International Journal of Neuropsychopharmacology (2005), **8**, 59–63. Copyright © 2004 CINP
DOI: 10.1017/S1461145704004602

ARTICLE

Obesity among outpatients with major depressive disorder

George I. Papakostas, Timothy Petersen, Dan V. Iosifescu, Alana M. Burns, Andrew A. Nierenberg, Jonathan E. Alpert, Jerrold F. Rosenbaum and Maurizio Fava

Depression Clinical and Research Program, Massachusetts General Hospital Harvard Medical School, Boston, MA, USA

Abstract

Studies focusing on the prevalence of obesity in major depressive disorder (MDD), or the impact of excess body fat on the treatment of MDD are lacking. The aim of the present work is to systematically study obesity in MDD outpatients. A total of 369 MDD outpatients enrolled in an 8-wk trial of 20 mg fluoxetine had height and weight measured at baseline. We then examined: (1) the prevalence of being overweight or obese, (2) the relationship between obesity and a number of demographic and clinical variables, and, (3) the relationship between relative body weight and obesity with clinical response. We found that more than 50% of patients were overweight [body mass index (BMI) $\geqslant$25 kg/m^2], while 20% were obese (BMI $\geqslant$30 kg/m^2). Obese patients presented with worse somatic well-being scores than non-obese MDD patients, but they did not differ with respect to depression severity, anxiety, somatic complaints, hopelessness or hostility. Greater relative body weight, but not obesity, predicted non-response. In conclusion, greater relative body weight was found to place MDD outpatients at risk for fluoxetine resistance.

Received 24 November 2003; Reviewed 31 March 2004; Revised 2 May 2004; Accepted 16 May 2004

Key words: Fluoxetine treatment, major depressive disorder, obesity

Introduction

Obesity is a major public health concern. An estimated half of the current US population is overweight [National Task Force on the Prevention and Treatment of Obesity (NTFPTO), 2000], defined as a body mass index (BMI) of 25 kg/m^2 or greater, while the prevalence of obesity in the general population, defined as a BMI of 30 kg/m^2 or greater, has been estimated at 20% for men and 25% for women (Flegal et al., 1998). In addition, the prevalence of obesity has increased more than 50% from 1960 to 1994 (Flegal et al., 1998). Although the adverse impact of obesity on medical illness and all-cause mortality has been well-characterized (Katzmarzyk et al., 2002; NTFPTO, 2000; Pi-Sunyer, 1993; Raman, 2002), less is known about the relationship between obesity and depression. In fact, studies specifically reporting on the prevalence of obesity in major depressive disorder (MDD) or on the impact of excess body fat on the treatment of MDD are lacking. Given the increasing prevalence of obesity in the general population, studies are needed to better define the role of obesity in MDD, and specifically on treatment response with standard antidepressants such as the selective serotonin reuptake inhibitors (SSRIs). The purpose of the present study was to systematically study excess body weight and obesity in MDD outpatients, with a focus on the treatment of MDD.

Address for correspondence: Dr G. I. Papakostas, Massachusetts General Hospital, Department of Psychiatry, Depression Clinical and Research Program, 15 Parkman Street, WACC 812, Boston, MA 02114, USA.
Tel.: (617) 726-6697 *Fax*: (617) 726-7541
E-mail: gpapakostas@partners.org

Methods

A total of 384 outpatients, aged 18–65 yr, who met criteria for a current major depressive episode (MDE) according to the *Structured Clinical Interview for DSM-III-R – Patient Edition* (SCID-P; Spitzer et al., 1989), who were medication-free for at least 2 wk, with a baseline 17-item Hamilton Depression Rating Scale (HAMD-17; Hamilton, 1960) score of $\geqslant$16 were enrolled into an 8-wk, fixed-dose, open-label trial of 20 mg fluoxetine conducted at the Massachusetts General Hospital (MGH) Depression Clinical and Research Program (DCRP). Patients were recruited from November 1992 to January 1999 with the use

of radio advertisements, newspaper advertisements or were referred from colleagues. Institutional Review Board (IRB)-approved written informed consent was obtained from all study participants. Patients who were non- or partial-responders to this open trial were enrolled in a 4-wk, double-blind, triple-dummy, randomized study comparing high dose fluoxetine with augmentation of fluoxetine with either desipramine or lithium. The results of the double-blind study are reported elsewhere (Fava et al., 2002). The present study focuses on the first phase of the trial.

