Weight gain with antipsychotics: What role does leptin play?

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. 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). 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.

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. 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.

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. 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.

Numerous subsequent prospective trials of patients treated with olanzapine and clozapine confirmed previous 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.

Clinical Point
Patients taking clozapine or olanzapine experienced increases in adiposity, weight, and leptin levels.
Leptin and weight gain 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.

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. Several antipsychotic studies measured metabolic outcomes along with serum leptin levels but did not specifically calculate correlation coefficients between leptin and other parameters. Nonetheless, in many instances leptin levels increased significantly without significant changes in serum insulin or other glycemic or lipid measures. One cross-sectional study in bipolar subjects also found no correlation between any glucose or lipid parameter and leptin levels. A few studies reported significant correlations among leptin and serum insulin, glucose, and serum triglycerides, 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, but the absence of a weight-matched control group limits interpretation of these findings. To separate diagnosis and treatment effects, Arranz 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)—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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places. In two bipolar studies, the rate of discontinuation for adverse events in patients receiving 10 mg Lexapro was not significantly different from the rate in placebo. The rate of discontinuation for adverse events in patients assigned to a fixed dose of 20 mg Lexapro was 10%, which was significantly different from the rate of discontinuation for adverse events in patients receiving 10 mg Lexapro (6%) and placebo (5%). The rate of discontinuation for adverse events in the 20 mg Lexapro-treated patients was the result of a higher incidence of treatment-emergent adverse events in the 20 mg Lexapro group than in the 10 mg Lexapro or placebo group (5% and 2%, respectively). A significantly greater rate of discontinuation occurred in the 20 mg Lexapro treatment group than in the 10 mg Lexapro treatment group for the following adverse events: abdominal cramp (1% vs. 0%), abdominal distension (1% vs. 0%), abdominal pain (1% vs. 0%), abdominal swelling (1% vs. 0%), anorexia (1% vs. 0%), and bloating (1% vs. 0%).

Adverse events that were associated with discontinuation of at least 1% of patients treated with Lexapro, for which the rate was at least twice that of placebo treated patients, were nausea (6%) and ejaculation disorder (2% of male patients).

Generalized Anxiety Disorder
Among the 842 patients who received Lexapro in the 6-week, placebo-controlled, double-blind trial (continuous treatment), the incidence of treatment-emergent adverse events was comparable to that of placebo and was consistent with the adverse event profile in clinical trials of Lexapro.
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.

References

Related Resource


Drug Brand Names

- Amantadine - Symmetrel
- Olanzapine - Zyprexa
- Aripiprazole - Abilify
- Clozapine - Clozaril
- Haloperidol - Haldol
- Ziprasidone - Geodon
- Nizatidine - Axid

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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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