Imipramine and Diet Counseling with Psychological Support in the Treatment of Obese Binge Eaters: A Randomized, Placebo-Controlled Double-Blind Study

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Abstract: **Objective:** *This study with 31 obese binge eaters (body mass index [BMI] 39.5 ± 8.6 kg/m^2 [SD]) was designed to assess whether diet counseling with psychological support and imipramine or placebo has an effect on the frequency of binge eating, body weight, and depression during an 8-week treatment phase. This was followed by an open medication-free phase of 6 months of continuous diet counseling with psychological support.* **Methods:** *Randomized double-blind placebo-controlled study of 8 weeks followed by an open phase of 6 months. Patients were evaluated in medical visits by a semistructured videotaped interview, psychometric questionnaires, and hematochemical parameters.* **Results:** *From Week 0 to 8, a significant reduction in binge frequency occurred in both treatment conditions (7.1 ± 4.1 to 2.8 ± 3.0 binges per week [imipramine] vs. 7.1 ± 4.1 to 5.4 ± 5.1 [placebo],* $p < .01$*). Patients on imipramine lost −2.2 ± 1.8 kg compared to placebo-treated subjects (+0.2 ± 3.3 kg,* $p < .001$*). On follow-up, only the patients initially treated with imipramine continued to lose weight (−5.1 ± 2.8 kg [imipramine] vs. 2.2 ± 6.8 kg [placebo],* $p < .001$ *[differences to Week 0]). While both treatment conditions were associated with significant improvements on a rater's measure of depressive symptoms (Hamilton Depression Scale) at Week 8, only the patients treated with imipramine still showed a significant improvement at Week 32. Scores on the Self Depression Rating Scale did not show a group difference but a significant reduction at Weeks 8 and 32, compared to baseline.* **Discussion:** *These results suggest that adding low-dose imipramine to diet counseling with psychological support helps patients losing weight even for at least 6 months off medication. The effect might include a psychological priming of weight loss during the double-blind phase that continues at least for half a year*

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after stopping the drug. © *1999 by John Wiley & Sons, Inc.* Int J Eat Disord 26: 231–244, 1999.

Key words: *obese binge eaters; diet counseling; imipramine treatment; double-blind, placebo-controlled trial; psychological support*

INTRODUCTION

Obesity is a common disorder in industrialized countries. In the United States, one third of the female and one fifth of the male population are obese (Rand & Kuldau, 1990; Flegal, 1996). In Switzerland, 20–40-year-old subjects are particularly overweight (Suter, Weissner, & Gruene, 1993). Moreover, obesity is associated with various health risks, serious morbidity, and excessive mortality. A comparison of the mortality rate among obese (body mass index [BMI] >35 kg/m^2) and nonobese young men in the age group 24–34 years demonstrated a 12-fold excess mortality rate (Drenick, Bale, & Seltzer, 1980) even if newer studies show a more important link to fat distribution (Björntorp, 1992; Kissebah & Krakower, 1994). Most treatment modalities for obesity have been only modestly successful, weight losses are usually minor, and maintenance of weight loss over time is poor (Marcus, Wing, & Hopkins, 1988).

In addition, an important subset of the obese population engages in binge eating. In one study, 20–46% of the obese women who had applied for admission to a weight loss program in the United States reported binge eating at least twice weekly (de Zwaan, Nutzinger, & Schoenbeck, 1992). These patients basically met criteria for bulimia defined in the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association [APA], 1980 [DSM-III], 1989 [DSM-III-R]). Normal young people in the United Kingdom have been reported to binge 4.7 times a month on average (Wardle, 1980). In addition, young women asked to characterize binge eating placed greater emphasis on loss of control and less on the quantity eaten (Spitzer, Devlin, & Walsh, 1991). Moreover, binge eating was reported in up to 71.2% in defined subgroups (Spitzer et al., 1991), suggesting that binging is not an isolated pathology, but rather part of a syndrome. When binge eating is defined as the episodic intake of large amounts of food, followed by guilt feelings, self-deprecatory ideation, and restrictive dieting (Stunkard, 1959), only a small proportion (<5%) of the obese population was classified as binge eaters (Stunkard, 1996).

The association between eating behavior and psychosocial development is well established (Hammer, 1992). Suffering from obesity has equally adverse psychological and social consequences (Wadden & Stunkard, 1985). When compared to obese non-binge eaters, obese binge eaters are significantly younger at the onset of therapy (de Zwaan & Mitchell, 1992; Keefe, Wyshogrood, Weinberger, & Agram, 1984; Lowe & Caputo, 1991); begin dieting earlier (de Zwaan et al., 1992); follow stricter diets (Keefe et al., 1984; Gormally, Black, & Rardin, 1982); and become overweight earlier in life (de Zwaan et al., 1992; Loro & Orleans, 1981). They also report significantly more depressive symptoms (Marcus et al., 1988; Marcus, Wing, Ewing, Kern, Gooding, et al., 1990; Wing, Marcus, Epstein, Blair, & Burton, 1989) and more sexual and psychiatric complaints (Marcus, Wing, Ewing, Kern, McDermott, et al., 1990).

Medium to long-term studies with fluoxetine, a bicyclic antidepressant, revealed defined effects on several important parameters independently of depression and binge eating state (Ferguson & Feighner, 1987; Marcus, Wing, Ewing, Kern, McDermott, et al., 1990). A 52-week placebo-controlled trial with fluoxetine (Marcus, Wing, Ewing, Kern,

McDermott, et al., 1990) demonstrated that independent of binge and nonbinge status, patients treated with behavioral modification plus fluoxetine showed a higher weight reduction than placebo-treated patients. However, after withdrawing fluoxetine, a greater weight gain was observed in formerly fluoxetine-treated patients when compared to placebo (Marcus, Wing, Ewing, Kern, McDermott, et al., 1990). Unfortunately, the results of this study are compromised by a high dropout rate (>50%) and a lacking effect of fluoxetine on binge eating frequency and depression. Moreover, neither diet counseling nor psychological support was provided in this study.

