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Weight gain with antipsychotics: What role does leptin play?

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Might antipsychotics disturb the appetite-suppressing effects of this hormone?

Clinical studies indicate that clozapine and olanzapine carry a high risk of treatment-related metabolic dysfunction—including weight gain, hyperlipidemia, and glucose intolerance—but certain patients with high metabolic liabilities who take atypical antipsychotics do not necessarily develop these adverse effects. Though the underlying mechanism for atypical antipsychotic-related weight gain is strongly associated with central histamine H1 antagonism and increased appetite, the pharmacologic basis for other metabolic changes is not fully understood and may involve weight-independent mechanisms.

One potentially relevant research area is peptide hormones' impact on the regulation of food intake, body weight, and other metabolic parameters. As research has elucidated the properties of 1 of these hormones—leptin—investigators have started to examine possible correlations between changes in serum levels of leptin and weight gain during atypical antipsychotic treatment.

This article summarizes available clinical data on the interaction of atypical antipsychotics with leptin and indicates directions for future research on interactions between psychotropic medications and metabolic hormones.

Leptin's function

Since its initial sequencing as the product of the obese (ob) gene in 1994, leptin has garnered substantial attention as a metabolic regulatory hormone.[1] Leptin is

produced primarily by fat cells as part of a long-term central feedback mechanism involving central control of appetite and peripheral metabolic activity regulation. Leptin is a 167 amino acid, 16-kilodalton protein that binds to cell surface receptors (the product of the diabetes [db] gene) at both central (ventromedial hypothalamic) and peripheral sites (liver, skeletal muscle, and pancreatic β-cells).[2]

Evidence for leptin's activity is seen in ob/ob mice, whose genetic inability to produce leptin is manifested phenotypically in overeating and obesity. Administering recombinant leptin to these mice results in reduced appetite and weight loss.[3]

On average, women have greater fat mass and higher serum leptin levels than men. Humans rarely have mutations in both copies of the ob gene, but those who do are severely obese and respond to exogenous leptin. Heterozygotes are not quite as heavy.

Leptin circulates in a free form but in humans is predominantly bound to the soluble leptin receptor (sOB-R). Levels of sOB-R increase with weight loss—with concomitant decreases in leptin levels—and these effects can be seen even during 72-hour fasts.[4] Leptin levels are positively correlated with fat mass, but the fact that obese individuals have chronically elevated leptin levels argues for some level of leptin insensitivity or resistance to the hormone's appetite-suppressing effects.[2]

Drug effects

Clozapine and olanzapine. Literature on leptin and antipsychotic-related obesity is relatively well developed. The first papers focused on the association between clozapine and olanzapine and increases in serum leptin levels.[5,6] As patients gained substantial weight on clozapine and olanzapine, serum leptin also rose, but neither weight nor leptin changes were seen in patients exposed to haloperidol or those who did not receive antipsychotics.[6]

Numerous subsequent prospective trials of patients treated with olanzapine[4,7,8] and clozapine[9-11] confirmed previousl established associations among use of these medications, weight gain, and increased serum leptin levels. Olanzapine- and clozapine-exposed subjects experienced marked increases in adiposity, weight, and serum leptin (***Box 1***). [5,9,12-16]

Other agents. For agents associated with less weight gain liability—such as high-potency typical antipsychotics,[12,17,18] sulpiride,[19] quetiapine,[18] or risperidone[20,21]—comparative trials noted modest weight gain and leptin increases. Prospective trials of weight-modifying strategies using adjunctive amantadine[8] or nizatidine[22] found positive effects of the adjunctive medication, with proportional decreases in leptin levels compared with antipsychotics alone.

Because the other 2 atypical antipsychotics—ziprasidone and aripiprazole—

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Box 1

Leptin levels increase early in antipsychotic treatment

Most of the weight gain associated with olanzapine and clozapine therapy occurs over the first 6 months of treatment and then plateaus between months 6 and 12. Leptin changes, however, do not parallel weight changes during extended antipsychotic treatment.

A prospective 10-week clozapine trial by Bromel[5] found that leptin levels peaked early in treatment—at week 2—followed by a subsequent decrease and then a steady rise, though not to the peak levels seen earlier. This pattern was replicated in Monteleone's 32-week prospective clozapine study, again with the initial peak in serum leptin levels occurring at week 2.[9]

Despite these fluctuations, overall leptin levels during longer-term antipsychotic treatment are highly correlated with weight and body mass index changes. Cross-sectional studies with patients on various medications generally found that those exposed to olanzapine and clozapine were heavier and had higher serum leptin levels.[12-14] Younger and thinner patients—regardless of medication—have lower serum leptin levels[15] and the association between the medication and leptin levels disappears when adjustments are made for differences in body mass index (BMI).[16] Once BMI is accounted for, antipsychotics appear to have no effects on leptin physiology independent of their effects on adiposity.

Clinical Point

Patients taking clozapine or olanzapine experienced increases in adiposity, weight, and leptin levels

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Leptin and weight gain

Clinical Point

Elevated serum leptin levels are associated with adverse metabolic markers, including insulin activity and serum triglycerides

Box 2

Do women have higher leptin levels than men?

