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Adiponectin Moderates Antidepressant Treatment Outcome in the Combining Medications to Enhance Depression Outcomes Randomized Clinical Trial

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Abstract

Background: Major depressive disorder (MDD) is often comorbid with metabolic diseases such as obesity, cardiovascular disease, and type 2 diabetes. A potential link between these disorders is adiponectin, an adipocyte-derived circulating hormone with insulin-sensitizing, anti-inflammatory, and neuroplasticity effects. Reductions in plasma levels of adiponectin have been reported in both humans with depression and in the chronic-defeat mouse model of depression. However, the predictive value of adiponectin for treatment response to depression has not been determined.

Methods: We investigated the potential predictive effect of baseline adiponectin levels in patients who provided plasma and were undergoing one of three pharmacological treatments (escitalopram monotherapy; escitalopram plus bupropion; and venlafaxine plus mirtazapine) in the Combining Medications to Enhance Depression Outcomes clinical trial (n=160). Specifically, we assessed whether adiponectin moderates—that is, differentially predicts—treatment response among the treatment arms. Improvements with treatment were assessed using change in the clinician-rated 30-item Inventory of Depressive Symptomatology (IDS-C) from baseline through week 12. Moderator effects were tested using separate pairwise repeated measures mixed-effects models with a treatment-arm-by-adiponectin interaction.

Results: Baseline adiponectin levels moderated treatment outcome between two combination therapies. Specifically, low adiponectin predicted better response to escitalopram plus bupropion compared to venlafaxine plus mirtazapine, whereas high adiponectin predicted better response to venlafaxine plus mirtazapine compared to escitalopram plus bupropion ($F=4.84$, $p=0.03$). Adiponectin levels did not correlate with baseline depression severity ($r=-0.03$, $p=.59$).

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Conclusions: Antidepressant selection for patients with MDD can be personalized using pre-treatment blood-based biomarkers, such as adiponectin, thereby improving treatment outcomes.

Keywords

Adiponectin; Major Depressive Disorder; SSRI; Bupropion; CO-MED; Metabolic Disorder

1. INTRODUCTION

Major depressive disorder (MDD) is heterogeneous and characterized by depressed mood, anhedonia, neurovegetative changes and altered cognitive function [1, 2]. Development of MDD is predicted by both genetic and environmental influences [3, 4] and has a high lifetime risk: 7%-12% for men and 20%-25% for women [1]. Evidence from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) clinical trial [5] suggests that of individuals receiving depression medications, over two-thirds will not achieve remission following initial treatment and nearly one-third will not attain remission even after four adequate treatment regimens [6, 7]. The absence of prognostic and prescriptive biomarkers represents a significant barrier to effective treatment outcomes [8], as the current methodology is largely guided by a subjective, trial-and-error paradigm [9]. Identification of moderators (i.e., baseline characteristics which predict *differential* treatment outcome among medications) will be critical for improving treatment efficacy [10]. It is becoming increasingly clear that a biomarker or panel of biomarkers may enable the stratification of patients into more homogenous sub-groups based on their underlying pathophysiology [7, 11–13], which could aid in quickly identifying the best treatment approach—a welcome step toward personalized medicine.

MDD is often comorbid with metabolic disorders such as type 2 diabetes [14], obesity [15–17], and cardiovascular disease [18]. The relationship of MDD with these conditions is longitudinal and frequently bidirectional, with each condition increasing the risk of developing the other [19–21]. Adiponectin, an adipokine, is a suggested mediator of MDD related to metabolic disorders. Adiponectin is an abundant, anti-inflammatory protein that modulates glucose and fatty acid metabolism [22, 23]. Plasma levels of adiponectin positively correlate with insulin sensitivity and inversely correlate to body weight, particularly visceral fat mass [24, 25]. Increasing evidence suggests that the physiological role of adiponectin extends beyond its peripheral metabolic effects [26, 27]. Although adiponectin is produced peripherally, adiponectin receptors (adipoR1 and adipoR2) are abundantly expressed in discrete brain regions generally affected with mood disorders, including the amygdala, hypothalamus, cortex, and hippocampus [28–30], suggestive of a central role. The low abundance of central adiponectin [31–33] makes its direct role(s) difficult to interpret. However, studies conducted in rodents following i.c.v. injection of adiponectin suggests that adiponectin ameliorates central nervous system inflammation [34], stimulates proliferation of adult hippocampal neural stem/progenitor cells [35], facilitates extinction of contextual fear [36], and possesses anxiolytic and antidepressant effects [37, 38]. Further, adiponectin is associated with the antidepressant effects of physical exercise and ketamine [38, 39].