Imipramine and desipramine, two tricyclic antidepressants, are significantly more effective than placebo in increasing dietary restraint and reducing binge eating, binge duration, and hunger in slightly obese binge eating subjects (Agras, Dorian, Kirkley, Arnow, & Bachman, 1987; Alger, Schwalberg, Bigaouette, Michalek, & Howard, 1991) as well as in normoweight, nonpurging bulimics (McCann & Agras, 1990; Pope, Hudson, Jonas, & Yurgelun-Todd, 1983) in short-term studies of 8–12 weeks duration. Both groups on antidepressants reported higher reductions in depression scores than placebo- treated subjects (Alger et al., 1991; McCann & Agras, 1990). However, no definite effect on body weight was observed when diet counseling was not administered.

Until now, the long-term effects of medication with diet counseling and psychological support as well as the effects of postcessation of imipramine on binging, mood, *and* weight were not available. Moreover, no data are published on the effects of imipramine and diet counseling with psychological support on all three characteristic parameters of obese binge eaters.

This study was designed to determine if a combination of imipramine therapy and diet counseling with psychological support is more effective in treating obese binge eaters than placebo and diet counseling with psychological support in reducing all three characteristic parameters of obese binge eaters (i.e., overweight, binge eating periods, and depression). This study also determines if the weight loss achieved during the 8 weeks of drug therapy is maintained for a follow-up period of 6 months after cessation of imipramine, with diet counseling with psychological support continuing during this time.

SUBJECTS AND METHODS

Subjects

The medical charts of 500 patients were screened. All had consulted our counseling center for weight problems (Medical Outpatient Clinic of the University of Berne, Switzerland) during the last 2 years. One hundred charts were considered suitable for the study. Inclusion criteria consisted of a diagnosis of binge eating (according to DSM-IV criteria [APA, 1994]; code number 307.51, with the parameters A and C); overweight or obesity (defined as a BMI >27.5 kg/m^2); and age 20–60 years. Exclusion criteria included endocrine disorders; diabetes mellitus; pregnancy; arterial hypertension; renal diseases; pulmonary diseases including chronic obstructive lung disease and bronchial asthma; use of psychoactive medication or appetite suppressants; contraindications for drugs with anticholinergic side effects; psychiatric disorders such as cyclothymia, schizophrenia, major depression, personality disorders, and concomitant psychotherapy; other eating disorders were excluded equally, especially bulimia nervosa (fulfilling all criteria of DSM-IV) or anorexia nervosa. However, depressive symptoms often found in the obese were not contraindications to participation. Medical as well as psychiatric diagnoses were made

using internationally accepted standards (e.g., DSM-IV or ICD-10). All potential participants were contacted by phone and informed about the purpose and protocol of the study. Of these, 27 women and 4 men agreed to participate. This relatively low rate of only one third is mostly due to concerns of patients about the influence of psychological support on their daily life.

The study protocol was approved by the Ethical Committee of the University of Berne.

Study Design

In this double-blind, placebo-controlled randomized study, 15 patients were assigned to imipramine (25 mg three times per day [TID]) and 16 subjects to placebo treatment for 8 weeks. Placebo tablets, furnished by the hospital pharmacy, were identical in size, color, and taste to the active medication administered. After the first 8-week period, the randomization code was broken and imipramine or placebo was discontinued. A supervised 6-month follow-up period without any drugs but with continuation of diet counseling with psychological support was performed. Adherence to medication was controlled by using the dosette system, checking for the tablets taken, and questioning the patients during the diet counseling sessions.

Subjects were seen regularly by one of the investigators (C.G.) as depicted in Table 1 (medical visit). (1) Patients were interviewed following a semistructured interview scheme (Table 1). After the interviews, the Hamilton Depression Scale (HAMD; Hamilton, 1967) and Self Depression Rating Scale (SDS; Brown & Zung, 1972) were completed by all patients. At the end of the placebo-controlled double-blind study phase (time point 8), all patients were requested to complete an additional psychometric questionnaire (Patient Termination Record [PTR; Guy, 1976]) to assess eventual secondary effects of medication. (2) After each interview, patients were seen by another physician for documentation of weight (SECA scale, model 708, Gribi AG, Berne, Switzerland), height, and blood pressure (sphygmomanometer Erkameter, Baden, Switzerland); determination of waist-to-hip ratio; and a brief additional physical check-up. (3) Blood samples for the determination of plasma glucose and total serum cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides, potassium, creatinine, hemoglobin, and liver parameters were taken after an overnight fast (Table 1). All hematochemical analyses were performed in the Inselspital Laboratory, a Swiss reference lab.

Evaluation of Binge Eating Episodes

Defining the binge eating state took place during the information and inclusion interview. We assessed binge eating by using DSM-IV criteria. During the semistructured

Table 1. Study design

Time Points (Weeks)	Preinclusion (–4 Weeks)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32
Diet counseling	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆		◆		◆		◆
Interview (videotaped)		◆		◆		◆												◆
Questionnaires		◆		◆		◆				◆								◆
Medical visit		◆		◆		◆				◆								◆
Randomization		◆																
Code opening						◆												
Blood draw		◆				◆												◆
Phone call	◆													◆				

Note: Shaded area = double-blind placebo-controlled randomized phase; nonshaded area = open study phase (without imipramine in both groups).

interview, questions were asked about weekly frequencies of binge eating episodes, duration of the episodes, drive to eat more, feelings during the binges, emotions and concerns after termination of binging, the approximate quantity of food ingested, and other parameters.

