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Research report

Body weight as a predictor of antidepressant efficacy in the GENDEP project

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ABSTRACT

Background: Being overweight or obese may be associated with poor response to antidepressants. The present report explores the moderation of antidepressant response by body weight to establish the specificity to antidepressant mode of action, type of depressive symptoms and gender.

Methods: Height and weight were measured in 797 men and women with major depression treated with escitalopram or nortriptyline for twelve weeks as part of the Genome Based Therapeutic Drugs for Depression (GENDEP) project. Body mass index (BMI) and obesity (BMI > 30) were tested as predictors of change in depressive symptoms using mixed linear models.

Results: Higher BMI and obesity predicted poor response to nortriptyline but did not significantly influence response to escitalopram. The moderation of response by body weight was due to differential improvement in neurovegetative symptoms, including sleep and appetite. The relationship between body weight and change in neurovegetative symptoms was moderated by gender with obese men responding less to nortriptyline and obese women having poorer response to both antidepressants.

Limitations: As no placebo arm was included, the specificity of findings to antidepressants is relative. Lack of specific measures precluded accounting for differences in body fat distribution.

Conclusions: Body weight should be considered in the assessment of depression as it may inform the selection of antidepressant treatment.

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1. Introduction

Depression is a common and disabling condition (Kruijsaar et al., 2003). A number of antidepressant drugs are available, but great individual variability in response to each of them makes the outcome of treatment uncertain.

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Therefore, predictors of response to specific antidepressants are needed to inform treatment in individual cases (Nierenberg, 2003). Body weight is easily obtainable and is likely to influence drug response through pharmacokinetic and pharmacodynamic mechanisms (Greenblatt et al., 2002). Three independent studies suggest that higher relative body weight or obesity predict poor response to antidepressants (Khan et al., 2007; Kloiber et al., 2007; Papakostas et al., 2005). However, these three studies differ in several important aspects, precluding useful summary conclusions. First, it is unclear whether body weight moderates response to all antidepressants to similar extent as no previous study compared the relative effect of body weight on response to different antidepressants. One study showed a small effect of body weight on response to fluoxetine (Papakostas et al., 2005) and two studies investigated combined groups of patients treated by various antidepressants (Khan et al., 2007; Kloiber et al., 2007). Second, it is uncertain whether a continuous measure of body weight or categorical definition of obesity should be used as predictor of response. One previous study favoured body mass index as a continuous measure (Papakostas et al., 2005), and two studies used categorical definitions of overweight (Kloiber et al., 2007) or obesity (Khan et al., 2007). Third, it is unknown whether body weight and obesity are associated with differential response in all depressive symptoms as most studies used heterogeneous measures grouping weakly correlated symptoms into a single score (Bagby et al., 2004; Bech, 2006; Uher et al., 2008). One study suggested a specific association between body weight and neurovegetative symptoms of depression, such as sleep and appetite (Kloiber et al., 2007). Finally, it is possible that effects of body weight differ by gender as sex-specific associations between obesity and depression have been reported (Blaine, 2008; Carpenter et al., 2000; Lim et al., 2008) and one study found a significant gender-by-obesity interaction in predicting the outcome of antidepressant treatment (Khan et al., 2007).

In GENDEP, we test the hypothesis that body weight differentially predicts response to two antidepressants with distinct modes of action: the serotonin-reuptake inhibiting escitalopram and the predominantly noradrenaline-reuptake inhibiting nortriptyline. We compare body mass index, a continuous measure of body weight relative to height, with categorical definition of obesity as predictors of outcome. In addition to the overall change in depression severity, we explore the role of body weight and obesity in moderating change in specific internally consistent symptom dimensions, derived by factor analysis of categorical variables and including observed mood, cognitive symptoms, and neurovegetative symptoms (Uher et al., 2008). Finally, we systematically explore the role of body weight in relation to gender.

2. Methods

2.1. Study design and sample

The Genome Based Therapeutic Drugs for Depression (GENDEP) is a twelve-week open-label part-randomized multi-centre clinical and pharmacogenetic study with two active pharmacological treatment arms (Uher et al., 2009). It was designed to establish clinical and genetic determinants of

therapeutic response to two antidepressants with contrasting primary modes of action: nortriptyline (a tricyclic antidepressant with strong affinity to noradrenaline transporter) and escitalopram (a selective serotonin-reuptake inhibitor). Eight-hundred-and-eleven adults diagnosed with ICD-10/DSM-IV unipolar major depression of at least moderate severity established in the SCAN interview (Wing et al., 1998) were recruited in eight European countries: Belgium, Croatia, Denmark, Germany, Italy, Poland, Slovenia, and UK, between July 2004 and December 2007. Recruitment was restricted to individuals of white European parentage. Personal or family history of bipolar disorder or schizophrenia and active substance dependence constituted exclusion criteria. The study was approved by ethics boards in all participating centres. All participants provided a written consent after the procedures were explained. GENDEP is registered at EudraCT (No.2004-001723-38, <http://eudract.emea.europa.eu>) and ISRCTN (No. 03693000, <http://www.controlled-trials.com>). A detailed description of the GENDEP sample and design is available elsewhere (Uher et al., 2009).