We assessed whether baseline adiponectin level moderated treatment outcome among participants of the Combining Medications to Enhance Depression Outcomes (CO-MED) clinical trial [40], in which MDD participants were treated with either escitalopram monotherapy or one of two different antidepressant medication combinations (escitalopram plus bupropion or venlafaxine plus mirtazapine). Depression severity was assessed over the course of a 12-week acute treatment phase. In this report, we examined the relationship between treatment group, baseline peripheral adiponectin, and depression severity by addressing the following questions:

- 1) Does baseline adiponectin level correlate with severity of depressive symptoms?
- 2) Does baseline adiponectin level differentially predict treatment outcome to antidepressant medications?
- 3) Does adiponectin level change with treatment?

2. METHODS AND MATERIALS

2.1 Participants:

CO-MED was a single-blind, 7-month prospective, randomized clinical trial that enrolled 665 adult outpatients (ages 18-75) at six primary and nine psychiatric care sites from March 2008 to February 2009 [40]. Participants had at least moderately severe, non-psychotic major depression and met the DSM-IV-TR criteria for either recurrent or chronic depression (current episode of depression lasting at least 2 years). Participants had an index episode lasting at least two months and a symptom severity score of at least 16 on the 17-item Hamilton Depression Rating Scale (HAM-D) [41]. Individuals with any psychotic illness or bipolar disorder and those in need of hospitalization were ineligible. Institutional review boards at each participating site reviewed and approved the CO-MED protocol. Study participants provided written informed consent before commencing any study-related assessments or procedures.

2.2 Antidepressant treatment:

Eligible participants were randomized to one of three treatment arms, each consisting of a primary open-label SSRI or SNRI antidepressant, given at study entry, and a secondary, single-blinded non-SSRI medication that began at week two. Treatment arms were: escitalopram (up to 20 mg/day) plus placebo; escitalopram (up to 20 mg/day) plus sustained-release bupropion (up to 400 mg/day); or extended-release venlafaxine (up to 300 mg/day) plus mirtazapine (up to 45 mg/day). Medications were delivered using measurement-based care [42]. Dose adjustments were made based on scores on the 16-item Quick Inventory of Depressive Symptomatology-Clinician-Rated (QIDS-C), which is extracted from the 30-item IDS-C [43]. Adverse side effects were measured on the Frequency, Intensity, and Burden of Side Effects Rating Scale [44]. A detailed treatment regimen has been previously described [40].

2.3 Assessments:

Baseline assessments included sociodemographic and illness features, the self-administered Comorbidity Questionnaire (SCQ) to establish the presence, severity, and functional impact of a range of common concurrent medical conditions, body mass index (BMI), HAM-D, QIDS-SR, and IDS-C. At baseline, the presence of anxious features was determined from the anxiety subscale of HAM-D [45], while IDS-C subscales [46] were used to assess the presence of melancholia, atypical symptoms, and sleep disturbances. A comprehensive table of baseline characteristics is detailed in the primary outcome manuscript [40].

Acute phase treatment visits were planned at baseline and weeks 1, 2, 4, 6, 8, 10, and 12. At each study visit, the IDS-C and QIDS-SR were assessed. For this report, treatment outcome was measured by change in IDS-C score. The IDS-C was preferred over QIDS-SR as it not only assesses the 9 core symptoms of MDD (based on the DSM) but also evaluates associated symptoms (e.g., anxiety, irritability) and items relevant to melancholic or atypical symptom features [43].

