

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 clozapine⁹⁻¹¹ confirmed previous established associations among use of these

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 Bromel⁵ 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 levels¹⁵ 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.

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 amantadine⁸ or nizatidine²² 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—

Clinical Point

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



Leptin and weight gain

Clinical Point

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

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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 sig-

nificant 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, Arranz²⁸ 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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placebo. In two fixed-dose studies, the rate of discontinuation for adverse events in patients receiving 10 mg/day Lexapro was not significantly different from the rate of discontinuation for adverse events in patients receiving placebo. The rate of discontinuation for adverse events in patients assigned to a fixed dose of 20 mg/day Lexapro was 10%, which was significantly different from the rate of discontinuation for adverse events in patients receiving 10 mg/day Lexapro (4%) and placebo (3%). Adverse events that were associated with the discontinuation of at least 1% of patients treated with Lexapro, and for which the rate was at least twice that of placebo, were nausea (2%) and ejaculation disorder (2% of male patients). **Generalized Anxiety Disorder** Among the 429 GAD patients who received Lexapro 10-20 mg/day in placebo-controlled trials, 8% discontinued treatment due to an adverse event, as compared to 4% of 427 patients receiving placebo. Adverse events that were associated with the discontinuation of at least 1% of patients treated with Lexapro, and for which the rate was at least twice the placebo rate, were nausea (2%), insomnia (1%), and fatigue (1%). **Incidence of Adverse Events in Placebo-Controlled Clinical Trials Major Depressive Disorder Table 2** enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 715 depressed patients who received Lexapro at doses ranging from 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied. The most commonly observed adverse events in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, sweating increased, fatigue, and somnolence (see TABLE 2). **TABLE 2: Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Major Depressive Disorder* (Percentage of Patients Reporting Event) Body System/Adverse Event (Lexapro (N=715) and Placebo (N=592)):** Autonomic Nervous System Disorders: Dry Mouth (6% and 5%), Sweating Increased (5% and 2%), Central & Peripheral Nervous System Disorders: Dizziness (5% and 3%), Gastrointestinal Disorders: Nausea (15% and 7%), Diarrhea (8% and 5%), Constipation (3% and 1%), Indigestion (3% and 1%), Abdominal Pain (2% and 1%), General: Influenza-like Symptoms (3% and 4%), Fatigue (3% and 2%), Psychiatric Disorders: Insomnia (9% and 4%), Somnolence (6% and 2%), Appetite Decreased (3% and 1%), Libido Decreased (3% and 1%), Respiratory System Disorders: Rhinitis (5% and 4%), Sinusitis (3% and 2%), Urge/epididymitis/Ejaculation Disorders: (9% and <1%), Impotence (3% and <1%), Anorgasmia (2% and <1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo > Lexapro: headache, upper respiratory tract infection, back pain, pharyngitis, inflamed injury, anxiety. †Primarily ejaculatory delay. ‡Denominator used for males only (N=225 Lexapro; N=188 placebo). §Denominator used for females only (N=490 Lexapro; N=404 placebo). **Generalized Anxiety Disorder Table 3** enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia (see TABLE 3). **TABLE 3: Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder* (Percentage of Patients Reporting Event) Body System/Adverse Event (Lexapro (N=429) and Placebo (N=427)):** Autonomic Nervous System Disorders: Dry Mouth (9% and 5%), Sweating Increased (4% and 1%), Central & Peripheral Nervous System Disorders: Headache (24% and 17%), Paresthesia (2% and 1%), Gastrointestinal Disorders: Nausea (18% and 8%), Diarrhea (8% and 6%), Constipation (5% and 4%), Indigestion (3% and 2%), Vomiting (3% and 1%), Abdominal Pain (2% and 1%), Flatulence (2% and 1%), Toothache (2% and 0%). **General:** Fatigue (8% and 2%), Influenza-like symptoms (5% and 4%), Musculoskeletal: Neck/Shoulder Pain (3% and 