Most—but not all—cross-sectional studies of patients receiving antipsychotic treatment have found higher serum leptin levels in women than men, even when men had greater body mass index (BMI).[13,28,29] In several prospective trials, this gender discrepancy gradually disappeared as men's serum leptin increased.[12,30] Data from 1 long-term study of patients treated with clozapine indicate that leptin changes were independent of gender and proportional to weight gain,[9] but other analyses that examined both weight and fat depots continued to find significant gender effects.[25] One notable exception was McIntyre's 6-month randomized adjunctive study of risperidone vs olanzapine in symptomatic bipolar patients on mood stabilizers, in which women had greater increases in serum leptin with either antipsychotic.[20]

were found to be weight-neutral or have the lowest weight-gain burden, few studies have examined the relationship between leptin with weight gain in patients taking these drugs. One study reported no significant body weight or leptin level change in patients after 4-week trial of ziprasidone.[23]

Other metabolic parameters

In humans, elevated serum leptin levels are associated with adverse metabolic markers, particularly those associated with insulin activity (including insulin itself) and serum triglycerides.[24] Several antipsychotic studies measured metabolic outcomes along with serum leptin levels but did not specifically calculate correlation coefficients between leptin and other parameters.[7,8,11,16,17,19]

Nonetheless, in many instances leptin levels increased significantly without significant changes in serum insulin or other glycemic or lipid measures.[11,25] One cross-sectional study in bipolar subjects also found no correlation between any glucose or lipid parameter and leptin levels.[26] A few studies reported significant correlations among leptin and serum insulin,[13,27] glucose,[15] and serum triglycerides,[18] although most did not control for body mass index (BMI).

Diagnosis effects

As the association was established between antipsychotic-induced weight gain and changes in serum leptin, investigators sought to understand whether disease influences modified the drug effects.

Schizophrenia. One early cross-sectional analysis of 14 olanzapine-treated schizophrenia patients noted that 57% had elevated serum leptin when compared with normal levels adjusted for BMI and gender,[27] but the absence of a weight-matched control group limits interpretation of these findings.

To separate diagnosis and treatment effects, Arranz[28] performed a cross-sectional study of 50 drug-naïve schizophrenia patients, 50 drug-free schizophrenia patients, and 50 unmatched healthy controls. Leptin levels across all cohorts were positively correlated with age and BMI, and—as found in several other studies (***Box 2***)[9,12,13,20,25,28-30]—women had higher levels than men in all 3 cohorts. The antipsychotic-free patients were older and heavier than the other 2 cohorts and had higher serum leptin levels, but neuroleptic-naïve schizophrenia subjects did not differ from controls. The absence of BMI matching between the drug-free patients and other cohorts limits the ability to make definitive statements about the treatment's impact on leptin levels.

Other studies removed these limitations by matching schizophrenia patients with controls on the basis of gender, BMI, and—in some cases—age. These studies indicate conclusively that—when matched appropriately with nonpsychiatric subjects—patients with schizophrenia do not

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exhibit greater-than-expected serum leptin levels, regardless of antipsychotic drug exposure.[7,11,12,19,26,28-31]

Other diagnoses. The only controlled comparative study of medication-treated bipolar patients vs matched controls also reported no significant difference in leptin levels.[26] Interestingly, a 6-month prospective study of risperidone in autistic children noted no increase in serum leptin despite a 5.6-kg mean weight gain.[21]

Lastly, a single 12-week prospective trial compared the effects of antipsychotics on levodopa psychosis in Parkinson's disease subjects treated with olanzapine (n=10), risperidone (n=10), quetiapine (n=10), or solely with antiparkinsonian medications (n=10); an unmedicated, healthy cohort (n=8) served as controls.[32] Only olanzapine was associated with significant weight gain, but BMI changes were positively correlated with changes in leptin levels across all cohorts.

Clinical implications

Driven by obesity's public health impact, researchers have achieved a basic understanding of the regulation of appetite and body weight, including identifying genetic polymorphisms and other obesity risk markers. Evidence exploring the association between peptide metabolic regulatory hormones and antipsychotic-induced weight gain and metabolic dysfunction is accumulating.

Overall, evidence strongly suggests that leptin levels increase during long-term antipsychotic treatment and are highly correlated with weight and BMI changes. Although the increase in serum leptin often parallels substantial weight gain, these changes appear to be more the result of weight gain than a direct effect of the antipsychotic on the leptin feedback pathway.[29] Virtually none of the papers we reviewed examined the association between leptin and glucose-insulin measures independent of the effect of weight changes.

continued

Leptin and weight gain

Clinical Point

Evidence exploring a potential link between metabolic regulatory hormones and antipsychotic-induced weight gain is accumulating

Predicting weight gain? Because increased serum leptin is likely the result of weight gain in patients taking antipsychotics, measuring leptin for clinical prediction or monitoring of weight gain may not be very useful. Measuring weight or BMI will be more feasible in most clinical settings. However, leptin level changes may help us understand the potential mechanism of hormonal feedback and its physiologic effect in weight gain.

Medications such as olanzapine and clozapine carry substantial metabolic burdens but are effective treatments for some patients who do not respond to other antipsychotics. Elucidating mechanisms by which antipsychotic medications affect metabolic parameters remains important for:

- quantifying patient risk
- informing the frequency and targets of metabolic monitoring during antipsychotic therapy
- permitting the development of novel agents without these limitations.

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Related Resource

- Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet. 2009;373(9657):31-41.

Drug Brand Names

Amantadine • Symmetrel
Aripiprazole • Abilify
Clozapine • Clozaril
Haloperidol • Haldol
Nizatidine • Axid
Olanzapine • Zyprexa
Quetiapine • Seroquel
Risperidone • Risperdal
Ziprasidone • Geodon

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Bottom Line

Strong evidence suggests increased leptin levels are highly correlated with weight gain and body mass index increase during antipsychotic treatment. These increases appear to be more the result of weight gain than a direct impact of the antipsychotic on the leptin feedback pathway.

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