2.2. Interventions

Two antidepressants were selected that represent the two most common mechanisms of action among commonly used antidepressants and have a good efficacy record. Escitalopram is a highly selective inhibitor of the serotonin transporter with no effect on noradrenaline-reuptake (Sanchez et al., 2003). Nortriptyline is a tricyclic antidepressant with a hundred times higher affinity for the noradrenaline transporter than for the serotonin transporter (Sanchez and Hyttel, 1999).

Participants for whom the two antidepressants were clinically considered to be at equipoise were randomly allocated to receive escitalopram or nortriptyline using a random number generator, stratified by centre and performed independently of the assessing clinician: 233 were randomized to escitalopram and 235 to nortriptyline. Patients with contraindications for one of the drugs were allocated non-randomly to the other antidepressant: 225 to escitalopram and 118 to nortriptyline. Previous non-response or adverse reaction to one of the study antidepressants or a related drug and medical conditions constituting relative contraindications were the most common reasons for non-random allocation. Escitalopram was initiated at 10 mg daily and increased to a target dose of 15 mg daily within the first two weeks, and could be further increased to 20 mg daily (and up to 30 mg in cases where there was clinical agreement that higher dose is needed). Nortriptyline was initiated at 50 mg daily and titrated to a target dose of 100 mg daily within the first two weeks, and could be further increased to 150 mg daily (and up to 200 mg in cases where there was clinical agreement that higher dose is needed). Other psychotropic medication was not allowed with the exception of occasional use of hypnotics. Compliance was monitored weekly by self-reported pill count and plasma levels of antidepressants were measured at week 8. Of the 811 participants, 628 (77%) completed eight weeks and 527 (65%) completed twelve weeks on the originally allocated antidepressant. Individuals randomly allocated to nortriptyline were more likely to discontinue treatment than individuals allocated non-randomly or those allocated to escitalopram. Individuals treated with escitalopram and nortriptyline improved to a similar degree

on traditional measures of depressive symptoms (Uher et al., 2009).

2.3. Measures

Body weight and height were measured by calibrated medical scales and measures at baseline assessment before the initiation of study medication. Body mass index (BMI), a continuous measure of body weight relative to height, was calculated as body weight in kilograms divided by squared height in meters (kg m^{-2}). Categorical definitions of underweight ($\text{BMI} < 19$), overweight ($25 < \text{BMI} < 30$) and obesity ($\text{BMI} > 30$) follow the recommendations of the World Health Organisation (WHO, 1998) and the US National Institute of Health Clinical Guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults (NIH, 1998) and are consistent with previous reports (Khan et al., 2007; Kloiber et al., 2007; Papakostas et al., 2005).

Depression severity was measured weekly with three established scales: the clinician-rated 10-item Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), the 17-item Hamilton Rating Scale for Depression (HRSD-17) (Hamilton, 1967), and the self-report 21-item Beck Depression Inventory (BDI) (Beck et al., 1961). The MADRS and HRSD-17 were administered by trained psychologists and psychiatrists, who achieved high inter-rater reliability on recorded interviews (Uher et al., 2008). A psychometric analysis found that MADRS was more internally consistent and had higher information content than HRSD-17 and, therefore, MADRS is used as the primary outcome measure (Uher et al., 2008). We further found that depressive symptoms could be better described by three symptom dimensions derived by categorical item factor analysis: observed mood, cognitive symptoms and neurovegetative symptoms. The dimensional scores are obtained based on a graded item-response theory model fitted to non-overlapping sets of items and using the previously reported item parameters (Uher et al., 2008) in MULTILOG-7 (Thissen et al., 2003). The *observed mood* dimension comprises clinician-rated items assessing core mood symptoms, anxiety and activity. The *cognitive symptoms* dimension includes items assessing pessimism, guilt, suicidality and the majority of self-report items from the BDI. The *neurovegetative symptoms* dimension comprises insomnia, poor appetite, weight loss and decreased libido.