Diet Counseling

Patients were given 30 min of individual diet counseling by one of our two dietitians (R.M., S.L.) on a biweekly basis. Nutritional counseling covered the following topics: qualitative and quantitative composition of food, appropriate nutrition between meals, eating patterns, and food diaries. The latter were assessed following the regulations of the Swiss Association for Nutrition, where one of our dietitians belongs to the executive committee (R.M.). Our dietitians and a physician (C.G.) assessed the patients' binging behavior, estimated frequency of their binge eating episodes (according to DSM-IV criteria), and asked if they had a sense of loss of control and subsequent dysphoric mood. Additionally, an adapted German questionnaire was used at all time points when patients were seen by our dietitians, akin to the Gormally binge eating scale (Gormally et al., 1982). Moreover, patients were asked openly about psychological concerns at every counseling date. If yes, they were advised in a behavioral style adapted to their respective problems. All special events encountered by the patients were reported to the dietitians and noted in the chart.

Psychological Parameters

A slightly abridged version of the 21-item HAMD was completed by the interviewer himself (C.G.). All the split-screen video-registered interviews were then rated by a rater blind to the interviewer's rating (K.L.-H.). Two items were omitted because of their inappropriateness for this study group: Item 16 as it concerns weight loss, which is desirable for obese patients and consequently not an indication of depression in our patient group; Item 17 — conceived to assess understanding of the disease — was inappropriate because of the study population, who did not suffer exclusively from depression. If considerable discrepancy between the two raters was observed, differences were openly discussed in an attempt to reach consensus. However, the overall interrater correlation for the HAMD assessment was high before any correction ($r = .89$, $p < .001$).

After the interviews, patients were asked to complete a slightly abridged version of the 20-item SDS. Items 5 and 7 were omitted as they dealt with food intake and weight reduction in an inverse sense (Fairburn & Garner, 1986).

Parts of our questionnaire constructed with inclusion of elements of Gormally's scale also denote psychological parameters, namely feelings of loss of control during binging or mood state before a binge eating attack (see above).

Psychological Support

All patients were provided with regularly scheduled behavioral-oriented psychological support. One approach included an individual-oriented evaluation of actual problems (weight, relations in the family, professional concern, personal difficulties) that took place after each diet counseling session. The duration of these sessions was 15–35 min. The second approach consisted of behavioral-oriented group therapy that took place monthly and was guided by an assistant dietitian and supervised by a physician (K.L.-H.). The

number of patients per session varied form 10 to 14 and three parallel groups were conducted during the study. The duration of a group session was 1½ hr. The session opened with individuals weighing, a discussion of eating habits followed, the problems faced in following the diet regimen were addressed, and advice was directly placed in this moment. Then a discussion about personal experiences with overweight was added and advice was given only when there was an opportunity to generalize them for the whole group. Despite initial skepticism, most patients were very satisfied about the opportunity to share their concerns with others.

Statistical Analysis

All the data presented in text and the tables are expressed as *M* ± *SD*. In the figures, the *SEM* was used instead of the *SD*. Comparison of results was performed by analysis of variance (ANOVA) for repeated measures using the Bonferroni/ Dunn correction and with a post-hoc Fisher PLSD *t* test, where appropriate.

RESULTS

Subjects' Baseline Characteristics and Clinical Events

The two groups of obese subjects were similar with respect to age, waist-to-hip ratio, systolic and diastolic blood pressure, binge eating episodes, scores on the SDS and HAMD, and fasting serum concentrations of glucose, total cholesterol, and other hematochemical parameters (sodium, potassium, creatinine, total leukocyte count, uric acid, alanine transaminase [ALT], and aspartate transaminase [AST]) (Table 2). However, compared with imipramine-treated subjects, placebo-treated subjects exhibited a higher body weight (*M:* 114.8 ± 29.4 kg [*SD*], median:107.5 ± 15.6 kg [*SEM*] vs. *M:* 95.9 ± 14.2 kg [*SD*], median: 96.4 ± 9.9 kg [*SEM*], $p < .05$) and a higher BMI (*M:* 43.2 ± 9.4 kg/m^2 [*SD*], median: 39.9 ± 2.4 kg/m^2 [*SEM*] vs. *M:* 36.1 ± 6.2 kg/m^2 [*SD*], median: 36.6 ± 1.6 kg/m^2 [*SEM*] for imipramine, $p < .02$). This was due to two heavily obese patients who were randomly assigned to the placebo group.

Twenty-nine of the 31 participating patients completed the study. One male patient,

Table 2. Subject's characteristics

Parameters (Units)	Placebo (*N* = 14)	Imipramine (*N* = 15)	*P* Value
Age (years)	35.7 ± 10.3	40.7 ± 10.9	NS
Body weight (kg)	114.8 ± 29.5	96.0 ± 14.2	<.05
Body weight index (kg/m^2)	43.2 ± 9.4	36.1 ± 6.3	<.02
Waist-to-hip ratio	1.01 ± 0.07	0.96 ± 0.07	NS
Blood pressure, systolic (mmHg)	131.4 ± 13.5	132.3 ± 18.0	NS
Blood pressure, diastolic (mmHg)	87.5 ± 9.1	87.0 ± 9.4	NS
Self-Rating Depression Scale (SDS)[a]	35.0 ± 5.8	35.3 ± 6.3	NS
Hamilton Depression Scale (HAMD)[a]	21.3 ± 12.0	22.6 ± 9.8	NS
Binge eating episodes (N)	7.1 ± 4.9	7.1 ± 4.1	NS
Serum glucose (mmol/l)	5.7 ± 1.3	5.6 ± 1.2	NS
Total serum cholesterol (mmol/l)	5.5 ± 0.9	5.3 ± 1.1	NS

Note: Values are given as mean ± standard deviation.
[a]Score values.

who had complained of hunger, sweating, palpitations, arrhythmia, and general malaise during the first 10 days of treatment, consequently dropped out of the placebo group. One female patient discontinued active medication due to skin eruptions and an aversion to tablet intake. Following the 8-week study phase, no difference in the total number of adverse side effects was observed between the two groups using the PTR score. However, anticholinergic effects (constipation, dry mouth, blurred vision) were more often reported in the imipramine group (seven vs. three times, $p < .05$).

