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Research Article

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Tolerability of Weight Gain from Psychotropic Medications in Depressed Patients

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Abstract

Background: Obesity is becoming increasingly prevalent and puts patients at increased risk for many health problems. Weight gain from psychotropic medications, including medications given to treat depression, can be a common problem and may affect a patient's willingness to continue such a medication if this problem occurs. Our aims were to determine how much weight depressed patients in an outpatient setting would be willing to gain based on degree of potential improvement in their depression. The associations between demographic characteristics, such as biological sex, age, current BMI, and severity of depression at time of survey, and willingness to gain weight were also examined.

Methods: The sample included 26 patients from an outpatient adult behavioral medicine clinic who had a diagnosis of either major depressive disorder, bipolar disorder I, or bipolar disorder II. Participants also must have had a score of 5 or higher on the Patient Health Questionnaire-9 (PHQ-9). Patients were excluded from the study if they met diagnostic criteria for a substance use disorder in the last six months, comorbid anxiety or personality disorder, psychotic symptoms during the current depressive episode, or have any history of an eating disorder. A questionnaire was given to patients who met these criteria exploring how much weight they were willing to gain based on potential improvement in their depressive symptoms with a medication given to treat their depression.

Results: Eighteen (69.2%) participants indicated they would not like to gain weight with this medication, 2 (7.7%) stated they would like to gain weight with the medication, and 6 (23.1%) reported they did or did not mind if they gained weight with the medication. The 18 participants that reported they would not like to gain weight were asked 2 follow-up questions: 1) How much weight would you be willing to gain before you stopped the medication if you observed 100% improvement in your symptoms? and 2) How much weight would you be willing to gain before you stopped the medication if you observed 50% improvement in your symptoms? The amount of weight patients willing to gain based on 100% improvement, ranged from 0 to 100, with a mean of 18.16 (SD = 21.49). The amount of weight patients willing to gain based on 50% improvement, ranged from 0 to 50, with a mean of 10.26 (SD = 12.41). Females in our study were willing to gain less weight than males to achieve either response or remission with their depression. The relationship between continuous variables: age, weight, BMI, and PHQ-9 scores indicate a weakly negative correlation with age and the amount of weight willing to be gained for remission and response, a small negative correlation with weight and BMI on the amount of weight willing to be gained for remission and response, and a small and medium level of negative correlation with severity of depression for amount of weight willing to be gained for remission and response respectively.

Conclusions: Our results indicate that patients are willing to gain more weight with psychotropic medications given to treat depression if they were promised to achieve remission, as opposed to only a response, from the medication. The continuous variables in our study: Age, weight, BMI, and PHQ-9 scores all show some degree of negative correlation with the amount of weight willing to be gained. It is important for providers to explore concerns about weight gain that patients with depression may have prior to prescribing medications that may potentially cause weight gain in terms of alternative approaches such as medication less likely to result in weight gain or psychotherapy. Strategies should also be discussed to address weight gain should it occur such as diet and exercise or medications available to help the patient lose weight.

Introduction

Obesity, defined by a body mass index (BMI) greater than 30 kg/m^2, is becoming increasingly prevalent with an estimated one third of the population classified as either overweight or obese [1]. The consequences of weight gain can include increased risk of hypertension, dyslipidemia, coronary artery disease, stroke, sleep apnea, osteoarthritis, many types of cancer, and may impact one's self esteem and result in reduced social interaction [2,3].

Obese patients may also be at higher risk of depression and the relationship between obesity and depression may be bidirectional. A systematic review by Luppino, et al. showed that obesity seems to be a risk factor for unipolar depression and unipolar depression seems to be a risk factor for obesity after analyzing long term studies [4]. The mechanism proposed behind obesity increasing risk of depression is likely complex but may involve biological factors such as inflammation and neuroendocrine changes as well as the negative effect of obesity on self-esteem those who are obese may struggle with. The authors also report that depression may increase the risk of obesity through long term activation of the HPA axis as well as unhealthy diet and lack of physical activity.

