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Impact of Atypical Antipsychotic Therapy on Leptin, Ghrelin, and Adiponectin

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Abstract

Background—Many adverse effects of atypical antipsychotic treatment are associated with antagonism of monoamine receptors; however, data indicate that important metabolic effects, such as hypertriglyceridemia and impairment in glucose/insulin homeostasis, may not be related to these mechanisms, leading investigators to explore alternative hypotheses. Promising candidates include a possible impact of antipsychotics on peptide hormonal regulators of metabolic control such as leptin, ghrelin, and adiponectin. The purpose of this review is to summarize recent data on changes in these hormones during atypical antipsychotic treatment.

Methods—A Medline search was performed for papers published from January 1999 to January 2007 using key words antipsychotic, atypical antipsychotic, and individual atypical antipsychotic drug names cross-referenced with leptin, ghrelin, and adiponectin.

Results—The bulk of the published work focused on changes in body weight and serum leptin, with far less data on ghrelin, and adiponectin, and non-weight metabolic changes. Leptin changes were directly related to a medication's weight gain liability, with no added antipsychotic effects on leptin signaling. Conflicting results emerged for the other markers, but all three long-term studies on ghrelin showed increased levels in patients on atypical antipsychotics with weight gain liabilities.

Conclusions—Leptin increases during antipsychotic treatment are a result of weight gain rather than a direct impact of atypical antipsychotics on leptin physiology. Preliminary long-term data show increased ghrelin levels, but this finding must be replicated. The association with antipsychotic effects on glucose and lipid metabolism and these hormones remains virtually unstudied. Future research should indicate whether ghrelin and other peptide hormones may be useful predictors of weight gain or metabolic changes in patients on antipsychotics.

Background

Atypical antipsychotics (AAPs) have been increasingly used for the management of patients with a variety of psychotic disorders and severe behavioral disturbances. In the past decade there has been a growing concern among clinicians and researchers that use of AAPs may be related to potentially serious adverse metabolic effects, including weight gain, hyperlipidemia and glucose intolerance (Koller et al., 2001; Allison and Casey, 2001; Wirshing et al., 2002; Koller and Doraiswamy, 2002; Meyer, 2002; Jin et al., 2002; Koller et al., 2003; Koller et al., 2004; Jin et al., 2004; Meyer and Koro, 2004; Sathyapakash and Henry, 2004; Newcomer, 2005). Clinical studies indicate that certain antipsychotics carry a high risk of treatment-related

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metabolic dysfunction (e.g. clozapine and olanzapine) (American Diabetes Association, 2004; Lieberman et al., 2005), but this research also suggests that certain patients taking AAPs with high metabolic liabilities do not necessarily develop these adverse effects. Though the underlying mechanism for AAP-related weight gain is strongly associated with central histamine H₁ antagonism (Kim et al., 2007) and increased appetite (Kroeze et al., 2003), the pharmacological basis for other metabolic changes is not fully understood and may involve weight-independent mechanisms (Houseknecht et al., 2007).

One research area, of potential relevance to antipsychotic adverse effects, relates to the impact of the peptide hormones leptin, ghrelin and adiponectin on the regulation of food intake, body weight, and other metabolic parameters. Since its initial sequencing as the product of the *ob* gene in 1994, leptin has garnered significant attention as a metabolic regulatory hormone (Zhang et al., 1994). The name leptin derives from the Greek word “leptos”, meaning thin, and is produced primarily by fat cells as part of a long term central feedback mechanism involving central control of appetite, and peripheral regulation of metabolic activity. Leptin is a 167 amino acid 16-kiloDalton protein that binds to cell surface receptors (the product of the *db* gene) at both central (ventromedial hypothalamic) and peripheral sites (liver, skeletal muscle, and pancreatic β -cells) (Friedman, 2002). Stimulation of hypothalamic leptin receptors decreases the effects of appetite stimulating hormones such as melanin-concentrating hormone, endogenous cannabinoids and neuropeptide Y, while increasing the activity of appetite suppressing hormones such as α -melanocyte stimulating hormone, bombesin, and corticotrophin-releasing factor (Friedman, 2002). While leptin’s main effect is on weight, peripherally leptin agonism stimulates metabolic activity by skeletal muscle through increased utilization of fatty acids, and increased effects of insulin.