Effect of 8 Weeks of Imipramine Therapy

The subjects on imipramine demonstrated a weight loss of −2.2 ± 1.8 kg (or −2.3 ± 1.9% or a total sum of weight loss of −32.4 kg for the whole group). The placebo-treated subjects' weight remained essentially stable (+0.2 ± 3.3 kg, or +0.2 ± 2.9%, or a total weight gain of +3.1 kg for the whole group; $F = 10.2$, $p = .0002$) (Figure 1, Table 3). Mean HAMD scores decreased significantly in imipramine-treated subjects (−9.6 ± 7.1 in absolute values, −50.7 ± 33.7%, $F = 8.4$, $p < .001$). In placebo- treated patients, no significant (−3.7 ± 9.0 for absolute values, −4.7 ± 32.3%, p = NS) change was observed (Figure 2). SDS scores were reduced from 35.3 ± 6.3 to 28.9 ± 5.8 (p = NS) and from 35.0 ± 5.8 to 30.8 ± 7.3 (p = NS) in imipramine and placebo-treated subjects, respectively. There was only significance for the difference of both groups to time point 0 ($F = 14.9$, $p < .0001$). Binge eating episodes were reduced from 7.1 ± 4.1 to 2.8 ± 3.0 per week (absolute values) or −72.7 ± 35.7% in imipramine-treated subjects ($F = 8.4$, $p < .001$) and from 7.1 ± 4.1 to 5.4 ± 5.1 per week (absolute values) or −28.3 ± 30.5% (p = NS) in placebo-treated subjects (Figure 3). A slight but insignificant shorter duration of binges in imipramine-treated individuals was noted (from 3.3 ± 1.0 to 1.8 ± 1.5 hr per week). The sum of change of SDS score during the 8-week study was −65 in placebo and −95 in imipramine- treated patients. Systolic and diastolic blood pressure, serum cholesterol, and glucose concentrations as well as the other hematochemical parameters (sodium, potassium, creatinine, total leukocyte count, uric acid, ALT, and AST) and waist-to-hip ratio remained stable during the 8-week study in both groups.

Effect of Imipramine 6 Months after Discontinuation of Medication

Obese subjects formerly on imipramine demonstrated a continuing mean weight loss with continuing diet counseling and psychological support during the following 6 months of −1.9 ± 6.3 kg (absolute values) or −5.0 ± 2.8% ($F = 10.2$, $p < .001$). Placebo-treated subjects regained weight in the range of 3.0 ± 2.2 kg (absolute values) or 2.1 ± 6.0% (p = NS) (Figure 1). The group difference between imipramine and placebo groups remained significant ($F = 16.7$, $p < .001$) even at this time point. The sum of weight gain in formerly placebo- treated subjects was +30.6 kg, whereas imipramine-treated subjects lost a total sum of −76 kg during the entire 8 study months. Scores of HAMD increased after stopping imipramine (+2.8 ± 1.9 absolute values, +26.4 ± 13.4%) or placebo (+3.3 ± 3.9 absolute values, +26.4 ± 17.0%) in both groups ($p < .01$) (Figure 2). However, HAMD scores were still significantly lower in formerly imipramine-treated subjects when compared with baseline values (32 vs. 0 weeks, $F = 5.0$, $< .01$). In formerly placebo- treated subjects, HAMD scores were similar to those observed at baseline (32 vs. 0 weeks, p = NS). Compared to placebo, formerly imipramine- treated subjects demonstrated lower HAMD scores even 6 months (32 weeks) after stopping therapy (19.1 ± 8.8 for imipramine vs. 12.6 ± 5.8 for placebo [absolute values] or −34.3 ± 20.3% vs. +21.5 ± 50.3%, respectively; F =

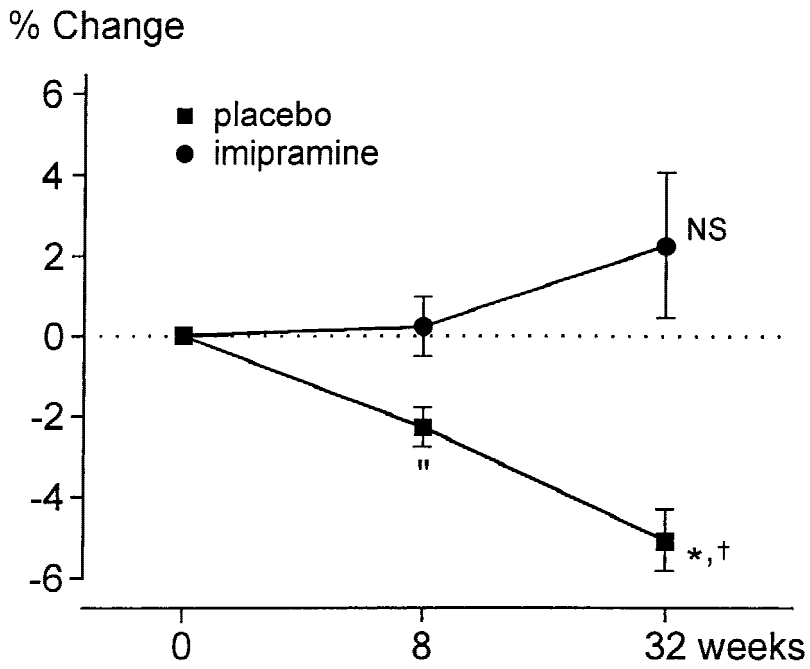

Figure 1. Effect of imipramine and placebo on weight change (%) during 8 weeks on and 24 weeks off therapy. "$p < .05$ for group differences (t test, Fisher PLSD) at time point 8 weeks. *$p = .0003$. Bonferroni/Dunn correction imipramine versus placebo (critical difference = 1.64), intergroup comparison. †$p = .0002$ ANOVA, category: imipramine group, $F = 10.2$, intragroup comparison.