2.4 Collection and measurement of biological markers:

Of the 665 randomized CO-MED participants, a subset signed additional consents for a biomarkers study and provided blood samples, from which plasma was extracted and analyzed. Peripheral venous blood was drawn into EDTA purple-top blood collection tubes and shipped from study sites by next day priority delivery to RUCDR Infinite Biologics (Piscataway, NJ), where plasma was isolated upon receipt. Plasma was stored at -80°C until assayed.

Using CO-MED samples, several blood-based biomarkers have been analyzed and reported previously [47–50]. This particular study aimed to evaluate adiponectin, specifically, for its potential moderating effect on treatment outcome. The subset of participants who provided baseline plasma and had interpretable adiponectin measurements in this study was $n=160$. Additionally, 101 participants also provided plasma at week 12 (or at study exit, if earlier than week 12) and these samples were used for baseline-to-exit analyses. ELISA kits were used to quantify total adiponectin (EZHADP-61K, EMD Millipore, Billerica, MA). Inter-assay and intra-assay coefficients of variation were 0.5%-10%. The assay conditions were controlled and standardized, and the kits were from the same lot to optimize reproducibility.

2.5 Statistical methods

Baseline characteristics were compared among treatment groups using analysis of variance or chi-square tests for continuous or categorical variables, respectively, except where noted. Kendall correlations were computed between baseline adiponectin levels and baseline clinical characteristics. A repeated measures mixed-effects model was used to test baseline adiponectin (log transformed) as a moderator of treatment effect for the IDS-C. Intercepts were treated as random effects, and all other effects were treated as fixed. Comparison of the three treatment arms was carried out through three pairwise comparisons: escitalopram monotherapy versus escitalopram plus bupropion; escitalopram monotherapy versus venlafaxine plus mirtazapine; and escitalopram plus bupropion versus venlafaxine plus mirtazapine. Baseline IDS-C, gender, age, and BMI (or C-reactive protein [CRP], in

supplemental analysis) were included as covariates in analyses. For each adiponectin model, all 2-way, 3-way, and 4-way interactions were included with the following subsets: 1) adiponectin, age, time, and treatment group; 2) adiponectin, gender, time, and treatment group and; 3) adiponectin, BMI (or CRP), time, and treatment group. Interaction terms were retained in the final model (Supplemental Tables 2 and 3) if their removal resulted in a significant reduction in the goodness of fit. Partial correlations between baseline-to-exit change in adiponectin levels and baseline-to-exit change in IDS-C were computed with adjustment for gender, age, and baseline BMI. Because of the preliminary nature of this analysis, no adjustment was made for multiple comparisons, and $p < 0.05$ defined significance for all tests.

3. RESULTS

3.1 Baseline characteristics

Sociodemographic information, clinical characteristics, and treatment outcomes of the entire CO-MED study population ($n=665$) have been previously described [40, 51, 52], and characteristics of the current subgroup did not significantly differ from those previously reported. Table 1 shows baseline categorical and continuous variables for the subset of individuals for whom baseline adiponectin levels were available ($n=160$). No baseline characteristic significantly differed across treatment arms, with the exception of age; participants in the venlafaxine plus mirtazapine group were younger than those of the other two groups. Baseline adiponectin levels did not significantly differ between treatment arms.

Age, BMI, IDS-C and baseline adiponectin levels—Correlational analyses were performed between baseline adiponectin levels and several clinical or biological features. As expected, adiponectin did not correlate with age (Kendall correlation, $r = 0.0561$) but did inversely correlate with BMI (Kendall correlation, $r = -0.20$, $p = 0.002$). Baseline adiponectin level did not correlate with baseline depression severity as measured with the IDS-C (Kendall correlation, $r = -0.03$). Consistent with previous reports [23, 25], adiponectin levels were higher in females than males ($p = 0.021$, Supplementary Table 1).