2.4. Statistical analysis

All available weekly data on response to antidepressants in subjects with available measures of height and weight were included in the analyses. The effects of BMI and obesity on response to antidepressants were tested using linear mixed models fitted with maximum likelihood. The mixed models account for the clustering of individuals within centres, allow use of all repeated measurements, and provide unbiased estimates in the presence of dropout without imputation (Gueorguieva and Krystal, 2004; Lane, 2008). It has been repeatedly demonstrated that mixed models are preferable to end-point analyses with last-observation-carried forward procedure (Lane, 2008; Mallinckrodt et al., 2001). All models included fixed effects of time (linear and quadratic), baseline depression severity, drug, age and sex, and random effects of

individual and recruitment centre. To account for correlations between repeated observations, the intercept and slope of time were allowed to vary randomly between subjects. Each predictor was first tested for main effect across the whole sample. In a second step, we tested the interaction between drug (escitalopram vs. nortriptyline) and the predictor (BMI or obesity). Third, we tested the interaction between gender and the predictor and, finally, the three-way interaction between drug, gender and the predictor of interest. Where significant interactions were found, we proceeded to subgroup analyses with mixed linear models to characterise the interaction. Nested models with and without a predictor or interaction of interests were compared using likelihood ratio tests. Statistical significance threshold for all analyses was set at $\alpha = 0.05$, uncorrected. To compare non-nested models with alternative predictors (continuous BMI vs. categorical obesity), we used the Bayesian Information Criterion (BIC) (Schwartz, 1978). BIC, calculated from the maximised likelihood with a correction for number of parameters estimated in the model, is commonly used to select the best fitting and most parsimonious models. Smaller BIC indicates a better model, with differences of less than 5 considered as negligible and differences more than 10 considered as strong evidence favouring one model over another (Raftery, 1995). Statistical analyses were performed in STATA 10.

3. Results

3.1. Sample characteristics

Weight and height at baseline were measured in 797 (98%) of the 811 GENDEP participants. The 14 subjects with missing data on weight did not significantly differ on depression severity or other clinical or demographic characteristics. For subjects with available data on height and weight, the demographic and clinical characteristics, and medication history by treatment arm are shown in Table 1. More subjects were non-randomly allocated to treatment with escitalopram than with nortriptyline. The groups treated by escitalopram and nortriptyline were similar on most clinical and demographic characteristics. Significantly more subjects treated with nortriptyline had recurrent depression ($\chi^2(1) = 6.59$, $p = 0.01$) and had history of previous treatment with antidepressants ($\chi^2(1) = 4.30$, $p = 0.04$) compared to subjects treated with escitalopram. These differences were restricted to non-randomly allocated participants. There was no difference on clinical or demographic variables between subjects who were randomly allocated to escitalopram and nortriptyline. To control for potential measured and unmeasured confounders associated with non-random allocation, we performed a series of sensitivity analyses restricted to the randomly allocated subjects. In addition, recurrence of depression was entered as a covariate in all analyses.

3.2. Body weight at baseline

The male subjects had an average body weight of 83.8 kg and body height 1.79 m, giving them an average BMI of 26.2. The female subjects had an average body weight of 67.8 kg and height 1.64 m, giving them an average BMI of 25.1. In addition to gender, baseline BMI was significantly associated with age and

Table 1
Baseline sample characteristics

	Escitalopram		Nortriptyline	
	n/mean	%/S.D.	n/mean	%/S.D.
Number	467		330	
Randomly allocated	226	48.4%	215	34.9%
Female	285	61.0%	212	64.0%
Age	42.8	11.6	42.7	11.8
Married/cohabiting	276	59.1%	187	56.7%
Unemployed	99	21.2%	77	23.3%
Recurrent depression	262	56.1%	215	65.2%
Duration of current episode (weeks)	22.1	17.2	21.1	18.3
History of taking any antidepressant	203	43.5%	168	50.9%
History of taking SSRI	133	28.5%	122	37.0%
History of taking tricyclics	72	15.4%	58	17.6%
History of taking mirtazapine	23	4.9%	22	6.7%
Taking an antidepressant at recruitment	89	19.1%	81	24.6%
Taking hypnotics at recruitment or any time during the study	191	40.9%	114	34.6%
MADRS total score	28.3	6.6	29.2	6.8
Observed mood	0.93	0.57	0.96	0.60
Cognitive symptoms	0.73	0.68	0.78	0.70
Neurovegetative symptoms	0.69	0.72	0.78	0.71
BMI (weight/height ²)	25.4	4.7	25.7	5.1
Obese (BMI > 30)	67	14.4%	48	14.6%
Overweight (25 < BMI < 30)	155	33.2%	115	34.9%
Underweight (BMI < 19)	25	5.4%	14	4.2%

Demographic and clinical characteristics at baseline are given as counts and percentages for categorical variables and mean and standard deviations for continuous variables.

centre of recruitment. On average, BMI increased by 0.86 points for every 10 years of age (95%CI 0.57 to 1.15) and was significantly lower in subjects recruited in Italy and Poland than in other centres. Therefore, age, sex and centre of recruitment were included in all analyses. Baseline BMI was not significantly related to depression severity, recurrence, episode duration, medication history, mode of allocation, treatment arm, marital or occupational status.