Statement of the problem

Treatment with antidepressant medications may put patients at increased risk of weight gain through a variety of mechanisms based on the specific receptors that are antagonized by the antidepressant [5,6]. Blockade of the H1 receptor activates hypothalamic AMPK which signals a negative energy balance and stimulates appetite. The H1 receptor also seems to be important for leptin's anorexiant effect. Antagonism of the 5-HT2C receptor may act to inhibit satiety and thus promote overeating and may also be involved in leptin resistance. Some antipsychotic medications also share these mechanisms of medication induced weight gain among others.

Changes in weight can vary among antidepressants with antidepressants such as amitriptyline, nortriptyline, and mirtazapine tending to cause weight gain and bupropion being associated with weight loss. The effect on long term weight changes from SSRI's are not quite clear though patients may lose weight acutely with SSRI treatment [7]. Weight gain from second generation antipsychotics which are commonly used agents for treatment resistant depression and bipolar depression can be common. Weight gain from olanzapine can be especially common [8].

In addition to the negative effects of weight gain mentioned above, unwillingness to start or early discontinuation of medications that may cause weight gain are important considerations when prescribing such medications. A survey of 241 primary care patients revealed that participants were only willing to gain 5.37 pounds for a non-life-threatening psychiatric condition and 12.70 pounds for a life-threatening psychiatric condition [9]. Psychotropic-induced weight gain from antidepressants, lithium, and antipsychotic medications is a common cause for non-adherence which may place patients in danger of exacerbation of psychiatric illness and psychiatric hospitalization [10].

Purpose of the study

The purpose of this cross-sectional, exploratory study was to determine the amount of weight that psychiatric outpatients in a Midwestern clinic were willing to gain if they were to achieve either remission of their depression or a response to the medication (at least a 50% reduction in depressive symptoms). The associations between demographic characteristics, such as biological sex, age, current BMI, and severity of depression at time of survey, and willingness to gain weight were also examined. The following research questions were examined:

1. Is there a difference in the amount of weight patients would be willing to gain based on antidepressant response?
2. Is there a difference between males and females in the amount of weight they would be willing to gain based on antidepressant response?
3. Is there a relationship between age, weight, BMI, severity of depression, and the amount of weight a patient would be willing to gain based on antidepressant response?

Methods

Participants and setting

Participants: Twenty-six individuals were recruited from an outpatient adult behavioral medicine clinic. Prior to recruiting participants, approval was obtained from Oklahoma State University Center for Health Science's Institutional Review Board. Inclusion criteria consisted of healthy patients 18 years of age or older having a diagnosis of either major depressive disorder, bipolar disorder I, or bipolar disorder II. Participants also must have had a score of 5 or higher on the Patient Health Questionnaire-9 (PHQ-9) [11]. The PHQ-9 is a brief self-report tool used for screening, diagnosing, and monitoring the severity of depression based upon DSM-V criteria for a major depressive episode. Patients were excluded from the study if they met diagnostic criteria for a substance use disorder in the last six months, comorbid anxiety or personality disorder, psychotic symptoms during the current depressive episode, or have any history of an eating disorder.

Instruments: Demographic information, such as age, biological sex, weight, BMI, and psychiatric diagnosis, was collected for each participant and patients were then given the following questionnaire to complete.

1) Your doctor has prescribed a new medication to treat your depression. Some medications for depression may cause weight gain. If you were to gain weight after taking this how would you feel about this? Please check one of the following boxes:

A. I would not like to gain weight with this medication.

B. I would like to gain weight with this medication.

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C. I don't mind if I gain weight or not with this medication.

If you answered B or C you may stop.

