with those days when this did not occur there was a significant increase in the mood scores associated with these abnormal behaviours. This was similar for the two groups and thus not affected by mianserin. These data suggest that bulimia is not a manifestation of an underlying affective disorder as such but that mood changes are more likely to be a secondary part of the syndrome.

A further finding of the study is the general overall improvement in the patients associated with regular contact with a psychiatrist interested in their condition and progress. Those encounters, which in no way would have met the criteria of insight-directed psychotherapy, appear to have been therapeutic. This general improvement is probably related to the fact that many of the subjects entering the trial had been struggling secretly for long periods with their bingeing and vomiting and the associated feelings of guilt and loss of control. Entry into the trial represented for many of them the first attempts to seek help for their distressing condition. This concept of general improvement seen in subjects after inclusion in treatment trials of the present sort always needs to be considered when claims of the efficacy of special forms of treatment are being made.

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Discussion

G. Russell

The design of Professor Wakeling's study is an impeccable one. I was pleased in a way to hear his conclusions because they fit in with my understanding of the nature of bulimia nervosa. It can be assumed that depressive symptoms are secondary to the eating disorder, and do not explain its fundamental aetiology. Bulimic patients do stress what a distressing experience it is to go through life preoccupied with thoughts of food, one's body image and one's appearance. Every day they resolve to give up the habit of gorging food, and every day they fail.

Table 3 of the paper, showing the ratings of the two groups, indicated that the drug-treated group started off with higher scores on both the depressive scale and the anxiety scale. Was account taken of this in the analysis of the results?

A. Wakeling

These two groups were not significantly different. The mianserin treated group scored a little higher than the placebo group, but the scores signified fairly low levels of depression anyway.

A. Coppen

'Is it difficult to achieve steady state plasma levels? Do you have any data on that?'

A. Wakeling

These patients were really urgently asking for help.

We gave them the drug last thing at night after all the vomiting, which I think is the important point of the question. We have obtained blood samples on all these patients which could be checked through in due course. Incidentally, we had hoped to widen this trial to include patients with anorexia nervosa, but anorexia patients are notoriously difficult about taking anything, let alone daily tablets. I am confident that the bulimia patients showed good compliance but I agree it would be interesting to confirm this from the mianserin blood levels.

J. Feighner

Throughout our inpatient and outpatient depression studies we see from time to time patients who cycle fairly rapidly and who present with the pattern that has been described, which we call 'bulimarexia'. One of the things I am intrigued by, and we are going to re-assess our own data, is the fact that the pure selective serotonin re-uptake inhibitors, such as zimelidine, fluoxetine and fluvoxamine, have a more specific and beneficial effect on this pattern of eating. I would be curious of Professor Wakeling's own experience with this phenomenon.

A. Wakeling

It would surprise me really if drugs acting in such a specific way had an impact on these patients. Controlled trials on these compounds are not being tried, as far as I know.

R. de Buck

Professor Wakeling, what was the rationale for