Effect of comedication of bupropion and other antidepressants on body mass index

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***Abstract*:**
Background: Weight gain as an adverse effect of monotherapy of antidepressant has been well-studied. The effects of augmentation therapy involving multiple antidepressants, on weight changes needs to be adequately addressed.
Objective: To study the co-medication effects of bupropion in combination with six individual antidepressants on body mass index (BMI) using EMR based data analysis.
Methods: Allscripts data warehouse was used to identify patients on monotherapy of five selective serotonin reuptake inhibitor (SSRI) drugs, escitalopram, sertraline, citalopram, paroxetine, fluoxetine, one selective norepinephrine reuptake inhibitor (SNRI) duloxetine and the aminoketone, bupropion for at least 180 days. We also identified patients on co-medication of SSRI/SNRI drugs with bupropion. Six ANCOVA models were built to compare the short term effects on BMI, among monotherapy and co-medication groups. The patients' clinical conditions and demographics were included to account for confounding effects.
Results: Monotherapy of all the SSRI/SNRI drugs showed significant weight increase, consistent with that of previous studies. The co-medication of bupropion and escitalopram showed a significantly higher increase in BMI than monotherapy (P = 0.0102). The increase in BMI in the other five co-medication groups was not significantly different from their respective monotherapy groups.
Conclusion: Our study reports an adverse weight gain on co-medication of escitalopram and bupropion, which warrants further validation studies. Considering co-medication effects of antidepressants on weight is important to design robust depression treatment plans.

Keywords: antidepressants, bupropion, BMI, comedication, EMR

Introduction

Body weight changes, in particular weight gain, has been associated in multiple studies with the use of antidepressants [Serretti and Mandelli, 2010]. The National Health and Nutrition Examination Surveys of 2005–2008 suggest that about 11% of Americans aged above 12 years-old were on antidepressants. Antidepressants were the third largest prescription medication, majorly prescribed for depression, and their rate of use increased nearly 400% from 1988–1994 through 2005–2008 [Pratt *et al.* 2011]. Depression has been reported to have close and reciprocal association with the highly prevalent and often comorbid conditions such as obesity and diabetes mellitus [Anderson *et al.* 2001; Luppino *et al.* 2010]. Considering the staggering statistics on antidepressant use, weight gain as an adverse effect of antidepressants can be a threatening public health hazard with serious consequences in chronic metabolic conditions.

Antidepressants such as tricyclics and monoamine oxidase inhibitors have been repeatedly associated with weight gain. The second generation of antidepressants, selective serotonin reuptake inhibitors (SSRIs), which were initially expected to have less effect on weight, later proved to have close association with weight gain [Deshmukh and Franco, 2003; Ranjbar *et al.* 2013]. On the contrary, bupropion of the aminoketone class has been consistently associated with weight neutral to modest weight loss effects [Harto-Truax *et al.* 1983; Croft *et al.* 2002; Jain *et al.* 2002]. While time and dose dependent weight gain on monotherapy of

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antidepressants have been broadly elaborated, the comedication effects of antidepressants as a result of augmentation strategy [Moret, 2005] have not been widely addressed. For instance, the anecdotal evidence of reduction in weight gain on addition of bupropion to weight inducing antidepressants like SSRIs and selective norepinephrine reuptake inhibitors (SNRIs) has not been elaborated [Deshmukh and Franco, 2003; Demyttenaere and Jaspers, 2008].

Studying the comedication effects of bupropion with the most commonly prescribed antidepressants, SSRIs, can be particularly beneficial. It can help us design weight management strategies for depression patients, promote greater compliance to antidepressant therapy and prevent metabolic comorbidities as a consequence of adverse weight gain. With current body of evidence on adverse effects of antidepressants revolving around randomized clinical trials and animal models, and more contemporary studies like electronic medical record (EMR) based data analysis, encompassing the real clinical population, can be valuable [Blumenthal *et al.* 2014].