3.2 Adiponectin is a moderator of antidepressant treatment response

In the CO-MED cohort, adiponectin was a significant moderator of differential treatment outcome between the two combination therapies—escitalopram plus bupropion (Esc/Bup) versus venlafaxine plus mirtazapine (Ven/Mirt) (Supplementary Table 2; adiponectin by treatment group by time interaction, $F = 4.84$; $p = 0.029$). To examine the characteristics of the interaction, Figure 1 presents the model-generated trajectory for a participant with a low level of adiponectin (25th percentile; 5.6 $\mu\text{g/ml}$) or a high level of adiponectin (75th percentile; 13.55 $\mu\text{g/ml}$) with all other covariates set to mean levels. Participants with low levels of adiponectin at baseline (Figure 1A) demonstrated a greater decrease in depressive symptoms over 12 weeks of treatment with Esc/Bup (red line) than with Ven/Mirt (blue line). Participants with high levels of adiponectin (Figure 1B) demonstrated the opposite effect; Ven/Mirt treatment decreased depressive symptoms more than Esc/Bup treatment.

Pairwise comparisons were similarly analyzed with escitalopram monotherapy versus each combination therapy. However, as shown in Supplementary Table 2, baseline adiponectin did not moderate treatment outcome for escitalopram monotherapy (Esc/Pbo) versus either the Esc/Bup group ($F=0.02$, $p=0.89$) or the Ven/Mirt group ($F=1.86$, $p=0.17$).

C-reactive protein (CRP)—a global marker of inflammation—has previously been identified as a moderator of treatment response in the same CO-MED cohort [49]. Thus, to ensure that the moderating effect of adiponectin was not confounded by variables not controlled for, we conducted analyses in which CRP was used as a covariate in place of BMI. For each pairwise comparison, we found the same pattern of significance or nonsignificance as that described above (Compare Supplemental Tables 2 and 3). When comparing the two combination therapies (Esc/Bup versus Ven/Mirt), the moderating effect was even more pronounced when controlling for CRP (Supplementary Table 3; adiponectin by treatment group by time interaction, $F=6.7$; $p=0.01$), suggesting BMI is a more conservative covariate.

3.3 Baseline-to-exit changes in adiponectin with antidepressant treatment

Since baseline adiponectin was a moderator of treatment response across combination therapies, we next calculated whether adiponectin levels were associated with the change in IDS-C over time or fluctuated differentially across interventions. Within-patient baseline-to-exit changes are shown in Table 2. Correlations were calculated following adjustment for baseline age, gender, BMI, and IDS-C. Adiponectin levels did not correlate with change in IDS-C with any treatment, and adiponectin levels remained relatively steady between baseline and exit timepoints. Only in the Ven/Mirt treatment group was there a trend toward altered levels from baseline to week 12 (i.e., decreased adiponectin, $p=0.069$).

4. DISCUSSION

In this study, we showed that adiponectin moderates the treatment effect of escitalopram plus bupropion versus venlafaxine plus mirtazapine in a subset of participants from the CO-MED clinical trial. While previous studies have shown an association between changes in adiponectin levels with antidepressant treatment and prediction of outcome [16, 17, 29, 34], to our knowledge this is the first study in humans which shows that baseline adiponectin may effectively guide treatment selection.

Previously, Machado-Viera et al. demonstrated that low baseline adiponectin levels predicted effective treatment response to acute ketamine administration [39]. Further, the lower the baseline level of adiponectin, the greater the improvement, as measured by performance on the Montgomery-Asberg Depression Rating Scale 1-day post-injection. While their study demonstrated the predictive value of baseline adiponectin level, here, we extend these findings and show that adiponectin level moderates differential treatment response between two therapies. If validated, these data have important clinical implications, as quantification of adiponectin levels from a simple blood draw may guide physicians with choosing an effective first-line treatment for depression. Health improvements could be obtained sooner, and remission rates could be higher.

