Aripiprazole Partial Agonism at 5-HT_{2C}: A Comparison of Weight Gain Associated With Aripiprazole Adjunctive to Antidepressants With High Versus Low Serotonergic Activities

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ABSTRACT

Objective: 5-HT_{2C} receptor antagonists are thought to contribute toward increased appetite and obesity. Aripiprazole acts as a partial agonist at the 5-HT_{2C} receptor; hence, it is thought to cause little or no significant weight gain when used alone. We theorize that, in the presence of antidepressants with high serotonergic activity, aripiprazole acts as an antagonist at the 5-HT_{2C} receptor, thus increasing the potential for weight gain. Conversely, in environments with low serotonergic activity, aripiprazole acts as an agonist at the 5-HT_{2C} receptor, therefore having less potential for weight gain.

Method: A retrospective electronic medical record chart review of the Veterans Integrated Service Network 22 Veterans Affairs database was performed comparing patients' weight and body mass index (BMI) while taking aripiprazole alone (n = 1,177), versus aripiprazole plus a high-serotonergic antidepressant (citalopram, fluoxetine, paroxetine, sertraline, or venlafaxine) (n = 145), versus aripiprazole plus a low-serotonergic antidepressant (bupropion) (n = 77) for a minimum continuous duration of 6 months of aripiprazole monotherapy or combination treatment. The study was conducted from January 2010 through June 2011.

Results: In our patient population, only the aripiprazole plus high-serotonergic antidepressants group had a statistically significant increase in weight ($P = .0027$) and BMI ($P = .0016$).

Conclusions: Our data suggest that, in the presence of antidepressants with high serotonergic activity, aripiprazole may act as an antagonist at the 5-HT_{2C} receptor, resulting in weight gain. Conversely, when aripiprazole is used in the presence of antidepressants with low serotonergic activity, it may act as an agonist and result in little or no weight gain. This varying effect at the 5-HT_{2C} receptor may explain why aripiprazole has not been associated with significant weight gain in previous studies focusing on schizophrenia and bipolar disorder.

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Most antipsychotic medications are associated with an increased risk of weight gain. A proposed mechanism is the antagonism at the 5-HT_{2C} receptor, which has been associated with an increase in food intake.[1] In contrast, agonism at the 5-HT_{2C} receptor, as produced by fenfluramine and *m*-chlorophenylpiperazine, may lead to suppression of appetite.[2,3] Tecott and colleagues[4] developed a strain of mice lacking the gene for the 5-HT_{2C} receptor. These mice demonstrated increased obesity. In a meta-analysis, De Luca et al,[5] looking primarily at the 759C/T promoter polymorphism (rs3813929) of the X-chromosome–linked *HTR2C* gene, provided data suggesting a 5-HT_{2C}-receptor association with weight changes; however, they noted heterogeneity among the studies and suggested the need for larger studies. Furthermore, a study by Kirk et al[6] showed a significant increase in weight in rats after 5 days of daily doses of olanzapine and the 5-HT_{2C} antagonist SB 243213 but not the histamine-1 (H_1) antagonist. Stark et al,[7] using the 5-$HT_{1B/2C}$ agonist *m*-chlorophenylpiperazine and subsequently a 5-HT_{1B} and 5-HT_{2C} antagonist in non-anesthetized male rats, showed decreased fast-induced refeeding only with 5-HT_{2C}.

In support of the previous data, there are important molecules interacting with the brain nervous system that regulate feeding and energy balance by influencing the signaling pathways of these areas. Only a few of these mediators have been described. In a recent publication, Wang et al[8] showed that Abelson helper integration site 1 (Ahi1) protein directly influences 5-HT_{2C}. Fasting increases Ahi1, which leads to decreased expression of 5-HT_{2C}.[8] Subsequently, knockdown of Ahi1 leads to increased expression of 5-HT_{2C}, which results in decreased food intake and body weight.