We report here, the results of an EMR based data mining analysis that studied the comedication effects of bupropion with six antidepressants, namely escitalopram, sertraline, citalopram, paroxetine, fluoxetine and duloxetine, on body mass index (BMI) over a short-term treatment period.

Methods

Defining clinical cohorts from EMR

The clinical cohorts were derived from Allscripts data warehouse, with over 6 million de-identified patient records containing information on demographics, medications, problems, laboratory test results, vaccination and allergies dating from 1990 to 2012.

Six individual models were built for each of the six antidepressants, namely escitalopram, sertraline, citalopram, fluoxetine, paroxetine and duloxetine. Each antidepressant model included three cohorts of patients, where 'X' refers to the respective antidepressant: (i) a cohort on 'X' for at least 180 days, but not on bupropion; (ii) a cohort on bupropion for at least 180 days, but not on 'X'; and (iii) a cohort on 'X' and bupropion concurrently for at least 180 days. One universal 'bupropion' cohort was used across all the six models. Overall, 13 different cohorts were extracted (6 'X' cohorts, 6 'combination' cohorts and 1 'bupropion' cohort).

Weight changes were measured by the differences between 'treatment BMI' and 'baseline BMI'. 'Baseline BMI' was defined as the mean of BMI values taken within 90 days prior to the drug start date (for a combination cohort, the start date of the second drug was used). 'Treatment BMI' was defined as the mean of BMI values taken between 90 and 180 days after the drug start date.

All the dosing information available on the seven antidepressants was extracted from the data warehouse. Based on the US Food and Drug Administration (FDA) label information and the negligible number of records in the data set, very high and very low doses for each of the antidepressants were excluded. The dosing range included are as follows: 10 and 20 mg/day for escitalopram; 25, 50 and 100 mg/day for sertraline; 20 and 40 mg/day for citalopram; 10, 12.5 and 20 mg/day for paroxetine; 20 and 40 mg/day for fluoxetine; 30 and 60 mg/day for duloxetine; and 100, 150, 200 and 300 mg/day for bupropion. BMI change distribution was plotted across the above doses. The drug effect was constant within the respective dose range for each of the seven antidepressants (see Supplementary Figures 1 and 2).

In order to account for potential confounding factors that may affect the BMI, other clinical and demographics information for each patient other than their baseline BMI values were extracted. These factors included hyperlipidemia, hypertension [Brown *et al.* 2000], hypothyroidism [Nyrnes *et al.* 2005], diabetes mellitus type 2 [Bays *et al.* 2007], alcohol use [Suter, 2005; Sayon-Orea *et al.* 2011], gender and age. Problem name or, International Classification of Diseases 9 (ICD9) code or medication history, were used to extract the confounding factors. Except for age, the rest of the confounding factors were denoted as binary values.

Statistical methods

Arithmetic mean and standard deviation values were used to describe the patient characteristics. A paired *t*-test was conducted to test the difference between baseline and treatment BMI values. Analysis of covariance (ANCOVA) was followed to compare the treatment cohorts as well as test the significance of the covariates. The treatment cohorts represent the three different treatments in

Table 1. Demographics and clinical characteristics of cohorts.