3.3. Effect of body weight on primary outcome

Higher body mass index at baseline significantly predicted worse outcome on the MADRS scale in the whole sample ($\beta=0.0089$, 95%CI 0.0011 to 0.0166, $p=0.0253$) and this prediction was only slightly attenuated after controlling for sex, age and treatment arm ($\beta=0.0081$, 95%CI 0.0002 to 0.0161, $p=0.0456$). There was a significant interaction between drug and baseline BMI ($p=0.0456$) due to a significant effect of baseline BMI among nortriptyline-treated ($\beta=0.0174$, 95%CI 0.0059 to 0.0289, $p=0.0031$) but not among escitalopram-treated subjects ($\beta=0.0033$, 95%CI -0.0075 to 0.0141, $p=0.5469$). The two-way interaction between sex and baseline BMI and three-way interaction between drug, sex and baseline BMI were non-significant ($p=0.6114$ and $p=0.3165$ respectively).

3.4. Effect of body weight on specific dimensions of depressive symptoms

We further explored the effect of body weight on specific symptom dimensions of observed mood, cognitive and neurovegetative symptoms to characterise the nature of the moderating effect of body weight on antidepressant treat-

ment outcome. Across the whole sample, baseline BMI did not significantly moderate change in observed mood ($\beta=0.0068$, 95%CI -0.0010 to 0.0147, $p=0.0881$) or cognitive symptoms ($\beta=0.0054$, 95%CI -0.0028 to 0.0136, $p=0.1980$), but higher baseline BMI predicted less improvement in neurovegetative symptoms ($\beta=0.0210$, 95%CI 0.0123 to 0.0298, $p<0.0001$). As the effect of BMI was restricted to neurovegetative symptoms, we further explored the two facets of neurovegetative symptoms: disturbed sleep and loss of appetite. Higher baseline BMI was associated with less improvement in both sleep ($\beta=0.0216$, 95%CI 0.0110 to 0.0322, $p=0.0001$) and appetite ($\beta=0.0148$, 95%CI 0.0046 to 0.0250, $p=0.0045$).

Similarly, the interaction effects were restricted to neurovegetative symptoms. All three interaction terms (BMI \times drug, BMI \times sex, and BMI \times drug \times sex) were non-significant for observed mood or cognitive symptoms (all $p>0.1$). For neurovegetative symptoms there was a significant three-way BMI \times drug \times sex interaction ($p=0.0253$) in addition to a significant two-way BMI \times drug interaction ($p=0.0226$). The direction of association was the same in all sex-drug groups, with higher baseline BMI predicting worse outcome, but the strength of the association differed markedly by sex and drug. The effect of BMI on change in neurovegetative symptoms was strongest among men treated with nortriptyline ($\beta=0.03914$, 95%CI 0.0056 to 0.0727, $p=0.0224$), intermediate in women treated with either nortriptyline ($\beta=0.0240$, 95%CI 0.0093 to 0.0387, $p=0.0013$) or escitalopram ($\beta=0.0188$, 95%CI 0.0042 to 0.0334, $p=0.0118$) and weakest among men treated with escitalopram ($\beta=0.0151$, 95%CI -0.0053 to 0.0356, $p=0.1470$).

3.5. Obesity as a categorical predictor of outcome

In addition to continuous measure of body weight, we explored the categorical definition of obesity (BMI > 30) as a predictor of outcome. In the whole sample, obesity predicted worse outcome on MADRS ($\beta=0.1257$, 95%CI 0.0185 to 0.2330, $p=0.0215$). As for the continuous BMI measure, the moderating effect of obesity consisted primarily of a strong influence on change in neurovegetative symptoms ($\beta=0.2551$, 95%CI 0.1373 to 0.3729, $p<0.0001$). Obesity had a more modest but significant effect on observed mood ($\beta=0.1257$, 95%CI 0.0104 to 0.2227, $p=0.0313$) and a weak effect on cognitive symptoms ($\beta=0.1070$, 95%CI -0.0036 to 0.2176, $p=0.0578$).

For MADRS total score, there was a significant interaction between obesity and drug ($p=0.0347$), with obesity predicting a worse outcome among nortriptyline-treated subjects ($\beta=0.2701$, 95%CI 0.1067 to 0.4334, $p=0.0012$) but not among escitalopram-treated subjects ($\beta=0.0308$, 95%CI -0.1122 to 0.1737, $p=0.6730$) in both men and women (Fig. 1).