Opgen-Rhein et al,[9] looking at 128 patients with schizophrenia, demonstrated an association between the X-chromosomal *HTR2C* gene and antipsychotic-induced weight gain. They proposed that the underlying mechanism is related to a decrease in *HTR2C* gene expression that leads to a decrease in 5-HT–modulated activation of hypothalamic proopiomelanocortin neurons and inverse 5-HT_{2C} agonism in the presence of dopamine-2 (D_2) receptor antagonism. However, De Luca et al, looking at 3 functional polymorphisms (Cys23Ser, −759C/T, and (GT)12–18/(CT) 4–5) of the *HTR2C* gene in 139 patients with schizophrenia, reported no significant haplotype conferring risk for antipsychotic-induced weight gain.[5] In another study, Martin et al[10] randomized 39 patients to lorcaserin (a 5-HT_{2C} agonist) and 28 patients to placebo and demonstrated that weight loss is a result of decrease in energy intake, not as an increase in energy expenditure. Wang and Chehab[11] looked at the interaction between leptin and the 5-HT_{2C} in proopiomelanocortin neurons in regulating body weight. In a population of transgenic mice with overexpressing leptin (LepTg), without 5-HT_{2C} receptors, they demonstrated that, on a lean diet, the phenotype of LepTg mice was unaffected by the absence of 5-HT_{2C} receptors, whereas on a high-fat diet, LepTg/5-HT_{2C}-receptors–knockout mice showed an exacerbation of diet-induced obesity. Thus, on a carbohydrate-rich diet (or "chow diet"), the LepTg works independently of 5-HT_{2C}, while on a high-fat diet, the 5-HT_{2C} is needed for attenuation of obesity.

Preliminary evidence suggests that aripiprazole is a partial agonist at 5-HT_{2C}.[12] In the presence of antidepressants with high serotonergic activity,

Clinical Points

- There is still much to be learned about the mechanism(s) behind antipsychotic-induced weight gain.
- One theory behind aripiprazole's varying effects on weight gain is that, in the presence of high serotonergic activity, aripiprazole acts as an antagonist at the 5-HT_{2C} receptor, thus increasing the potential for weight gain. Conversely, when in an environment of low serotonergic activity, aripiprazole acts as an agonist at the 5-HT_{2C} receptor, thereby having less effect on weight.
- Further research into the 5-HT_{2C} receptor and other receptor subtypes and their relation to appetite and obesity is still needed.

aripiprazole may act as an antagonist at the 5-HT_{2C} receptor, thus increasing the potential for weight gain. In environments with low serotonergic activity, aripiprazole may act as an agonist at the 5-HT_{2C} receptor, thus having less effect on the potential for weight gain.[12] This varying effect at the 5-HT_{2C} receptor may explain why aripiprazole has not been associated with significant weight gain in previous studies focusing on schizophrenia and bipolar disorder. Therefore, we hypothesize that adjunctive use of aripiprazole along with antidepressants with low serotonergic activities may result in less weight gain compared to aripiprazole when used in the presence of antidepressants with high serotonergic activity.

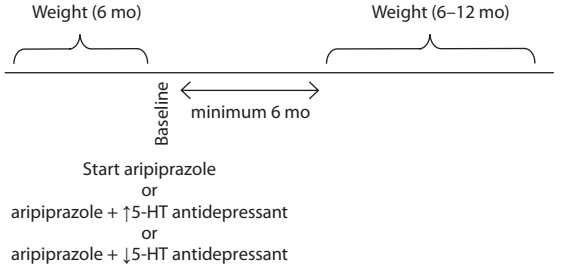
METHOD

A retrospective electronic medical record chart review of the Veterans Integrated Service Network (VISN) 22 Veterans Affairs (VA) database from January 1, 2003, until December 31, 2009, was performed after institutional review board approval (VISN 22 covers VA patients from all of Southern California and parts of Nevada). The chart review compared patients' weight and body mass index (BMI) while taking aripiprazole alone (n = 1,177), versus aripiprazole plus a high-serotonergic antidepressant (citalopram, fluoxetine, paroxetine, sertraline, or venlafaxine; n = 145), versus aripiprazole plus a low-serotonergic antidepressant (bupropion; n = 77). Patients had to be on continuous treatment for a minimum of 6 months, with continuous treatment defined as having no breaks in treatment greater than 90 days (Figure 1). Data were extracted electronically through an automated process. Extraction was repeated to ensure quality control of the data. The study was conducted from January 2010 through June 2011.

The baseline BMI was based on the last weight taken in the 180-day period prior to the start of aripiprazole monotherapy or combination drug therapy (T_0). The follow-up BMI was based on the first weight taken between 180 to 360 days after start of therapy.

We excluded patients with a lapse of drug therapy of 90 days or more, patients who were lost to follow-up, patients without sufficient data, and patients who had more than a 100-lb change in weight over the prior 6 months, assuming these were errors on data entry in the medical chart.

Figure 1. Timeline: Study of Weight Gain in Aripiprazole Adjunctive to Antidepressants With High Versus Low Serotonergic Activity



Symbols: ↑ = high, ↓ = low.