1%), Psychiatric Disorders: Somnolence (13% and 7%), Insomnia (12% and 6%), Libido Decreased (7% and 2%), Dreaming Abnormal (3% and 2%), Appetite Decreased (3% and 1%), Lethargy (3% and 1%), Yawning (2% and 1%), Urge/epididymitis/Ejaculation Disorders: (14% and 2%), Anorgasmia (6% and <1%), Menstrual Disorder (2% and 1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo > Lexapro: inflamed injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis. †Primarily ejaculatory delay. ‡Denominator used for males only (N=182 Lexapro; N=195 placebo). §Denominator used for females only (N=247 Lexapro; N=232 placebo). **Dose Dependency of Adverse Events** The potential dose dependency of common adverse events (defined as an incidence rate of $\geq 5\%$ in either the 10 mg or 20 mg Lexapro groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Lexapro-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day Lexapro-treated patients was greater (86%). **Table 4** shows common adverse events that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group. **TABLE 4: Incidence of Common Adverse Events* in Patients with Major Depressive Disorder Receiving Placebo (N=311), 10 mg/day Lexapro (N=310), 20 mg/day Lexapro (N=25):** Insomnia (4%, 7%, 14%), Diarrhea (5%, 6%, 14%), Dry Mouth (3%, 4%, 9%), Somnolence (1%, 4%, 9%), Dizziness (2%, 4%, 7%), Sweating Increased (<1%, 3%, 8%), Constipation (1%, 3%, 6%), Fatigue (2%, 2%, 6%), Indigestion (1%, 2%, 6%). *Adverse events with an incidence rate of at least 5% in either of the Lexapro groups and with an incidence rate in the 20 mg/day Lexapro group that was approximately twice that of the 10 mg/day Lexapro group and the placebo group. **Male and Female Sexual Dysfunction with SSRIs** Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. **Table 5** shows the incidence rates of sexual side effects in patients with major depressive disorder and GAD in placebo-controlled trials. **TABLE 5: Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials [In Males Only: Adverse Event (Lexapro (N=407) and Placebo (N=383)):** Ejaculation Disorder (primarily ejaculatory delay) (12% and 1%), Libido Decreased (6% and 2%), Impotence (2% and <1%). [In Females Only: Lexapro (N=737) and Placebo (N=636):] Libido Decreased (3% and 1%), Anorgasmia (3% and <1%). There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Prapriam has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. **Vital Sign Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Lexapro treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving Lexapro indicated that Lexapro treatment is not associated with orthostatic changes. **Weight Changes** Patients treated with Lexapro in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight. **Laboratory Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Lexapro treatment. **ECG Changes** Electrocardiograms from Lexapro (N=625), racemic citalopram (N=351), and placebo (N=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for Lexapro and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for Lexapro and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither Lexapro nor racemic citalopram were associated with the development of clinically significant ECG abnormalities. **Other Events Observed During the Premarketing Evaluation of Lexapro** Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the ADVERSE REACTIONS section, reported by the 1428 patients treated with Lexapro for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. All reported events are included except those already listed in Tables 2 & 3, those occurring in only one patient, event terms that are so general as to be uninformative, and those that are unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with Lexapro, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients. Cardiovascular - Frequent: palpitation, hypertension. Infrequent: bradycardia, tachycardia, ECG abnormal, flushing, varicose vein. Central and Peripheral Nervous System Disorders - Frequent: light-headed feeling, migraine. Infrequent: tremor, vertigo, restless legs, shaking, twitching, dyssequilibrium, tic, carpal tunnel syndrome, muscle contractions involuntary, sluggishness, coordination abnormal, faintness, hyperreflexia, muscular tone increased. Gastrointestinal Disorders - Frequent: heartburn, abdominal cramp, gastroenteritis. Infrequent: gastroesophageal reflux, bloating, abdominal discomfort, dyspepsia, increased stool frequency, belching, gastritis, hemorrhoids, gagging, polyposis gastric, swallowing