For neurovegetative symptoms, there was a significant three-way obesity \times drug \times sex interaction ($p=0.0171$) in addition to a two-way obesity \times drug interaction ($p=0.0039$). As with the continuous BMI measure, obesity was associated with worse outcome in all groups but the strength of effect differed by drug and sex: the effect of obesity on change in neurovegetative symptoms was strongest among men treated with nortriptyline ($\beta=0.4706$, 95%CI 0.1410 to 0.8002, $p=0.0051$), intermediate in women treated with either nortriptyline ($\beta=0.2767$, 95%CI 0.0429 to 0.5106, $p=0.0203$) or escitalopram ($\beta=0.2643$, 95%CI 0.0551 to 0.4735, $p=0.0133$) and weakest among men treated with escitalopram ($\beta=0.0786$, 95%CI

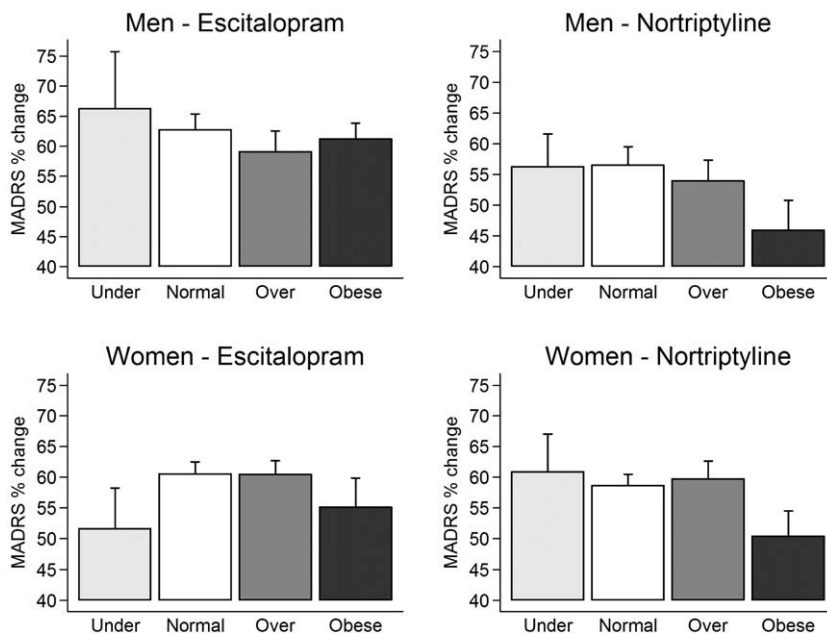


Fig. 1. Relationship between improvement on MADRS and baseline BMI category by drug and sex. The y axis represents the mean percentage change in MADRS total score over the twelve weeks of treatment. Error bars represent one standard error of the mean. The bars, starting from the left, represent subjects who were underweight (light gray bar; BMI less than 19), normal weight (white bar, BMI 19 to 25), overweight (gray bar; BMI 25 to 30), and obese (black bar, BMI more than 30) at baseline. The graphs are based on observed values with best unbiased linear estimates from linear mixed models imputed in place of missing values.

-0.1406 to 0.2978, $p=0.4821$; Fig. 2). All interaction terms were non-significant when observed mood or cognitive symptoms were the dependent variables.

Underweight (BMI<19) or overweight ($25<BMI<30$) were not significant predictors of outcome on MADRS or symptom dimensions (Figs. 1 and 2).