13.5, $p < .01$). In formerly imipramine-treated patients, binge eating episodes remained decreased at Week 32 but were slightly higher than at termination of imipramine therapy at Week 8 (4.1 ± 2.1 vs. 2.5 ± 2.9, $F = 5.0$, $p < . 0.1$). In formerly placebo-treated patients, binge eating episodes reached even the prestudy levels after 32 weeks (7.2 ± 4.3 at Week 32, 5.3 ± 51. at Week 8, 7.1 ± 4.9 at Week 0, p = NS vs. Week 8 or baseline) (Figure 3). The group difference between formerly imipramine-treated subjects to those having received placebo remained significant even at Week 32 for binge eating episodes ($F = 8.0$, $p < .01$). SDS score, systolic and diastolic blood pressure, serum cholesterol and glucose concentrations, serum sodium, potassium, creatinine, ALT, AST, uric acid, and total leukocyte count as well as waist-to-hip ratio remained similar 32 weeks after initiation of study when compared to 8 weeks in both study groups.

DISCUSSION

In this study, the effect of adding imipramine or placebo to diet counseling with psychological support on three characteristic parameters of binging obese subjects was assessed (i.e., binge eating frequency [number of episodes per week], body weight, and depression [HAMD and SDS scores]).

Effect on Weight

Our results demonstrate that imipramine prolonged weight loss even after treatment was discontinued. In binge eating obese subjects receiving regular dietary counseling with

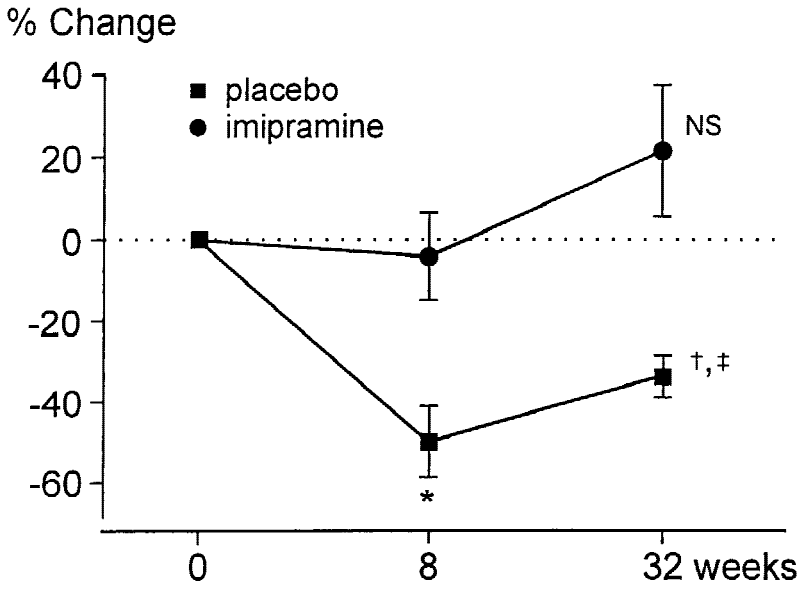

Figure 2. Effect of imipramine and placebo on depression scores in Hamilton Depression Scale during 8 weeks on and 24 weeks off therapy. *p = .02 for group differences (t test, Fisher PLSD) at time point 8 weeks, intergroup comparison. †p = .01 Bonferroni/Dunn correction imipramine vs. placebo (critical difference = 3.2), intergroup comparison. ‡p < .0001 ANOVA for category, imipramine group, F = 17.1.

psychological support, body weight decreased during the treatment phase as known for serotonin agonists such as dexfenfluramine (Salmela, Sotaniemi, & Viikari, 1981) and fluoxetine (Connolly, Gallagher, & Kesson, 1995). Body weight decreased further for at least 6 months in formerly imipramine but not in placebo-treated obese binge eating subjects (Figure 1). Moreover, placebo-treated obese subjects showed a slight but insignificant weight increase. Interestingly, in the study of Alger et al. (1991), no such weight change was observed under the double dosage of imipramine during the 8-week study. This might be because of the lack of diet counseling or psychological support in their patients or because of their subjects' substantially lower BMI compared to our population. These reasons might have forced Alger et al. to state in their study that any future work on this topic should include diet counseling and the administration of tricyclic antidepressants or placebo.

In addition, the study of Marcus, Wing, Ewing, Kern, McDermott, et al. (1990) with a 52-week duration of fluoxetine medication revealed a significant weight-lowering effect in the fluoxetine group despite a dropout rate of more than 50% of the patients treated. In slightly overweight bulimics treated by McCann and Agras (1990), no effect of treatment on weight was observable during the 12-week study period using desipramine despite the double dosage they used in comparison to our study. The different effects on weight with the same or other thymoleptic substances should be evaluated by future studies investigating the effect of medication with or without diet counseling and psychological support in binge eating obese subjects.