Three groups were identified:

Group 1: Aripiprazole monotherapy of at least 180 days' duration.

Group 2: Citalopram (50.3%), fluoxetine (18.6%), paroxetine (8.3%), sertraline (16.6%), or venlafaxine (6.2%) added to existing aripiprazole with at least 180 days of combination therapy.

Group 3: Bupropion added to existing aripiprazole with at least 180 days of combination therapy.

Data gathered were analyzed using SPSS, version 14 software (IBM, Armonk, New York) for standard deviation (SD), paired sample test and *t* test 2-tailed analysis, and analysis of variance.

RESULTS

All 3 groups were relatively similar at baseline, with the exception of a difference in age, BMI, and sex (Table 1). In the patients taking aripiprazole without an antidepressant (n = 1,177), patients gained a mean of 0.79 lb (SD = 17.31 lb) and had an increase in BMI of 0.11 kg/m^2 (SD = 2.55 kg/m^2), although neither change was statistically significant.

In patients taking aripiprazole with a high-serotonergic antidepressant (n = 145), there was a statistically significant mean increase in weight of 3.91 lb (SD = 15.48 lb) ($P = .0027$), as well as a statistically significant mean increase in BMI of 0.60 kg/m^2 (SD = 2.24 kg/m^2) ($P = .0016$).

In the third group, patients taking a combination of aripiprazole and a low-serotonergic antidepressant (n = 77), patients lost a mean of 0.53 lb (SD = 15.3 lb) and had a mean decrease in BMI of 0.09 kg/m^2 (SD = 2.31 kg/m^2), although neither change was statistically significant (Table 2).

DISCUSSION

Antipsychotic medications, both first- and second-generation, have the potential side effect of weight gain, with second-generation agents carrying a greater risk.[13–17] Allison et al[18] performed a meta-analysis comparing the weight gain

Table 1. Baseline Demographic and Clinical Characteristics of Patients: Study of Weight Gain in Aripiprazole Adjunctive to Antidepressants With High Versus Low Serotonergic Activity

Characteristic	Aripiprazole	Aripiprazole + ↑5-HT Antidepressant	Aripiprazole + ↓5-HT Antidepressant
Patients, n	1,177	145	77
Age,* mean ± SD, y	54.05 ± 11.13	55.36 ± 10.40	54.57 ± 10.13
Weight, mean ± SD, lb	211.60 ± 47.84	211.80 ± 46.85	220.15 ± 44.30
BMI,* mean ± SD, kg/m^2	31.19 ± 6.50	31.19 ± 6.25	32.59 ± 6.61
Sex,* n (%)			
Male	1,033 (87.8)	134 (92.4)	63 (81.8)
Female	144 (12.2)	11 (7.6)	14 (18.2)
Antidepressant, %	NA	Citalopram: 50.3 Fluoxetine: 18.6 Sertraline: 16.6 Paroxetine: 8.3 Venlafaxine: 6.2	Bupropion: 100

*Significant difference between groups ($P < .05$): age ($P = .0118$), BMI ($P = .0375$), and sex ($P = .0127$).
Abbreviations: 5-HT = serotonin, BMI = body mass index, NA = not applicable, SD = standard deviation.
Symbols: ↑ = high, ↓ = low.

Table 2. Weight Gain in Aripiprazole Adjunctive to Antidepressants With High Versus Low Serotonergic Activity

Variable	Aripiprazole	Aripiprazole + ↑5-HT Antidepressant	Aripiprazole + ↓5-HT Antidepressant
Patients, n	1,177	145	77
Baseline weight, mean ± SD, lb	211.60 ± 47.84	211.80 ± 46.85	220.15 ± 44.30
Follow-up weight, mean ± SD, lb	212.39 ± 47.99	215.72 ± 46.30	219.63 ± 45.37
Δ weight, mean ± SD, lb	0.79 ± 17.31	3.91* ± 15.48	−0.53 ± 15.30
Baseline BMI, mean ± SD, kg/m^2	31.19 ± 6.50	31.19 ± 6.25	32.59 ± 6.61
Follow-up BMI, mean ± SD, kg/m^2	31.31 ± 6.50	31.79 ± 6.23	32.50 ± 6.77
Δ BMI, mean ± SD, kg/m^2	0.11 ± 2.55	0.60** ± 2.24	−0.09 ± 2.31

*$P = .0027$, **$P = .0016$.
Abbreviations: 5-HT = serotonin, BMI = body mass index, NA =not applicable, SD = standard deviation.
Symbols: Δ = change, ↑ = high, ↓ = low.

of first- and second-generation antipsychotic medication. In this analysis, clozapine was found to be associated with the greatest weight gain, followed by olanzapine, risperidone, and ziprasidone, respectively. Parsons et al,[19] in a more recent comprehensive database analysis, found a median weight increase over 1 year of +0.49 lb/mo for haloperidol, −0.18 lb/mo for ziprasidone, +1.50 lb/mo for olanzapine, and +0.55 lb/mo for risperidone, compared to placebo, which demonstrated a weight loss of 0.32 lb/mo.