Variable	Escitalopram	Bupropion	Escitalopram and bupropion combination	Sertraline	Bupropion	Sertraline and bupropion combination
n	1622	606	66	1895	606	66
Age (mean ± SD)	54 ± 17	51 ± 14	50 ± 12	54 ± 17	51 ± 14	52 ± 13
Gender (% female)	75	76	77	78	76	85
Baseline BMI (mean ± SD)	29.53 ± 7.26	30.02 ± 7.42	30.12 ± 7.88	29.41 ± 7.01	30.02 ± 7.42	29.73 ± 7.29
Hyperlipidemia (%)	40	41	32	40	41	38
Hypertension (%)	43	54	32	43	54	38
Hypothyroidism (%)	15	16	15	16	17	17
Diabetes (%)	21	17	9	20	17	11
Alcohol use (%)	40	46	41	39	46	26
Variable	Citalopram	Bupropion	Citalopram and bupropion combination	Fluoxetine	Bupropion	Fluoxetine and bupropion combination
n	1744	606	87	1546	606	79
Age (mean ± SD)	54 ± 17	51 ± 14	51 ± 15	53 ± 15	51 ± 14	53 ± 13
Gender (% female)	74	76	80	77	76	80
Baseline BMI (mean ± SD)	30.10 ± 14.63	30.02 ± 7.42	29.66 ± 6.91	30.40 ± 7.44	30.02 ± 7.42	31.32 ± 8.70
Hyperlipidemia (%)	41	41	39	39	41	41
Hypertension (%)	47	54	41	39	54	44
Hypothyroidism (%)	13	16	14	14	17	14
Diabetes (%)	22	17	17	24	17	24
Alcohol use (%)	46	46	48	38	46	37
Variable	Paroxetine	Bupropion	Paroxetine and bupropion combination	Duloxetine	Bupropion	Duloxetine and bupropion combination
n	854	606	25	1047	606	57
Age (mean ± SD)	58 ± 16	51 ± 14	50 ± 14	55 ± 15	51 ± 14	55 ± 14
Gender (% female)	73	76	80	77	76	74
Baseline BMI (mean ± SD)	29.64 ± 6.99	30.02 ± 7.42	30.86 ± 7.64	30.88 ± 7.53	30.02 ± 7.42	31.00 ± 6.66
Hyperlipidemia (%)	44	41	36	46	41	44
Hypertension (%)	50	54	36	53	54	53
Hypothyroidism (%)	16	16	8	18	17	21
Diabetes (%)	22	17	4	29	17	7
Alcohol use (%)	42	46	28	46	46	39

BMI, body mass index; SD, standard deviation.

each model (main effect), and the covariates are the baseline BMI and the confounding factors listed above. An *F*-test was performed to determine the significance of the model fit with and without the inclusion of the treatment cohort. If significant, *post hoc* tests were performed to compare the treatment cohorts directly. *R* was used for all the data analysis.

Results

Cohort characteristics

Patient demographics and clinical information are provided in Table 1. Biases in the cohort characteristics exist. In particular, the majority of the cohort was female and the overall BMI among all the cohorts was skewed towards overweight category.

Model results

The ANCOVA models and the *post hoc* test results are summarized in Table 2. The universal bupropion cohort showed a slight decrease in BMI (-0.02) across all 6 models.

Escitalopram model

The treatment condition was significant ($F = 28.5$, $p < 0.001$) in the model, with patients on the combination treatment having the highest increase (1.31), followed by those on escitalopram monotherapy (0.58). The *post hoc* tests showed that the combination treatment cohort had a significantly higher BMI increase than either the escitalopram cohort ($p = 0.0102$) or the bupropion cohort ($p < 0.001$). In addition, the escitalopram cohort had a significantly higher BMI increase than the bupropion cohort ($p < 0.001$). The other significant covariates were baseline BMI ($p < 0.001$), hyperlipidemia ($p < 0.001$) and age ($p = 0.0117$). Higher baseline BMI, presence of hyperlipidemia and older age were all found to be associated with larger BMI increase.

Sertraline model

The treatment condition was significant ($F = 16.7$, $p < 0.001$) in the model, with patients on the combination treatment having the highest increase (0.65), followed by those on sertraline (0.45). The *post hoc* tests showed that the combination treatment cohort had a significantly higher BMI increase than the bupropion cohort ($p = 0.013$). In addition, the sertraline cohort had a significantly higher BMI increase than the bupropion cohort ($p < 0.001$). The other significant covariates were baseline BMI ($p < 0.001$) and age ($p = 0.0011$). Higher baseline BMI and older age were found to be associated with larger BMI increase.