Exclusion criteria included pregnant women and women of childbearing potential who were not using a medically accepted means of contraception, lactating women, patients with serious suicidal risk or serious, unstable medical illness, patients with a history of seizure disorder, patients with the DSM-III-R diagnoses of organic mental disorders, substance use disorders, including alcohol, active within the last year, schizophrenia, delusional disorder, psychotic disorders not elsewhere classified, bipolar disorder, or antisocial personality disorder, patients with a history of multiple adverse drug reactions or allergy to the study drugs, patients with mood-congruent or mood-incongruent psychotic features, current use of other psychotropic drugs, patients with clinical or laboratory evidence of hypothyroidism, patients whose depression had failed to respond in the past to a trial of either higher doses of fluoxetine (60–80 mg/d), or to the combination of fluoxetine and desipramine, or the combination of fluoxetine and lithium, patients who had failed to respond during the course of their current MDE to at least one adequate antidepressant trial, defined as 6 wk or more of treatment with either >150 mg imipramine (or its tricyclic equivalent) or >60 mg phenelzine (or its monoamine oxidase inhibitor equivalent).

During the screen visit, all enrolled patients signed an IRB-approved written informed consent form. A medical and psychiatric history, physical examination, serum chemistries, haematological measures, electrocardiogram (EKG), and urine pregnancy test were then performed. The 31-item of the Hamilton Rating Scale for Depression (HAMD-31) was also administered during the screen visit. The screen visit was conducted by experienced psychologists or psychiatrists. In our group, training in the use of instruments such as the HAMD-31 and SCID-P is done by peer review of videotaped interviews. Our inter-rater reliability for the use of the SCID-P was recently estimated as $\kappa = 0.80$ (Fava et al., 2000). At the conclusion of the screen visit, all enrolled patients were asked to return 1 wk later for the baseline visit.

Visits subsequent to the screen occurred at baseline and then every other week for a total of 8 wk. The HAMD-31 was administered during all study visits. In addition to the HAMD-31, the self-rated Symptom Questionnaire (Kellner, 1987) which contains subscales on depression (SQ-D), anxiety (SQ-A), anger/hostility (SQ-H), somatic symptoms (SQ-SS), and somatic well-being (SQ-SWB) along with the self-rated Beck Hopelessness Scale (BHS; Beck & Steer, 1988) were also administered during the baseline visit.

Patients who returned for their baseline visit were started on a 20 mg, fixed-dose regimen of fluoxetine. A responder was defined as having a 50% or greater reduction in HAMD-17 score from baseline to end-point. An intent-to-treat (ITT) analysis with the last observation carried forward was used to define the severity of depression at end-point, in which the last recorded HAMD-17 score substituted the end-point score for patients who prematurely discontinued the study. BMI was defined as weight (in kg)/height^2 (in m^2). A total of 369 patients had both height and weight measured at baseline, allowing for the calculation of baseline BMI.

Statistical tests

The National Institutes of Health Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults (NIH, 1998) define overweight as a BMI equal to or greater than 25 kg/m^2 and obesity as a BMI equal to or greater than 30 kg/m^2, with healthy weight corresponding to a BMI between 19 and 25. Defining overweight as a minimum BMI of 25 kg/m^2 is also consistent with recommendations of the WHO (1998). Appropriate parametric and non-parametric tests were used to compare differences in variables between obese and non-obese patients. With the use of separate logistic regressions we then tested for the relationship between (1) relative body weight (BMI as a continuous variable), (2) overweight status, (3) obesity, or (4) change in weight during the 8-wk trial and clinical response, controlling for gender and the severity of depression at baseline (HAMD-17 total score). We chose to control for gender because of a recent study showing a gender-based discrepancy in the relationship between body weight and MDD (Carpenter et al., 2000).