The effect of weight reduction may perhaps be understood physiologically (e.g., resetting the "adipostate" by altering serotonin and norepinephrine concentrations in central nervous system [CNS] synaptic clefts and thereby influencing eating behavior and satiety

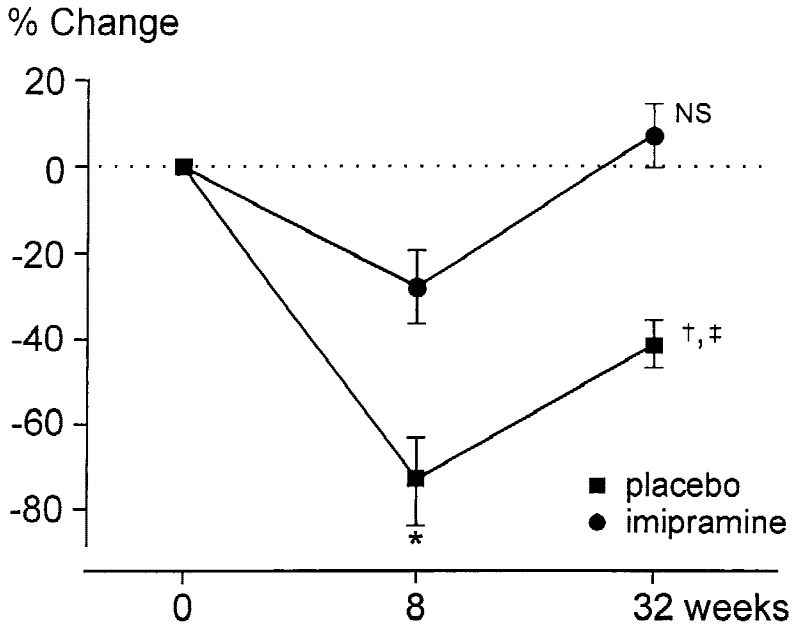

Figure 3. Effects of treatment on changes in binge eating frequency in patients treated with imipramine or placebo during 8 weeks on and 24 weeks off therapy. *$p < .02$ between groups (t test, Fisher PLSD), intergroup time point 8 weeks. †$p < .0008$ ANOVA, category: imipramine group, $F = 8.4$, intragroup comparison. ‡$p < .0001$ Bonferroni/Dunn correction imipramine versus placebo (critical difference = 11.4), intergroup comparison.

over a longer period of time). The psychological impact of the initial success of weight loss in this group may also lead to better diet compliance in the open phase (priming effect of medication induced initial weight losing) as was proposed by Clark, Cargill, Medeiros, and Pera (1996) in another context. This was demonstrated by our binge eating patients who received psychological support during the study. However, it is not clear why this intervention did not succeed in patients who did not receive imipramine in the double-blind phase. Whereas other studies showed distinct effects on weight by application of psychological interventions (Marcus, Wing, Ewing, Kern, McDermott, et al., 1990), our results in this group did not show a weight reduction effect of this approach. Nevertheless, at least no significant further weight gain was observed, pointing to a stabilization of obesity at a high but defined setting point, according to newer reserach results (Levin & Routh, 1996; Keesey & Hirvonen, 1997).

Effect on Binge Eating

Our results show a lower frequency of binge eating in the imipramine and placebo groups during the 8-week double-blind treatment phase. It is surprising to see a consistently lower binge eating frequency even 6 months after cessation of imipramine therapy, whereas formerly placebo-treated patients returned to their basal binge eating frequency (Figure 3). Therefore, the amount of calories ingested during a binge eating episode has to be different in the two groups, at least during the 8-week double-blind treatment phase where weight was lowered only in the imipramine group. This had been shown by our

Table 3. Effect of imipramine after 8- and 32-weeks of treatment compared to placebo

	Placebo Week 8		Imipramine Week 8		Placebo Week 32		Imipramine Week 32	
Parameter	*M* ± *SD*	Diff ± *SD*	*M* ± *SD*	Diff ± *SD*	*M* ± *SD*	Diff ± *SD*	*M* ± *SD*	Diff ± *SD*
Body weight (kg)	115.0 ± 29.4	0.2 ± 3.3	93.8 ± 14.4	–2.1 ± 1.7	117.0 ± 29.2	2.1 ± 6.8	90.8 ± 13.5	–5.0 ± 2.8
HAMD	16.0 ± 10.3	–3.5 ± 8.9	9.8 ± 7.0	–9.6 ± 7.1	19.2 ± 8.7	0.0 ± 4.9	12.6 ± 5.8	–6.8 ± 5.0
SDS	30.7 ± 7.3	–4.6 ± 4.3	28.9 ± 5.8	–6.3 ± 5.0	33.1 ± 6.8	–3.4 ± 4.1	32.2 ± 4.9	–3.6 ± 4.2
Binge eating episodes (*N*)	5.3 ± 5.1	–1.7 ± 2.9	2.5 ± 2.9	–4.5 ± 4.2	7.2 ± 4.3	0.0 ± 1.4	4.1 ± 2.1	–3.2 ± 2.9

Note: Values are given in *M* ± *SD* and in differences to time point 0 ± *SD*. HAMD = Hamilton Depression Scale; SDS = Self-Rating Depression Scale.

eating protocols, which revealed less binge eating episodes and reduced calorie intake as the result of shorter duration of the events and a lowered drive to eat more (see the Results section). In the study of Alger et al. (1991), binge eating episodes decreased under medication, but the duration of the episodes did not change. In the study of McCann and Agras (1990), the frequency of binges decreased for the desipramine group, but there was no discernible weight change.