Citalopram model

The treatment condition was significant ($F = 17.9$, $p < 0.001$) in the model, with patients on the citalopram treatment having the highest increase (0.49), followed by those on combination treatment (0.44). The *post hoc* tests showed that the sertraline cohort had significantly higher BMI increase than the bupropion cohort ($p < 0.001$). The other significant covariate was baseline BMI ($p = 0.0178$). Higher baseline BMI was associated with larger BMI increase.

Fluoxetine model

The treatment condition was significant ($F = 17.2$, $p < 0.001$) in the model, with patients on the fluoxetine treatment having the highest increase (0.50), followed by those on combination treatment (0.38). The *post hoc* tests showed that the fluoxetine cohort had a significantly higher BMI increase than the bupropion cohort ($p < 0.001$). The other significant covariate was baseline BMI ($p < 0.001$). Higher baseline BMI was associated with larger BMI increase.

Paroxetine model

The treatment condition was significant ($F = 24.6$, $p < 0.001$) in the model, with patients on the combination treatment having the highest increase (0.78), followed by those on paroxetine (0.66).The *post hoc* tests showed that the paroxetine cohort had a significantly higher BMI increase than the bupropion cohort ($p < 0.001$). The other significant covariate was baseline BMI ($p < 0.001$). Higher baseline BMI was associated with larger BMI increase.

Duloxetine model

The treatment condition was significant ($F = 14.9$, $p < 0.001$) in the model, with patients on the combination treatment having the highest increase (0.53), followed by those on duloxetine (0.46).The *post hoc* tests showed that the duloxetine cohort had a significantly higher BMI increase than the bupropion cohort ($p < 0.001$). The other significant covariates were baseline BMI ($p < 0.001$), alcohol use ($p = 0.0288$) and age ($p = 0.0251$). Higher baseline BMI, alcohol use and older age were all associated with larger BMI increase.

Discussion

The preponderance of evidence suggests that antidepressant medication can have an adverse effect on body weight. However, studies on comedication effects of antidepressants on body weight are lacking. Close attention to these studies are essential to tailor effective augmentation therapy. The combination of bupropion and SSRI is one such augmentation strategy, targeted at an efficient therapeutic effect with minimal SSRI induced side effects such as weight gain, sexual dysfunction and emotional detachment [Demyttenaere and Jaspers, 2008]. It is imperative to study the comedication effects of bupropion with individual

Table 2. Baseline and treatment BMI values and ANCOVA results.