Results

In total, 369 (96.0%) of the original 384 outpatients had both height and weight recorded at baseline. The sample consisted of 199 women (53.9%) and 170 men

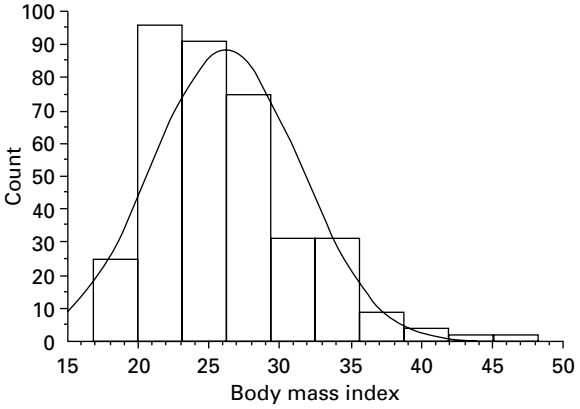

Figure 1. The distribution of MDD patients according to body mass index.

(46.1%). The mean age for the entire sample in years was 39.8±10.4 yr. In total, 312 (84.5%) out of 369 patients completed the study. Of these, 202 (54.7%) patients responded to treatment. The mean length of time in the study for responders was 7.6±1.2 vs. 6.5±2.7 for non-responders.

The mean baseline BMI for the entire sample was 26.5±5.2 kg/m². The distribution of BMI for the entire sample is presented in Figure 1. Of all 369 patients with BMI measured at baseline, 190 patients were overweight (51.4%). 94 of 199 women were overweight (47.2%) and 96 of 170 men (56.5%). There were 74 patients who were classified as obese (20.0%). Fifty out of 199 women (25.1%) and 24 out of 170 men (14.1%) were obese. Demographic and clinical characteristics of obese vs. non-obese MDD patients are presented in Table 1.

A logistic regression revealed that greater relative body weight predicted non-response ($p=0.049$, $\chi^2=3.843$, coefficient/S.E. = 1.960, 95% CI 1.000–1.076). There was a trend towards statistical significance for poorer outcome in patients who were overweight ($p=0.067$). The presence of obesity did not significantly predict outcome ($p=0.16$). The mean BMI in responders and non-responders was 25.9±5.2 kg/m² vs. 27.1±7.0 kg/m². There was no statistically significant change in weight during the trial (81.1±24.7 vs. 81.3±24.6 kg). Change in weight did not predict outcome.

Table 1. Demographic and clinical characteristics of obese vs. non-obese MDD patients

Characteristic	Obese ($n=74$)	Non-obese ($n=295$)	p
Duration MDE (yr)	4.0±7.5	3.2±5.5	>0.05
Number MDEs	25.3±40.7	18.6±35. 1	>0.05
Age onset (yr)	25.4±14.2	26.1±13.2	>0.05
HAMD-17	19.9±3.4	19.7±3.4	>0.05
Beck Hopelessness Scale	12.5±5.2	11.3±5.0	>0.05
SQ-Depression	17.4±5.4	16.9±4.6	>0.05
SQ-Anxiety	15.8±4.7	15.1±5.1	>0.05
SQ-Anger/Hostility	12.3±6.6	11.8±6.4	>0.05
SQ-Somatic symptoms	11.1±5.5	9.3±5.6	>0.05
SQ-Somatic well-being	1.1±1.5	2.0±2.1	0.018
Anorexia/current	0	0	>0.05
Anorexia/history	1	8	>0.05
Bulimia/current	1	1	>0.05
Bulimia/history	5	21	>0.05
Cigarettes (per day)	3.0±8.2	2.9±8.0	>0.05

SQ, Symptom Questionnaire.