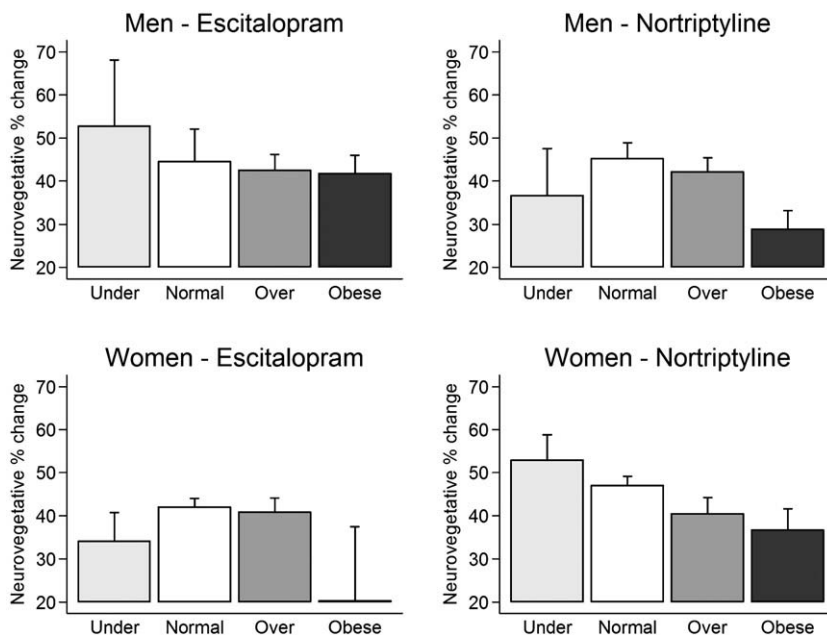


Fig. 2. Relationship between improvement in neurovegetative symptoms and baseline BMI category by drug and sex. The y axis represents the mean percentage change in the neurovegetative symptom score including items of sleep, appetite, weight and libido, over the twelve weeks of treatment. Error bars represent one standard error of the mean. The bars, starting from the left, represent subjects who were underweight (light gray bar; BMI less than 19), normal weight (white bar, BMI 19 to 25), overweight (gray bar; BMI 25 to 30), and obese (black bar, BMI more than 30) at baseline. The graphs are based on observed values with best unbiased linear estimates from linear mixed models imputed in place of missing values.

3.6. Comparison of continuous BMI and categorical obesity as predictors of antidepressant response

As either the continuous BMI or the categorical obesity measure significantly predicted change in depressive symptoms during treatment, we compared the relative fit of the two predictors using Bayesian Information Criterion (BIC). For the overall prediction of change in MADRS total score, the BIC was 10,965.4 if BMI was used as a continuous predictor and 10,964.7 if obesity was used as a categorical predictor. As the difference between the two is negligible, it can be concluded that continuous BMI or categorical definition of obesity are equally potent alternative predictors of outcome with antidepressant treatment.

3.7. Sensitivity analysis in randomly allocated subjects

To test whether the results are not due to a selection bias due to the non-random allocation of a proportion of subjects to antidepressants, we repeated the analyses in the restricted sample of randomly allocated participants. For MADRS total scores, the drug-by-BMI interaction remained significant in the randomized sample ($p=0.0473$) with a strong effect of baseline BMI among nortriptyline-treated ($\beta=0.0192$, 95%CI 0.0062 to 0.0322, $p=0.0039$) but no effect among escitalopram-treated subjects ($\beta=0.0001$, 95%CI -0.0156 to 0.0171, $p=0.9283$). The results for specific symptom dimensions were also similar in the randomised sample with higher baseline BMI predicting less improvement in neurovegetative symptoms ($\beta=0.0199$, 95%CI 0.0084 to 0.0314, $p=0.0007$) but not on observed mood or cognitive symptoms.

Categorically defined obesity (BMI>30) predicted less improvement in neurovegetative symptoms among randomly allocated participants ($\beta=0.2283$, 95%CI 0.0712 to 0.3854, $p=0.0044$). Effects of obesity on change in MADRS total score, observed mood and cognitive symptoms were consistent with the whole sample analysis (all within one standard error of measurement), but were not significant due to the smaller size of the randomized sample. Obesity predicted poor outcome among individuals who were randomly allocated to treatment with nortriptyline ($\beta=0.2667$, 95%CI 0.0713 to 0.4621, $p=0.0075$) but not in those randomly allocated to escitalopram ($\beta=-0.0004$, 95%CI 0.2026 to 0.2019, $p=0.9972$). Interaction terms did not reach significance in the reduced sample.

3.8. Testing alternative explanations

To test whether the association between higher baseline BMI and worse outcome among nortriptyline-treated subjects is not due to reduced compliance or inadequate dosage of nortriptyline, we have repeated the analyses after correcting for the dose and self-reported compliance. As dose is drug-specific, these analyses were limited to single treatment arm. The effect of baseline BMI on outcome among nortriptyline-treated subjects remained essentially unchanged after accounting for these potential confounders (for MADRS: $\beta=0.0163$, 95%CI 0.0041 to 0.0286, $p=0.0091$). Similarly, the effect of categorically defined obesity on outcome among nortriptyline-treated subjects remained similar after accounting for dose, and compliance (for MADRS: $\beta=0.2416$, 95%CI 0.0682 to 0.4150, $p=0.0063$).

3.9. Exploring plasma levels of antidepressants as a mediator

To investigate whether the effect of body weight on outcome is pharmacokinetically mediated, we have explored the role of plasma levels of antidepressants and their proximal metabolites. As plasma levels are not comparable between the two antidepressants, these analyses were performed separately for each antidepressant.