Based on the results of our study, it appears that aripiprazole may indeed exhibit varying effects at the 5-HT$_{2C}$ receptor, possibly acting as an antagonist in the presence of antidepressants with high serotonergic activity. Several studies demonstrate that aripiprazole is a partial agonist at 5-HT$_{2C}$.[12] Aripiprazole may be an agonist in environments with low 5-HT$_{2C}$ stimulation and an antagonist in conditions of high 5-HT$_{2C}$ stimulation.[12] In the presence of antidepressants with high serotonergic activity, aripiprazole may act as an antagonist at the 5-HT$_{2C}$ receptor, thus increasing the potential for weight gain. In environments with low serotonergic activity, aripiprazole may act as an agonist at the 5-HT$_{2C}$ receptor, thus having less potential for weight gain. This varying effect at the 5-HT$_{2C}$ receptor may explain why aripiprazole has not been associated with significant weight gain in previous studies focusing on schizophrenia and bipolar disorder.

Antagonism at the histamine-1 (H_1) receptor has also been associated with weight gain.[20–24] Wirshing et al[25] found an exponential relationship between the medications' H_1 receptor affinities (dose-dependent) and maximum weight gain. Both olanzapine and clozapine have very strong binding affinity to both 5-HT$_{2C}$ and H_1 receptors compared to other antipsychotic medications, which may explain increases in appetite and thus weight gain, while peripheral M_3 muscarinic receptor antagonism also contributes to obesity (which might explain the dose-dependent weight gain with

these medications and not with other second-generation antipsychotic medications.[26,27]

Multiple studies[28–33] have established aripiprazole, a partial agonist at several G-protein–coupled receptors (D_2 and 5-HT_{1A}) and functional antagonist at several serotonin receptors, including 5-HT_{2A}, 5-HT_{2B}, and 5-HT_6, as an effective treatment for symptoms of schizophrenia and bipolar mania, with a low potential for weight gain. In long-term studies in schizophrenia and bipolar disorder,[34,35] aripiprazole treatment has not been associated with a mean increase in body weight from baseline. In some cases, small decreases in mean body weight have been observed.[36,37] However, in a study[38] with aripiprazole adjunctive to standard antidepressant therapy, particularly escitalopram, fluoxetine, paroxetine, sertraline, or venlafaxine, for patients with *DSM-IV* major depressive disorder, the weight gain associated with aripiprazole (3.74 lb) is significantly higher than with placebo (0.88 lb). Our results support this observation that patients on a combination of a high-serotonergic antidepressant with aripiprazole showed a statistically significant increase in weight of 3.91 lb ($P = .0027$), as well as a statistically significant increase in BMI of 0.60 kg/m^2 ($P = .0016$).

CONCLUSION

In our study, patients taking a combination of a high-serotonergic antidepressant with aripiprazole showed a statistically significant increase in weight of 3.91 lb, as well as statistically significant increase in BMI of 0.60 over 6 months. However, those patients taking aripiprazole without an antidepressant had no significant changes in either weight or BMI over 6 months. Those patients taking aripiprazole with a low-serotonergic antidepressant also showed no significant changes in weight or BMI over the 6-month period.

We theorize that aripiprazole's partial agonism at the 5-HT_{2C} receptor explains the weight gain found in studies in which aripiprazole is used as adjunctive treatment with antidepressants.

This study supports the limited data regarding weight gain liability in patients treated with a combination of high-serotonergic antidepressants and aripiprazole. Further studies are needed to understand the mechanisms involved and consequently to minimize side effects, such as weight gain and its implications.

Drug names: aripiprazole (Abilify), bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), clozapine (Clozaril, FazaClo, and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), haloperidol (Haldol and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), risperidone (Risperdal and others), sertraline (Zoloft and others), venlafaxine (Effexor and others), ziprasidone (Geodon).

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