2) If you answered that you would **not** like to gain weight with this medication, how much weight would you be willing to gain before wanting to stop the medication if it improved your depression by 100%, knowing that your depression may return if you did stop your medication? Please list number of pounds here - (If none, write "0 pounds")

3) If you answered that you would **not** like to gain weight with this medication, how much weight would you be willing to gain before wanting to stop the medication if it improved your depression by 50% knowing that your depression may return if you did stop your medication? Please list number of pounds here - (If none, write "0 pounds")

Data analyses: All analyses were conducted using IMB SPSS 29. Descriptive statistics related to demographic characteristics are reported. Prior to all analyses, assumptions such as normality and homogeneity of variance were assessed. Specifically, normality was examined using the Shapiro-Wilk (SW) test for normality, skewness and kurtosis statistics, and boxplots to further determine whether outliers were present. Levene's test was used to determine if the homogeneity of variance assumption was satisfied. Both parametric and nonparametric analyses were conducted when appropriate.

Results

Participants

A total of 26 participants (males, *n* = 14; females, *n* = 12) participated in the study. Across all participants, ages ranged from 19 to 74, with a mean age of 37.11 (SD = 14.63). Weight ranged from 104 to 285, with a mean weight of 191.96 (SD = 52.77). Whereas BMI ranged from 19.02 to 46, with a mean BMI of 29.40 (SD = 6.99). According to calculated BMI, 8 (30.8%) participants were classified as "normal," 13 (50%) were classified as "obese," and 5 (19.2%) as "overweight." A total of 23 participants (88.5%) were diagnosed with MDD and 3 (11.5%) were diagnosed with BPAD-1. Regarding the PHQ-9, scores ranged from 6 to 22 across all participants, with a mean score of 14.23 (SD = 4.95). Descriptive statistics are displayed in Table 1.

Research Question 1: Is there a difference in the amount of weight patients would be willing to gain based on antidepressant response?

Eighteen (69.2%) participants indicated they would not like to gain weight with this medication, 2 (7.7%) stated they would like to gain weight with the medication, and 6 (23.1%) reported they did or did not mind if they gained weight with the medication. The 18 participants that reported they would not like to gain weight were asked 2 follow-up questions: 1) How much weight would you be willing to gain before you stopped the medication if you observed 100% improvement in your symptoms? and 2) How much weight would you be willing to gain before you stopped the medication if you observed 50% improvement in your symptoms? The amount of weight patients willing to gain based on 100% improvement, ranged from 0 to 100, with a mean of 18.16 (SD = 21.49). The amount of weight patients willing to gain based on 50% improvement, ranged from 0 to 50, with a mean of 10.26 (SD = 12.41).

A dependent t-test was conducted to determine if there was a difference between the amount of weight the patient was willing to gain based on 100% versus 50% symptom improvement. The assumption of normality was tested for the distributional shape of the paired differences. Review of the SW test for normality (SW= 0.32, *df* = 19, $p < 0.001$)

Table 1: Descriptive statistics for males, females, and across all participants.

	M	Mdn.	SD	Std. Error of Mean	N
Males					
Age	32.71	32.00	8.41	2.25	14
Weight	202.38	196.00	50.82	14.09	13
BMI	28.52	30.16	5.64	1.51	14
PHQ-9	14.93	14.50	4.67	1.25	14
Females					
Age	42.25	43.00	18.70	5.40	12
Weight	180.67	178.00	54.69	15.79	12
BMI	30.42	29.87	8.45	2.44	12
PHQ-9	13.42	13.00	5.35	1.54	12
Total					
Age	37.11	33.50	14.63	2.87	26
Weight	191.96	187.00	52.77	10.55	25
BMI	29.40	30.16	6.99	1.37	26
PHQ-9	14.23	14.00	4.95	.97	26

M = mean; Mdn. = median; SD = standard deviation; Std. Error of Mean. = standard error of the mean; N = sample size; BMI = body mass index; PHQ-9 = Patient Health Questionnaire, i.e., a measure of depression; total = descriptive statistics across all participants.

and skewness (3.17) and kurtosis (11.95) statistics suggested that normality of the paired differences was not a reasonable assumption. Further, the boxplot suggested there was one outlier present. Ergo, both parametric (i.e., a dependent *t*-test) and nonparametric (i.e., Wilcoxon Signed-Rank test) analyses were conducted due to the small sample size and nonnormality. The dependent *t*-test indicated paired differences were statistically significantly different from 0, $t(18) = 3.07$, $p < 0.05$ [95% CI: 2.49, 13.30]. The effect size *d* (calculated as the mean difference divided by the standard deviation of the difference) was 11.21 (Hedges' correction = 11.72). Using Cohen's (1988) guidelines, this is interpreted as a large effect. Further, the Wilcoxon Signed-Rank test indicated there was a statistically significant difference between the amount of weight the patient was willing to gain based on 100% versus 50% symptom improvement, $z = -3.235$, $p < 0.01$.