At week 8, the median dose of escitalopram was 15 mg (interquartile range 10–20 mg) and the median dose of nortriptyline was 100 mg (interquartile range 75–125 mg).

Subjects treated with escitalopram had mean plasma levels 32.0 $\mu\text{g/L}$ (S.D. 21.9) of citalopram and 10.8 $\mu\text{g/L}$ (S.D. 4.5) of desmethyl-citalopram. As expected, dose of escitalopram at week 8 was significantly positively related to the plasma levels of citalopram ($b=1.78$, 95%CI 1.37 to 2.19, $p<0.001$) and desmethyl-citalopram ($b=0.44$, 95%CI 0.36 to 0.52, $p<0.001$). Body mass index was not related to plasma levels of citalopram ($b=0.04$, 95%CI -0.57 to 0.65, $p=0.900$) but was significantly negatively related to the plasma levels of its metabolite desmethyl-citalopram ($b=-0.26$, 95%CI -0.39 to -0.14 , $p<0.001$) after controlling for dose.

Subjects treated with nortriptyline had mean plasma levels 95.9 $\mu\text{g/L}$ (S.D. 55.2) of nortriptyline and 78.0 $\mu\text{g/L}$ (S.D. 48.0) of 10-hydroxy-nortriptyline. As expected, dose of nortriptyline at week 8 was significantly positively related to the plasma levels of nortriptyline ($b=0.48$, 95%CI 0.17 to 0.79, $p=0.003$) and 10-hydroxy-nortriptyline ($b=0.70$, 95%CI 0.44 to 0.95, $p<0.001$). Body mass index was negatively related to plasma levels of nortriptyline ($b=-2.47$, 95%CI -4.26 to -0.70 , $p=0.007$) but was not related to the plasma levels of its metabolite 10-hydroxy-nortriptyline ($b=-0.15$, 95%CI -1.67 to 1.37, $p=0.847$), controlling for dose. Plasma levels of nortriptyline were only weakly related to outcome as measured by MADRS ($\beta=0.001$, 95%CI -0.0001 to 0.0029, $p=0.066$) and were unrelated to improvement on the neurovegetative symptom dimension ($\beta=0.0003$, 95%CI -0.0015 to 0.0020, $p=0.765$). The relationship between baseline body mass index and outcomes of nortriptyline treatment on MADRS ($\beta=0.019$, 95%CI 0.007 to 0.031, $p=0.001$) and on the neurovegetative symptoms dimension ($\beta=0.028$, 95%CI 0.014 to 0.041, $p<0.001$) remained undiminished after controlling for plasma levels of nortriptyline. The results were similar for categorically defined obesity.

4. Discussion

Depression and obesity are common conditions that frequently co-occur and jointly represent a major public health problem. It has been reported that the presence of depression precludes successful treatment of obesity (Pagoto et al., 2007). Now, it is becoming clear that the presence of obesity also complicates the pharmacological treatment of depression. The previously reported finding that high relative body weight and obesity predict poor outcome of antidepressant treatment (Khan et al., 2007; Kloiber et al., 2007; Papakostas et al., 2005) has been robustly replicated and extended in the large GENDEP sample. Therefore, depression and obesity should be considered and managed together. Measures of body weight and height should be part of the assessment of depression and considered in treatment planning. Future clinical trials may evaluate the best

therapeutic approaches for individuals with depression and obesity (Schneider et al., 2008).

We have found that the moderation of response to antidepressants by body weight is relatively specific to the noradrenergic tricyclic antidepressant nortriptyline and plays little role in response to the selective serotonin-reuptake inhibitor escitalopram. The effect of obesity on response to nortriptyline appears to be substantial, with a mean difference of 10% of baseline depression scores, which is an effect size comparable to differences between active drug and placebo in recent randomized clinical trials (Walsh et al., 2002). If this finding is replicated, the presence of obesity may be considered when choosing between antidepressants. The finding that body weight and obesity play little role in response to escitalopram is not entirely consistent with previous reports that high relative body weight and obesity predict poor response to serotonin-reuptake inhibitors (Khan et al., 2007; Papakostas et al., 2005). However, while the effects of body weight and obesity on outcome among escitalopram-treated subjects have not reached significance in the present study, they point in the same direction, with obesity being associated with somewhat less good response to escitalopram, especially in women.