difficult. General - Frequent: allergy, pain in limb, fever, hot flushes, chest pain. Infrequent: edema of extremities, chills, tightness of chest, leg pain, asthma, syncope, malaise, anaphylaxis, fall, Hemic and Lymphatic Disorders - Infrequent: bruise, anemia, nosebleed, hematoma, lymphadenopathy cervical. Metabolic and Nutritional Disorders - Frequent: increased weight. Infrequent: decreased weight, hyperglycemia, thirst, bilirubin increased, hepatic enzymes increased, gout, hypercholesterolemia. Musculoskeletal System Disorders - Frequent: arthralgia, myalgia. Infrequent: jaw stiffness, muscle cramp, muscle stiffness, arthritis, muscle weakness, back discomfort, arthropathy, jaw pain, joint stiffness. Psychiatric Disorders - Frequent: appetite increased, lethargy, irritability, concentration impaired. Infrequent: jitteriness, panic reaction, agitation, apathy, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, amnesia, anxiety attack, bruism, carbohydrate craving, confusion, depersonalization, disorientation, emotional lability, feeling unreal, tremulousness nervous, crying abnormal, depression, excitability, auditory hallucination, suicidal tendency. Reproductive Disorders/Female - Frequent: menstrual cramps, menstrual disorder. Infrequent: menorrhagia, breast neoplasm, pelvic inflammation, premenstrual syndrome, spotting between menses. *% based on female subjects only. N=905 Respiratory System Disorders - Frequent: bronchitis, sinus congestion, coughing, nasal congestion, sinus headache. Infrequent: asthma, breath shortness, laryngitis, pneumonia, tracheitis. Skin and Appendages Disorders - Frequent: rash. Infrequent: pruritus, acne, alopecia, eczema, dermatitis, dry skin, folliculitis, lipoma, furunculosis, dry lips, skin nodule. Special Senses - Frequent: vision blurred, tinnitus. Infrequent: taste alteration, earache, conjunctivitis, vision abnormal, dry eyes, eye irritation, visual disturbance, eye infection, pupils dilated, metallic taste. Urinary System Disorders - Frequent: urinary frequency, urinary tract infection. Infrequent: urinary urgency, kidney stone, dysuria, blood in urine. **Events Reported Subsequent to the Marketing of Escitalopram** - Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with escitalopram treatment during postmarketing spontaneous and clinical trial experience and were not observed during the premarketing evaluation of escitalopram: Blood and Lymphatic System Disorders: hemolytic anemia, leukopenia, thrombocytopenia. Cardiac Disorders: atrial fibrillation, cardiac failure, myocardial infarction, torsade de pointes, ventricular arrhythmia, ventricular tachycardia. Endocrine Disorders: diabetes mellitus, hyperprolactinemia, SIADH. Eye Disorders: diplopia, glaucoma. Gastrointestinal Disorders: gastrointestinal hemorrhage, pancreatitis, rectal hemorrhage. General Disorders and Administration Site Conditions: abnormal gait. Hepatobiliary Disorders: fulminant hepatitis, hepatic failure, hepatic necrosis, hepatitis. Immune System Disorders: allergic reaction. Investigations: electrocardiogram QT prolongation, INR increased, prothrombin decreased. Metabolism and Nutrition Disorders: hypoglycemia, hypokalemia. Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis. Nervous System Disorders: akathisia, choreoathetosis, dysarthria, dyskinesia, dystonia, extrapyramidal disorders, grand mal seizures (or convulsions), hypoesthesia, myoclonus, nystagmus, seizures, tardive dyskinesia. Pregnancy, Puerperium and Perinatal Conditions: spontaneous abortion. Psychiatric Disorders: acute psychosis, aggression, anger, delirium, delusion, nightmare, paranoia, visual hallucinations. Renal and Urinary Disorders: acute renal failure. Reproductive System and Breast Disorders: priapism. Respiratory, Thoracic and Mediastinal Disorders: pulmonary embolism. Skin and Subcutaneous Tissue Disorders: angioedema, ecchymosis, erythema multiforme, photosensitivity reaction, Stevens Johnson Syndrome, toxic epidermal necrolysis, urticaria. Vascular Disorders: deep vein thrombosis, hypertension, orthostatic hypotension, phlebitis, thrombosis. Forest Pharmaceuticals, Inc. Subsidiary of Forest Laboratories, Inc. St. Louis, MO 63045 USA Licensed from H. Lundbeck A/S Rev. 01/09 © 2009 Forest Laboratories, Inc.

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	Olanzapine • Zyprexa
Aripiprazole • Abilify	Quetiapine • Seroquel
Clozapine • Clozaril	Risperidone • Risperdal
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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