Research Question 2: Is there a difference between males and females in the amount of weight they would be willing to gain based on antidepressant response?

An independent *t*-test was conducted to determine if there was a difference between males and females and the amount of weight they were willing to gain based on 100% symptom improvement. Sample data consisted of 10 males (M = 23.00, SD = 28.21) and 9 females (M = 12.78, SD = 9.05). The assumption of normality was tested for the distributional shape of the dependent variable for both males and females. Normality was not a reasonable assumption for males (SW = 0.633, $df = 10$, $p < 0.001$; skewness = 2.71; kurtosis = 7.91). However, the assumption of normality was met for females (SW = 0.92, $df = 9$, $p = 0.36$; skewness = 0.70; kurtosis = 0.37). Boxplots suggested one outlier among males. According to Levene's test, the homogeneity of variance assumption was satisfied ($F = 1.69$, $p = 0.21$). Due to the small sample size and violation of normality assumption, both parametric (i.e., an independent t-test) and nonparametric (i.e., Mann-Whitney test) analyses were conducted.

The independent *t*-test indicated there was not a statistically significant difference in the amount of weight willing to be gained between males and females, $t(17) = 1.04$, $p = 0.31$ [95% CI:-10.56, 31.01]. However, Cohen's *d* was 21.44 (hedges' correction = 22.45; Glass's delta = 9.05 indicating a large effect size. Further, the nonparametric Mann-Whitney test indicated there was no statistically significant difference between males and females, $U = 35.50$, $p = 0.28$.

Regarding 50% symptom improvement, sample data consisted of 10 males (M = 13.50, SD = 15.47) and 9 females (M = 6.67, SD = 7.07). Again, data was not normally distributed for males (SW = 0.79, $df = 10$, $p < 0.05$; skewness = 1.76; kurtosis = 3.01) but was for females (SW = 0.87, $df = 9$, $p = 0.11$; skewness = 0.95; kurtosis = -0.02). Boxplots suggested one outlier among males. According to Levene's test, the homogeneity of variance assumption was satisfied ($F = 2.12$, $p = 0.16$). Both parametric (i.e., an independent *t*-test) and nonparametric (i.e., Mann-Whitney test) analyses were conducted.

The independent *t*-test indicated there was not a statistically significant difference in the amount of weight willing to be gained between males and females, $t(17) = 1.21$, $p = 0.24$ [95% CI:-5.05, 18.71]. However, Cohen's *d* was 12.25 (hedges' correction = 12.83; Glass's delta = 7.07) indicating a large effect size. Further, the nonparametric Mann-Whitney test indicated there was no statistically significant difference between males and females, $U = 33.00$, $p = 0.36$ (Figure 1).

Research Question 3: Is there a relationship between age, weight, BMI, severity of depression, and the amount of weight a patient would be willing to gain based on antidepressant response?

Table 2 displays the Pearson's correlation coefficients between age, weight, BMI, severity of depression, and antidepressant response (100 and 50%). Variables found to be statistically significant included weight and BMI, $r = 0.87$,