While the association between body weight and outcome of antidepressant treatment appears to be replicable, its mechanism remains unclear. One possible explanation would be a pharmacokinetic mechanism where a larger distribution volume for lipophilic substances in obese subjects leads to inadequate plasma levels and hence a smaller therapeutic effect. The association of high body mass index with lower blood levels of nortriptyline but not escitalopram is consistent with such a mechanism. However, as the relationship between body weight at baseline and nortriptyline treatment outcomes remained unchanged after controlling for nortriptyline plasma levels, it is unlikely to be accounted for by a simple pharmacokinetic mechanism. Limitation of physical activity by obesity and psychosocial factors related to the stigmatisation of obesity may have contributed to the persistence of depression among obese subjects, but variables needed to disentangle such mediators have not been measured in the present study. Perhaps the strongest clue to the mechanism of a relationship between body weight and antidepressant treatment outcome comes from the differential predictive value of body weight for improvement in specific symptom dimensions.

Analyses of specific symptom dimensions in GENDEP indicated that moderation of antidepressant response by body weight is relatively specific to neurovegetative symptoms, including both sleep and appetite, and body weight has little influence on change in core depressive and cognitive symptoms during antidepressant treatment. This finding is consistent with previous reports of association between obesity and neurovegetative symptoms of depression (Kloiber et al., 2007) and obesity and somatic well-being (Papakostas et al., 2005). It may indicate that disturbance of appetite and sleep in obese depressed individuals is of different aetiology and may require a distinct approach to management. For example, sleep apnoea may be contributing to sleep disturbance in obese subjects (Smith et al., 2002), appetite disturbance and weight loss may be relative to a high baseline and both can be related to other associated physical disorders

(Farmer et al., 2008). If this finding is replicated, it is possible that obese depressed individuals can benefit from standard therapeutic approaches to depression but these may need to be complemented by specific interventions targeting sleep, nutrition and physical health.

Epidemiological studies indicate that the relationship between obesity and depression may be gender-specific, with a stronger relationship in women than in men (Blaine, 2008; Carpenter et al., 2000; Lim et al., 2008). One previous study also found a gender-by-obesity interaction in the moderation of antidepressant response, with a stronger effect of obesity in men than in women (Khan et al., 2007). In GENDEP, gender did not affect the overall response to antidepressants or the moderation of antidepressant response by body weight. However, gender did significantly interact with antidepressant and body weight when neurovegetative symptoms were considered as an outcome. It appears that the effect of body weight on change in neurovegetative symptoms of depression may be specific to nortriptyline in men, but generalises to both antidepressants in women. However, as this finding was unexpected and was not previously reported in literature, the role of gender should be interpreted with caution and should not lead to different management of depression in men and women unless replicated.

Previous studies have variously favoured the use of a continuous measure of relative body weight (Papakostas et al., 2005), categorical definition of overweight (Kloiber et al., 2007) or obesity (Khan et al., 2007) as predictors of antidepressant response. In GENDEP, we have found that continuous measure of relative body weight and categorical definition of obesity are equivalent predictors of outcome. In agreement with previous reports (Khan et al., 2007; Kloiber et al., 2007), we have found that subjects with weight in the overweight range (BMI between 25 and 30) did not differ from subjects with healthy body weight in their response to antidepressants. Therefore, being overweight does not seem to be of major concern in the treatment of depression. The role of being underweight remains uncertain, as the number of subjects with BMI below 19 was small and subsequently the analyses were underpowered. It appears that underweight women may respond less favourably to escitalopram, but this finding was not statistically significant in the GENDEP sample.

Additional analyses have confirmed that the results were not due to a bias introduced by non-random allocation of a proportion of participants and were not due to differential dosage or compliance. Indeed, the results appeared somewhat strengthened when the analyses were restricted to the randomly allocated participants and did not change with the introduction of dose, compliance and plasma levels as covariates. The GENDEP study compared two active antidepressants and did not include a placebo arm. This made the study more acceptable to participants and general practitioners. However, the lack of placebo means that the differential effect of body weight on response to study drugs is relative, as the effect of body weight on the natural course of depression and on placebo response is unknown. As the anthropometric measurements did not include measures of the distribution of body fat, we are unable to differentiate effects of body mass from effects of body fat content and visceral obesity, which could potentially explain gender differences in the moderation of antidepressant response by body weight.

In conclusion, we have confirmed that high body weight and obesity predict poor response to antidepressants. We have further extended this by finding that the moderation of antidepressant response by body weight is relatively specific to neurovegetative symptoms and to the noradrenergic antidepressant nortriptyline. The results appear to be robust and independent of allocation and dosage. Further study is needed to establish the role of obesity and body weight in response to non-pharmacological treatments and explore the role of gender and body fat distribution.

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Conflict of interest

Henigsberg and Kalember participated in clinical trials sponsored by pharmaceutical companies including GlaxoSmithKline and Lundbeck. Aitchison, Farmer and McGuffin and have received consultancy fees and honoraria for participating in expert panels from pharmaceutical companies including Lundbeck and GlaxoSmithKline.

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