Diet counseling with psychological support seems particularly useful when primed by adding imipramine at least for 8 weeks. Besides the psychological effects of successful weight reduction in patients treated initially with imipramine, one might assume a selective change in eating behavior independent of its antidepressant effect. This hypothesis is in line with findings in humans (Hill & Blundell, 1990; Levin & Routh, 1996) and animals (Leibowitz, 1990; Smythe, 1977). Collectively, the present results imply that imipramine has a long-lasting effect on weight loss and reduction of binge eating frequency that lasts considerably longer than its usual known influence on mood improvement. It can be concluded that an approach consisting of diet counseling only seems not to be worthwhile in obese binge eating subjects. This was confirmed by our results: our placebo-treated subjects lost no weight during the whole study period.

Effect on Depression Parameters

Overall depression rate was low for both imipramine and placebo-treated subjects at the beginning of the study. Depression as assessed by HAMD showed a significant reduction during the whole study for the imipramine-treated group, whereas the changes in HAMD score were only significantly different to baseline level in the placebo group at 8 weeks. On the other hand, the SDS score did not change significantly in placebo subjects during the whole study period. This is in contrast to results of other studies, which report a high depression rate in obese binge eating subjects or a decrease of depression rates (assessed by the Beck Depression Inventory) even in placebo-treated subjects (Alger et al., 1991). As depicted above, HAMD scores, but not the SDS score, decreased by more than 45% during the first 8 weeks of study in imipramine-treated subjects (Figure 2). After cessation of imipramine therapy, HAMD scores increased slightly, but were still significantly lower than at baseline and compared to the placebo-treated obese subjects. The improvement in depression scores in both groups in the course of the double-blind study phase (Figure 2) could be ascribed to the connection between the severity of depression and social isolation (Fairburn & Garner, 1986) as well as to the regular medical visits used only during the double- blinded phase of the study. Our finding that only obese subjects on imipramine therapy demonstrated a significant change in both depression scores

(HAMD and SDS) at time point 8 weeks might suggest that imipramine induces a new set-point of the adipostate. As mentioned above, this thesis has been proposed by another working group (Hill & Blundell, 1990) and seems to become more evident from research accumulated in animal experiments (Leibowitz, 1990; Smythe, 1977; Bray & York, 1979).

During the second, unblinded study phase, a marked discrepancy between self (SDS) and rater's estimation (HAMD) of depression was noted. From the point of validity, both scales are tested myriadly. We believe that the HAMD and SDS do not measure the same factors or symptoms of depression. This is true also for the BDI, which is known to be altered by bodily symptoms (Barsky, Wyshak, & Klerman, 1986). We believe that in the McCann and Agras (1990) study, the number of bodily symptoms known to decrease during an observational period, as may be any study per se, must not equally be assigned to lower depression rate in both treatment groups.

There is suspicion that the rater's estimation of depression severity (HAMD) would have been influenced in the open follow-up period. Alternatively, imipramine might imply a specific effect on eating behavior beside its known antidepressant effects as delineated above. Moreover, this is supported by the longer-lasting effect of imipramine on eating behavior than on depression (see above). Despite the effects of the treatment on depression and binge eating frequency over time, the question of adequate dosage may be raised. We used the lowest possible dosage in our study because of the well-known secondary effects that might have augmented the number of dropouts. We adopted the proposal of Schatzberg (1991) and used a total daily dosage of 75 mg of imipramine only.

CONCLUSION

In summary, this study demonstrates that in binge eating obese subjects, diet counseling with psychological support and imipramine therapy (even 6 months posttherapy) is effective in reducing body weight, binge eating frequency, and depression. Long-term (over 2 years) or intermittent treatment with imipramine and diet counseling with psychological support (e.g., every year for 3 months) might positively influence all the above-mentioned parameters. However, more research is needed before general use of this treatment modality can be recommended.

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REFERENCES

Agras, W., Dorian, B., Kirkley, B., Arnow, B., & Bachman, J. (1987). Imipramine in the treatment of bulimia: A double-blind controlled study. International Journal of Eating Disorders, 6, 29–38.

Alger, S., Schwalberg, M., Bigaouette, J., Michalek, A., & Howard, L. (1991). Effect of a tricyclic antidepressant and opiate antagonist on "binge eating" behavior in normoweight bulimics and obese, "binge eating" subjects. Amercian Journal of Clinical Nutrition, 53, 865–871.

American Psychiatric Association. (1980). Diagnostic and statistical manual of mental disorders (3rd ed.). Washington, DC: Author.

American Psychiatric Association. (1987). Diagnostic and statistical manual of mental disorders (3rd Rev. ed.). Washington, DC: Author.

American Psychiatric Association. (1994). Diagnostic and statistical manual of mental disorders (4th ed.). Washington, DC: Author.