Variable	Escitalopram	Bupropion	Combination
n	1622	606	66
Baseline BMI (mean ± SD)	29.53 ± 7.26	30.02 ± 7.42	30.12 ± 7.88
Treatment BMI (mean ± SD)	30.11 ± 7.37	30.00 ± 7.41	31.43 ± 8.45
BMI change (mean ± SD)	0.58 ± 1.87	-0.02 ± 2.16	1.31 ± 2.15
ANCOVA *F*-test *p* value	$F = 28.5$, $p < 0.001$		
Post hoc test *p* value escitalopram *versus* bupropion	<0.001		
Post hoc test *p* value escitalopram *versus* combination	0.0102		
Post hoc test *p* value bupropion *versus* combination	<0.001		
Variable	Sertraline	Bupropion	Combination
n	1895	606	66
Baseline BMI (mean ± SD)	29.41 ± 7.01	30.02 ± 7.42	29.73 ± 7.29
Treatment BMI (mean ± SD)	29.86 ± 7.16	30.00 ± 7.41	30.38 ± 7.47
BMI change (mean ± SD)	0.45 ± 1.86	-0.02 ± 2.16	0.65 ± 2.08
ANCOVA *F*-test *p* value	$F = 16.7$, $p < 0.001$		
Post hoc test *p* value sertraline *versus* bupropion	<0.001		
Post hoc test *p* value sertraline *versus* combination	0.716		
Post hoc test *p* value bupropion *versus* combination	0.013		
Variable	Citalopram	Bupropion	Combination
n	1744	606	87
Baseline BMI (mean ± SD)	30.10 ± 14.63	30.02 ± 7.42	29.66 ± 6.91
Treatment BMI (mean ± SD)	30.60 ± 14.68	30.00 ± 7.41	30.10 ± 7.41
BMI change (mean ± SD)	0.49 ± 1.80	-0.02 ± 2.16	0.44 ± 1.79
ANCOVA *F*-test *p* value	$F = 17.9$, $p < 0.001$		
Post hoc test *p* value citalopram *versus* bupropion	<0.001		
Post hoc test *p* value citalopram *versus* combination	0.9403		
Post hoc test *p* value bupropion *versus* combination	0.0687		
Variable	Fluoxetine	Bupropion	Combination
n	1546	606	79
Baseline BMI (mean ± SD)	30.40 ± 7.44	30.02 ± 7.42	31.32 ± 8.70
Treatment BMI (mean ± SD)	30.90 ± 7.51	30.00 ± 7.41	31.70 ± 8.45
BMI change (mean ± SD)	0.50 ± 1.83	-0.02 ± 2.16	0.38 ± 2.68
ANCOVA *F*-test *p* value	$F = 17.2$, $p < 0.001$		
Post hoc test *p* value fluoxetine *versus* bupropion	<0.001		
Post hoc test *p* value fluoxetine *versus* Combination	0.908		
Post hoc test *p* value bupropion *versus* combination	0.101		
Variable	Paroxetine	Bupropion	Combination
n	854	606	25
Baseline BMI (mean ± SD)	29.64 ± 6.99	30.02 ± 7.42	30.86 ± 7.64
Treatment BMI (mean ± SD)	30.29 ± 7.15	30.00 ± 7.41	31.64 ± 7.58
BMI change (mean ± SD)	0.66 ± 1.84	-0.02 ± 2.16	0.78 ± 2.27
ANCOVA *F*-test *p* value	$F = 24.6$, $p < 0.001$		
Post hoc test *p* value paroxetine *versus* bupropion	<0.001		
Post hoc test *p* value paroxetine *versus* combination	0.9766		
Post hoc test *p* value bupropion *versus* combination	0.0852		
Variable	Duloxetine	Bupropion	Combination
n	1047	606	57
Baseline BMI (mean ± SD)	30.88 ± 7.53	30.02 ± 7.42	31.00 ± 6.66
Treatment BMI (mean ± SD)	31.35 ± 7.56	30.00 ± 7.41	31.53 ± 6.89
BMI change (mean ± SD)	0.46 ± 2.00	-0.02 ± 2.16	0.53 ± 2.07
ANCOVA *F*-test *p* value	$F = 14.9$, $p < 0.001$		
Post hoc test *p* value duloxetine *versus* bupropion	<0.001		
Post hoc test *p* value duloxetine *versus* combination	0.9972		
Post hoc test *p* value bupropion *versus* combination	0.0822		

ANCOVA, analysis of covariance; BMI, body mass index; SD, standard deviation.

antidepressants on BMI, as adverse weight changes can be a consequential health hazard.

In our study, we observed that there was a statistically significant increase in average BMI on escitalopram, sertraline, citalopram, paroxetine, fluoxetine and duloxetine monotherapy after short-term use. Paroxetine showed the highest increase in BMI, a result consistent with previous studies [Aberg-Wistedt *et al.* 2000; Pae and Patkar, 2007]. Escitalopram followed suit with an increase in BMI similar to previous reports [Uher *et al.* 2011]. The average BMI increase was slight and similar on sertraline, citalopram, fluoxetine and duloxetine treatment. These are consistent with results from past studies [Bouwer and Harvey, 1996; Deshmukh and Franco, 2003; Wise *et al.* 2006; Ranjbar *et al.* 2013]. The mechanism of action behind the therapeutic effects and side effects of SSRIs have been well described. SSRIs target the negative allosteric regulation of serotonin reuptake pump, increasing serotonin concentration in specific regions which impacts other physiological functions like appetite, sleep and sexual function [Stahl, 1998; Ferguson, 2001; Raymond *et al.* 2001].