In the context of adiposity, low adiponectin levels may reflect a chronic inflammatory state because of its anti-inflammatory properties [53]. Thus, the finding of improved outcome with bupropion-containing combination therapy in depressed patients with low adiponectin is consistent with previous reports that indicated that inflammatory markers could predict differential response between antidepressants. Elevated levels of CRP, a non-specific marker of systemic inflammation, were shown to favor bupropion plus escitalopram over escitalopram monotherapy [49] and nortriptyline over escitalopram [54]. Elevated levels of other inflammatory markers, including interleukin-17 and platelet-derived growth factor also favor bupropion-containing combination therapy over SSRI monotherapy [48, 50], further supporting the utility of bupropion in depressed patients with elevated inflammatory markers. Adiposity, as a source of inflammation, may also be important in guiding antidepressant selection, as evidenced by two recent reports which found that depressed patients with moderate or severe obesity (BMI ≥ 35) responded poorly to SSRI monotherapy as compared to venlafaxine monotherapy [55] and the combination of bupropion and SSRI [56].

Drug-Specific Alterations of Adiponectin

As illustrated in Figure 2, aberrant adiponectin levels are frequently observed with depression and associated metabolic disorders. Several biological features (e.g., monoamine signaling, weight change, inflammation) may account for adiponectin dysregulation, and thus the disparate drug-specific mechanisms of action may explain adiponectin's moderating effect between the two combination therapies. Bupropion augments dopaminergic tone, and dopamine signaling undergoes a positive feedback cycle to increase adiponectin [57]. In rodent models, administration of the dopamine agonist, bromocriptine, significantly increased adiponectin levels [58]. Further, human subjects undergoing treatment for smoking cessation with bupropion display significantly enhanced circulating adiponectin [59]. Thus, by serving as a dopamine reuptake inhibitor [60], bupropion may be increasing dopamine availability and signaling, thereby enhancing adiponectin. However, unlike the aforementioned studies, our data failed to demonstrate a significant change over time in plasma adiponectin level with escitalopram plus bupropion treatment. It is important to note that the small sample size per treatment arm and the different assays used among studies may contribute to this discrepancy. It is also possible that levels of central, bioactive adiponectin were altered but not measured in this report.

High BMI and obesity have repeatedly been identified as inverse correlates of adiponectin level [25, 61], suggesting that weight affects adiponectin. Mirtazapine is one of few prescribed antidepressants associated with weight gain [62] and may subsequently cause decreased adiponectin levels. As exit weight was not recorded in all patients, we are unable to report an overall group effect on weight; however, of approximately 75% of participants for whom baseline-to-exit weight measurements were available, there was an average weight gain of 4.4 pounds with venlafaxine plus mirtazapine treatment (data not shown). Alongside the trend of decreased adiponectin levels in the venlafaxine plus mirtazapine group ($p = 0.069$; Table 2), this supports the premise that weight change affects adiponectin level, and in this case, weight gain with venlafaxine plus mirtazapine improves treatment outcome. This is consistent with a recent report showing that normal or underweight individuals (BMI

<25) responded best to venlafaxine-mirtazapine treatment, as compared to SSRI monotherapy or SSRI plus bupropion [56].

Limitations and Future Directions

This study is novel in reporting adiponectin as a moderator of antidepressant treatment response, but there are study design limitations that necessitate these data be considered preliminary in nature. First, participants were a subset of those enrolled in the CO-MED study, and analyses were done retrospectively. Only a relatively small percentage of participants provided plasma for analyses (~24%), and the resultant sample size per treatment group was small. The low number of participants in each group may explain why trends were observed, although most did not reach significance.

The collection of specimens and analysis of samples also presented limitations. We do not know at what time of day the blood draw was performed and whether patients were fasting, either of which may significantly impact plasma levels of any hormone, including adiponectin. Additionally, plasma was collected at baseline and treatment exit, but not throughout the course of treatment. Lastly, as the primary outcome of CO-MED was to evaluate the efficacy of monotherapy versus combination therapy, three pairwise comparisons were performed between treatment groups when testing for potential moderating effects, rather than first testing for an overall interaction.