Discussion

More than half of the present sample of outpatients with MDD were overweight, while 20% of patients were obese. Nearly 25% of women and 14% of men were found to be obese. These figures reflect the national average (Flegal et al., 1998; NTFPTO, 2000), with the exception of the somewhat lower prevalence of obesity among men from the present sample compared to the national average (14% vs. 20%). These results are also in line with studies looking at the incidence of obesity in bipolar disorder reported between 21% (McElroy et al., 2002) to 35.4% (Fagiolini et al., 2003).

Carpenter et al. (2000) were the first to report on the relationship between body weight and MDD. In an epidemiological study involving more than 40000 subjects nationwide, the authors reported that greater relative body weight was associated with an increased risk for past-year MDD and suicidal ideation among women while lesser relative body weight was associated with an increased risk for past-year MDD, suicidal ideation and suicide attempts among men. Shortly thereafter, Roberts et al. (2000) found that obesity, defined as a BMI at the 85th percentile or higher, predicted MDD after a 1-yr follow-up. This finding was soon replicated for longer follow-up periods (Roberts et al., 2003). While these reports suggest an increased risk of depression in obese patients, our study suggest that MDD outpatients are not more likely to be obese than their non-depressed counterparts. In addition, while obese MDD patients presented with worse somatic well-being scores than non-obese MDD patients, they did not differ on the basis of depression severity,

or in the severity of a number of depressive symptoms including anxiety, somatic complaints, hopelessness or hostility.

However, our study suggests that greater BMI is associated with an increased risk of non-response to treatment in MDD. Recently, Fagiolini et al. (2003) reported a shorter time to recurrence during the maintenance phase of treatment in obese than non-obese outpatients with bipolar I disorder. That a dichotomous definition of high or normal BMI such as obesity or being overweight did not significantly predict treatment response in our trial is in line with the aforementioned epidemiological study by Carpenter et al. (2000) that found a link between greater relative body weight (BMI continuous) and MDD, but not between obesity (dichotomous) and MDD. Thus, it may be that a definition of obesity as a minimum BMI of 30 kg/m² may not be best suited for the purposes of studying any adverse effects of excess weight on mood or the treatment of depression.

Limitations

One limitation of the present study is the absence of data on body fat distribution, which is an independent predictor of health risk (NIH, 1998). Another limitation is that of sampling bias. Clinical trials have a number of inclusion and exclusion criteria and as a result, patients in clinical trials do not directly reflect the typical outpatient population. This may be particularly true in the present study, since we excluded patients with severe/unstable medical illness. As a result, given the relationship between excess body fat and poor health status, many patients excluded on this basis may have been overweight or obese. An additional limitation is the lack of data on the treatment history of patients enrolled in the study which may have shed further light on the inter-relationship between relative body weight and treatment response in depression. Thus, the degree to which these findings generalize to a more heterogeneous population of depressed patients including those with severe severe/unstable medical illness remains to be determined. The final limitation is the absence of a control group which would help clarify to what degree the adverse impact of excessive body weight on outcome to pharmacotherapy with fluoxetine is mediated through decreasing drug or placebo response rates.

Conclusion

While some epidemiological studies suggest an increased risk of MDD in obesity, the prevalence of obesity in the present sample of outpatients with MDD does not appear to differ from the general population. In addition, while obese MDD patients presented with worse somatic well-being scores than non-obese MDD patients, they did not differ with respect to depression severity, anxiety, the number of somatic complaints, hopelessness or hostility at baseline than non-obese patients. However, greater relative body weight was found to place MDD outpatients at risk for fluoxetine resistance regardless of the severity of depression at baseline. Studies with less stringent inclusion/exclusion criteria or focusing on the medically ill may yield different results.