Bupropion monotherapy in our study presented a very slight decrease in BMI, accounting to a weight neutral effect. Most studies have witnessed a higher weight loss effect on long-term use [Harto-Truax *et al.* 1983; Gardner, 1985; Weisler *et al.* 1994; Settle *et al.* 1999; Croft *et al.* 2002; Jain *et al.* 2002]. The unique clinical profile of bupropion leading to dual norepinephrine and dopamine reuptake inhibition, devoid of serotonergic effects alleviates bupropion from the common side effects of older antidepressants, thereby accounting for the weight loss [Stahl *et al.* 2004]. It is important to note that, duration, adherence to therapy, dosing of bupropion and other life style factors such as diet and exercise can also impact the degree of weight loss [Croft *et al.* 2002; Jain *et al.* 2002; Fava *et al.* 2005; Calandra *et al.* 2012].

We observed that the increase in BMI, in five of the comedication cohort was not significantly different from their respective SSRI/SNRI monotherapy. Interestingly, the comedication of escitalopram and bupropion showed a significant increase in BMI from baseline that was significantly higher than the BMI increase on monotherapy. This finding is of high clinical importance as each unit increase in BMI, especially in the 25–45 kg/m category, can substantially increase the likelihood for diabetes and heart diseases and also contribute to soaring healthcare costs [Wang *et al.* 2006]. Also, a high BMI can strongly predispose to other fatal medical conditions such as stroke, dementia, Alzheimer's disease and site-specific cancers [Kurth *et al.* 2002; Whitmer *et al.* 2007; Bhaskaran *et al.* 2014].

Although differences in pharmacological effects of the drug compounds may play a role in differing weight gain patterns [Harvey and Bouwer, 2000; Serretti and Mandelli, 2010], it is difficult to explain the selective anomalous effect of the escitalopram and bupropion comedication. The weight gain observed in this comedication group is particularly disturbing, given that escitalopram is superior to other SSRIs owing to its high selectivity and efficacy [Sanchez *et al.* 2014]. Further clinical studies are warranted to confirm this comedication effect. Studies targeted at understanding the molecular aspects of weight gain, such as activation of weight-related signaling molecules and receptors can be particularly useful [Hinze-Selch *et al.* 2000].

Our study is one of the first EMR based analyses reporting the weight change effects on short-term antidepressant use. Similar to other EMR studies, ours has limitations with respect to the data extracted [Blumenthal *et al.* 2014]. For instance about 75% of patients in all the medication cohorts were female. We ran the models again excluding the male patients, but found that the results did not change dramatically. The magnitude of female population in our study is not surprising given the fact that, females are 2.5 times more likely to take antidepressants than males [Pratt *et al.* 2011] Also, the overall BMI of patients in all the medications cohorts was skewed to the overweight category, as opposed to the normal weight distribution desired in such studies. Also, the life style information about diet and exercise, which may have a substantial effect on the weight patterns observed among the patients were incomplete, and difficult to quantify and incorporate in our models.

Weight management in depression patients is a crucial aspect of a well thought out treatment plan. Apart from promoting adherence to the therapy, weight management can help in keeping other metabolic comorbidities at bay [Shrivastava and Johnston, 2010]. A prudent antidepression regimen can benefit from a careful selection of

antidepressants based on individual drugs and comedication risk profiles, also taking into account anthropometric measures and baseline metabolic assessment [Hasnain *et al.* 2012].

Conclusion

Our study sheds light on the short-term comedication effects of bupropion in combination with six other antidepressants, based on EMR data. The comedication of escitalopram and bupropion had (even) higher BMI increase than monotherapy, while other comedication cohorts have comparable BMI increase with their respective monotherapy cohorts. Evaluation of the synergistic effect of combination of antidepressants on weight changes could be an important selection parameter for designing antidepression therapy.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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