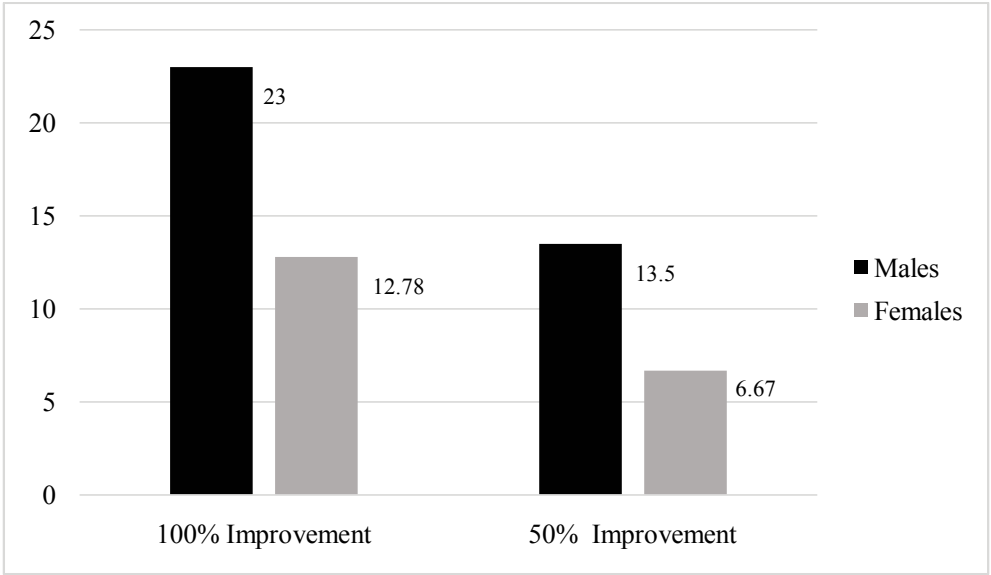

Figure 1: The average amount of weight males and females are willing to gain based on 100% improvement in depression symptoms and 50% improvement in depression symptoms.

Table 2: Pearson's correlation coefficients between age, weight, BMI, severity of depression, and antidepressant response (100 and 50%).

	Age	Weight	BMI	PHQ-9	100%	50%
Age	-	-0.18	-0.14	-0.11	-0.07	-0.09
Weight		-	0.87**	0.50*	-0.12	-0.14
BMI			-	0.41*	-0.13	-0.19
PHQ-9				-	-0.28	-0.36
100%					-	0.92**
50%						-

**indicates the correlation is significant at the 0.01 level; *indicates the correlation is significant at the 0.05 level

$p < 0.001$; weight and severity of depression, $r = 0.50$, $p < 0.05$; BMI and severity depression, $r = 0.41$, $p < 0.05$, and antidepression response, i.e., 100% versus 50%, $r = 0.92$, $p < 0.01$.

Discussion

Our results indicate that in general, patients are willing to gain more weight with psychotropic medications for depression if they were to achieve remission (100% improvement) as opposed to having a response (50% improvement) with the medication. Females in our study were willing to gain less weight than males to achieve either response or remission with their depression. The relationship between continuous variables: Age, weight, BMI, and PHQ-9 scores indicate a weakly negative correlation with age and the amount of weight willing to be gained for remission and response, a small negative correlation with weight and BMI on the amount of weight willing to be gained for remission and response, and a small and medium level of negative correlation with severity of depression for amount of weight willing to be gained for remission and response respectively.

Patients with depression should be made aware of the possibility of weight gain when starting certain medications as many may be unwilling to begin taking the medication or may wish to stop the medication later during treatment should weight gain occur and discontinuation of such medications may put the patient at risk of return of depression. Should weight gain occur, a decision will need to be made with the patient to either continue with the medication or address the weight gain through measures such as calorie reduction, exercise, or appetite suppressing medications or to switch to another medication less likely to cause weight gain Adding adjuvant medications such as stimulants, topiramate, bupropion, or naltrexone may have some benefit to addressing antidepressant associated weight gain [12]. Metformin may be helpful with weight gain associated with antipsychotics [8]. Newer medications such as GLP-1 receptor agonists (e.g., semaglutide) as well as GLP-1-glucose-dependent insulinotropic polypeptide co-agonists (e.g., tirzepatide) may show promise for use for these patients [13].

Ethical Statement

This study was submitted to ethics review by the Oklahoma State University Institutional Review Board prior to the collection of data.

Conflicts of Interest/Declarations

No conflicts of interest.

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Data Availability Statement

Data is available upon request.

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