Barsky, A., Wyshak, G., & Klerman, G. (1986). Hypochondriasis. An evaluation of the DSM-III criteria in medical outpatients. Archives of General Psychiatry, 43 (5), 493–500.
Björntorp, P. (1992). Abdominal fat distribution and disease: An overview of epidemiological data. Annals of Medicine, 24, 15–18.
Bray, G., & York, D. (1979). Hypothalamic and genetic obesity in experimental animals: An autonomic and endocrine hypothesis. Physiology Review, 59, 719–809.
Brown, G., & Zung, W. (1972). Depresson scales. Self- or physician's rating? Comprehensive Psychiatry, 13, 361–367.
Clark, M., Cargill, B., Medeiros, M., & Pera, V. (1996). Changes in self-efficacy following obesity treatment. Obesity Research, 4 (2), 179–181.
Connolly, V., Gallagher, A., & Kesson, C. (1995). A study of fluoxetine in obese elderly patients with diabetes type 2. Diabetic Medicine, 12 (5), 416–418.
de Zwaan, M., & Mitchell, J. (1992). "Binge eating" in the obese. Annals of Medicine, 24, 303–308.
de Zwaan, M., Nutzinger, D., & Schoenbeck, D. (1992). "Binge eating" in overweight females. Comprehensive Psychiatry, 33, 1–5.
Drenick, E., Bale, G., & Seltzer, F. (1980). Excessive mortality and causes of death in morbidly obese men. Journal of the American Medical Association, 243, 443–445.
Fairburn, C., & Garner, D. (1986). The diagnosis of bulimia nervosa. International Journal of Eating Disorders, 5 (3), 403–419.
Ferguson, J., & Feighner, J. (1987). Fluoxetine-induced weight loss in overweight non-depressed humans. International Journal of Obesity, 11 (Suppl. 3P), 163–170.
Flegal, K. (1996). Trends in body weight and overweight in the US population. Nutrition Review, 54 (4), S97–S100.
Gormally, J., Black, M.D.S., & Rardin, D. (1982). The assessment of "binge eating" severity among obese persons. Addictive Behavior, 7, 47–55.
Guy, W. (1976). Patient termination record in assessment manual for psychopharmacology early clinical drug evaluation program. Rockville, MD: pp. 245–252.
Hamilton, M. (1967). Development of a rating scale for primary depressive illness. British Journal of the Society of Clinical Psychology, 6, 278–296.
Hammer, L. (1992). The development of eating behavior in childhood. Pediatric Clinic of North America, 39, 379–394.
Hill, A., & Blundell, J. (1990). Sensitivity of the appetite control system in obese subjects to nutritiional and serotoninergic challenges. International Journal of Obesity, 14, 219–233.
Keefe, P., Wyshogrood, D., Weinberger, E., & Agras, W. (1984). "Binge eating" and outcome of behavioral treatment of obesity: A preliminary report. Behavior Research and Therapy, 22, 319–321.
Keesey, R., & Hirvonen, M. (1997). Body weight set-points: Detemination and adjustment. Journal of Nutrition, 127 (9), 1875S–1883S.
Kissebah, A., & Krakower, G. (1994). Regional adiposity and morbidity. Physiology Review, 74, 1–12.
Leibowitz, S. (1990). The role of serotonine in eating disorders. Drugs, 39, 33–48.
Levin, B., & Routh, V. (1996). Role of the brain in energy balance. American Journal of Physiology, 271 (3), 40–43.
Levin, B., & Routh, V. (1996). Role of the brain in energy balance and obesity. American Journal of Physiology, 271 (3, Pt. 2), R491–R500.
Loro Jr., A., & Orleans, C. (1981). "Binge eating" in obesity: Preliminary findings and guidelines for behavioral analysis and treatment. Addictive Behaviors, 6, 155–166.
Lowe, M., & Caputo, G. (1991). "Binge eating" in obesity: Toward the specification or predictors. International Journal of Eating Disorders, 10, 49–55.
Marcus, M., Wing, R., Ewing, L., Kern, E., Gooding, W., & McDermott, M. (1990). Psychiatric disorders among obese binge eaters. International Journal of Eating Disorders, 9, 69–77.
Marcus, M., Wing, R., Ewing, L., Kern, E., McDermott, M., & Gooding, W. (1990). A double-blind, placebo-controlled trial of fluoxetine plus behavior modification in the treatment of obese binge-eaters and non-binge-eaters. American Journal of Psychiatry, 147, 876–881.
Marcus, M., Wing, R., & Hopkins, J. (1988). Obese binge eaters: Affect, cognitions and response to behavioral weight control. Journal of Consulting and Clinical Psychology, 56, 433–439.
McCann, U., & Agras, W. (1990). Successful treatment of non-purging bulimia nervosa with desipramine: A double blind, placebo-controlled study. American Journal of Psychiatry, 147, 1509–1513.
Pope, G., Hudson, J., Jonas, J., & Yurgelun-Todd, D. (1983). Bulimia treated with imipramine: A placebo-controlled, double-blind study. American Journal of Psychiatry, 140, 554–558.
Rand, C., & Kuldau, J. (1990). The epidemiology of obesity and self-defined weight problems in the general population: Gender, race, age, and social class. International Journal of Eating Disorders, 9, 329–333.
Salmela, P., Sotaniemi, E., & Viikari, J. (1981). Fenfluramine therapy in non-insulin dependent diabetic patients. Diabetes Care, 4, 535–538.
Schatzberg, A. (1991). Dosing strategies for antidepressant agents. Journal of Clinical Psychiatry, 52 (Suppl.), 14–20.
Smythe, G. (1977). The role of serotonine and dopamine in hypothalamic pituitary function. Clinical Endocrinology, 7, 325–332.

Spitzer, R., Devlin, M., & Walsh, M. (1991). "Binge eating" disorder: To be or not to be in DSM-IV. International Journal of Eating Disorders, 10, 627–629.
Stunkard, A. (1959). Eating patterns and obesity. Psychiatric Quarterly, 33, 284–295.
Stunkard, A. (1996). Current views on Obesity. American Journal of Medicine, 100:230–236.
Suter, P., Weissner, B., Gruene, S, Spühler, T. & Vetter, W. (1993). Heureka study: prevalence of overweight and obesity in Switzerland. Schweizerische Medizinische Rundschau (PRAXIS), 47, 1359–1362.
Wadden, T., & Stunkard, A. (1985). Adverse social and psychological consequences of obesity. Annals of Internal Medicine, 103, 1062–1067.
Wardle, J. (1980). Dietary restraint and "binge eating." Behavioural Analysis and Modification, 4, 201–209.
Wing, R., Marcus, M., Epstein, L., Blair, E., & Burton, L. (1989). "Binge eating" in obese patients with type II diabetes. International Journal of Eating Disorders, 8, 671–679.