Acknowledgements

Supported by NIMH grant no. R01-MH-48-483-05 (M.F.), the American College of Neuropsychopharmacology/GlaxoSmithKline Fellowship in Clinical Neuropsychopharmacology (G.I.P.), and the Harvard Medical School/Kaplen Fellowship in Depression Research (G.I.P.).

Statement of Interest

None.

References

Beck AT, Steer RA (1988). Manual for the Beck Hopelessness Scale. San Antonio: Psychological Corp.

Carpenter KM, Hasin DS, David AB, Myles FS (2000). Relationships between obesity and DSM-IV major depressive disorder, suicide ideation, and suicide attempts: results from a general population study. *American Journal of Public Health 92*, 251–257.

Fagiolini A, Kupfer DJ, Houck PR, Novick DM, Frank E (2003). Obesity as a correlate of outcome in patients with bipolar I disorder. *American Journal of Psychiatry 160*, 112–117.

Fava M, Alpert JE, Nierenberg AA, Russell JM, O'Boyle M, Camilleri A, Harrison WM (2000). A validation study of a computerized management system for the diagnosis and treatment of depression. Report presented at the American Psychiatric Association Annual Meeting.

Fava M, Alpert J, Nierenberg A, Lagomasino I, Sonawalla S, Tedlow J, Worthington J, Baer L, Rosenbaum JF (2002). Double-blind study of high-dose fluoxetine versus lithium or desipramine augmentation of fluoxetine in partial responders and nonresponders to fluoxetine. *Journal of Clinical Psychopharmacology 22*, 379–387.

Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL (1998). Overweight and obesity in the United States: prevalence and trends, 1960–1994. *International Journal of Obesity and Related Metabolic Disorders 22*, 39–47.

Hamilton M (1960). A rating scale for depression. *Journal of Neurology Neurosurgery and Psychiatry 23*, 56–62.

Katzmarzyk PT, Craig CL, Bouchard C (2002). Adiposity, adipose tissue distribution and mortality rates in the Canada Fitness Survey follow-up study. *International Journal of Obesity and Related Metabolic Disorders 26*, 1054–1059.

Kellner R (1987). A Symptom Questionnaire. *Journal of Clinical Psychiatry 48*, 268–274.

McElroy SL, Frye MA, Suppes T, Dhavale D, Keck Jr. PE, Leverich GS, Altshuler L, Denicoff KD, Nolen WA, Kupka R, Grunze H, Walden J, Post RM (2002). Correlates of overweight and obesity in 644 patients with bipolar disorder. *Journal of Clinical Psychiatry 63*, 207–213.

National Task Force on the Prevention and Treatment of Obesity (NTFPTO) (2000). Overweight, obesity, and health risk. *Archives of Internal Medicine 16*, 898–904.

National Institutes of Health (NIH) (1998). Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report. *Obesity Research 6* (Suppl. 2), S51–S209.

Pi-Sunyer FX (1993). Medical hazards of obesity. *Annals of Internal Medicine 119*, 655–660.

Raman RP (2002). Obesity and health risks. *Journal of the American College of Nutrition 21*, S134–S139.

Roberts RE, Deleger S, Strawbridge WJ, Kaplan GA (2003). Prospective association between obesity and depression: evidence from the Almeida county study. *International Journal of Obesity and Related Metabolic Disorders 27*, 514–521.

Roberts RE, Kaplan GA, Shema SJ, Strawbridge WJ (2000). Are the obese at greater risk for depression? *American Journal of Epidemiology 152*, 163–170.

Spitzer RL, Williams JBW, Gibbon M, First M (1989). *Structured Clinical Interview for DSM-III-R – Patient Edition* (SCID-P). New York: New York State Psychiatric Institute, Biometrics Research Department.

WHO (1998). Obesity: preventing and managing the global epidemic. In: Report of a World Health Organization Consultation on Obesity, Geneva, 3–5 June 1997. Geneva, Switzerland: World Health Organization, pp. 1–276.