To confirm our preliminary finding that adiponectin moderates treatment response, a separate validation study cohort will be necessary for replication of our results. To evaluate whether pharmacological-induced variation in adiponectin levels accounts for differential efficacies, it will be necessary to quantify levels of adiponectin throughout the study, particularly at time points by which a treatment effect may be noticeable. Additionally, as numerous potential moderators of treatment outcome have now been identified, it will be interesting to test whether a composite, multivariate biomarker produces the strongest moderating effect(s).

Conclusion

These data suggest that adiponectin may be a valuable biomarker for identifying effective first-line treatment strategies within a heterogeneous population of MDD patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Moderating effect of adiponectin between combination therapies. Patients with a low level of baseline adiponectin (25th percentile) respond better to escitalopram plus bupropion therapy than venlafaxine plus mirtazapine therapy (A). Patients with a high level of baseline adiponectin (75th percentile) respond better to venlafaxine plus mirtazapine therapy than escitalopram plus bupropion (B).

Figure 2.

Conceptual model for the moderating effect of adiponectin. Adiponectin levels are reportedly altered in depression and associated metabolic disorders (A) which may be explained by changes in several biological features (B). In participants with relatively low adiponectin levels, escitalopram plus bupropion therapy may be superior because it can ameliorate symptoms associated with low adiponectin, such as inflammation and low monoamine signaling. In participants with relatively high adiponectin levels, venlafaxine plus mirtazapine may be superior because it can promote weight gain, which may decrease adiponectin.

Table 1:**Baseline Characteristics by Treatment Group**

	All	Esc/Pbo	Esc/Bup	Ven/Mirt		
Categorical	N	N	N	N	χ^2	p value
Total	160	47	54	59		
Gender					0.3	0.8504
Male	46	14	14	18		
Female	114	33	40	41		
Race					4.7	0.3212
White	107	26	39	42		
Black	40	15	11	14		
Other	13	6	4	3		
Hispanic	27	8	7	12	1.1	0.5785
Continuous	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F stat	p value
Age	44.2 (11.9)	46.8 (11.8)	46.1 (12.2)	40.3 (11)	5.2	0.0064
BMI	31.8 (9)	33.3 (11.5)	31.5 (7.5)	31.0 (8.3)	0.9	0.3970
IDS-C	38.2 (9.1)	37.9 (9.4)	37.4 (9.1)	39.3 (8.9)	0.6	0.5281
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)		p value
Adiponectin (µg/ml)	8.80 (5.60, 13.55)	8.58 (4.67, 15.69)	8.23 (5.91, 10.28)	9.71 (5.57, 14.00)		0.3584 *
CRP (mg/L)	0.19 (0.07, 0.59)	0.22 (0.08, 0.73)	0.21 (0.07, 0.62)	0.15 (0.06, 0.44)		0.3351 *

* Kruskal Wallis Test

Abbreviations: Esc/Pbo (escitalopram monotherapy); Esc/Bup (escitalopram plus bupropion); Ven/Mirt (venlafaxine plus mirtazapine); BMI (Body Mass Index); IDS-C (Inventory of Depressive Symptomatology-Clinician-Rated); CRP (C-reactive protein); SD (Standard Deviation); IQR (Interquartile Range)

Table 2:

Baseline-to-exit change in adiponectin level by treatment group

Group	Median Change (25 th , 75 th Percentile)	Change p-value *	Correlation with IDS-C	Correlation p-value
Esc/Pbo	0.047 (−2.57, 1.05)	0.5735	−0.156	0.4896
Esc/Bup	0.447 (−0.95, 1.83)	0.2861	−0.161	0.3876
Ven/Mirt	−0.591 (−3.07, 0.76)	0.0689	0.135	0.4941

* Wilcoxon signed rank test

Abbreviations: Esc/Pbo (escitalopram monotherapy); Esc/Bup (escitalopram plus bupropion); Ven/Mirt (venlafaxine plus mirtazapine); IDS-C (Inventory of Depressive Symptomatology-Clinician-Rated)