Evidence for leptin’s activity can be seen in *ob/ob* mice, whose genetic inability to produce leptin is manifested phenotypically in overeating and resultant obesity. The administration of recombinant leptin to these mice results in reduced appetite and subsequent weight loss (Halaas et al., 1995). Humans rarely have mutations in both copies of the *ob* gene, but those who do are severely obese and respond to exogenous leptin, while 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, effects that can be seen even during 72-hour fasts (Ebenbichler et al., 2005). 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 appetite suppressing effects of the hormone (Friedman, 2002). On average, women have greater fat mass than men, and have higher serum leptin levels.

Discovered in 1999, ghrelin is a potent hunger-inducing peptide hormone (Kojima et al., 1999). Once ghrelin was cloned and isolated from rat and human gut, assays indicate that it activates the receptor for growth hormone secretagogues, and regulates feeding behavior and energy metabolism through central activity (Horvath et al., 2001; Korner and Leibel, 2003; Gale et al., 2004). In particular, ghrelin enhances fat mass deposition and increases food intake by modulating hypothalamic appetite-regulating pathways through promotion of neuropeptide Y (NPY) and Agouti-related protein expression. Circulating levels of ghrelin increase before meals and are suppressed by the intake of nutrients. In human serum, non-acylated ghrelin is found in much higher amounts than acylated (bioactive) ghrelin (about 3–4% of total circulating ghrelin), and this ratio is closely maintained even after food intake (Lucidi et al., 2004).

Adiponectin, which was discovered independently by several groups, is a 244-amino acid protein secreted exclusively from adipose tissue (Nakano et al., 1996; Maeda et al., 1996). In humans, adiponectin levels have been shown to negatively correlate with body weight and

insulin levels. Adiponectin levels are decreased in states of insulin resistance, such as obesity and type 2 diabetes, although it remains unclear whether these decreased levels are a cause or effect of the insulin resistance (Weyer et al., 2001). Furthermore, recent studies suggested that changes in insulin sensitivity correlate more closely with changes in the proportion of high molecular weight (HMW) adiponectin than with total adiponectin in serum (Pajvani et al., 2003; Waki et al., 2003). Treatments that improve insulin sensitivity, such as weight reduction in obese individuals, are also accompanied by an increase in circulating adiponectin levels (Arita et al., 1999; Wang et al., 2006).

As the properties of these hormones have been elucidated in the experimental literature, investigators have started to examine possible correlations between changes in serum levels of these molecules and metabolic changes during AAP treatment. The goal of this burgeoning area of research is to explore additional mechanisms governing antipsychotic-associated metabolic changes, and to identify biomarkers of metabolic risk to guide medication selection. The purpose of this review is to summarize the available clinical data on the interaction of AAPs with leptin, ghrelin and adiponectin, and indicate directions for future research on interactions between psychotropic medications and metabolic hormones.

Methods

A Medline search was performed for papers published from January 1999 – January 2007 using key words antipsychotic, atypical antipsychotic, and individual atypical antipsychotic drug names (clozapine, risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone), cross-referenced with leptin, ghrelin and adiponectin. We further supplemented this search by reviewing the reference list of all papers identified.

Leptin

Drug Effects

Among the metabolically active neuropeptides, the literature on leptin and antipsychotic related obesity is relatively well developed (Table 1). The first papers emerged in the late 1990s, and focused on the association between antipsychotics associated with marked weight gain (olanzapine and clozapine) and increases in serum leptin levels (Bromel et al., 1998; Kraus et al., 1999). As patients gained substantial amounts of weight on clozapine and olanzapine, serum leptin also rose, but neither weight nor leptin changes were seen in patients exposed to haloperidol or in those who did not receive antipsychotic medication (Kraus et al., 1999). Numerous subsequent prospective trials of olanzapine-treated patients (Eder et al., 2001; Graham et al., 2005b; Ebenbichler et al., 2005; Murashita et al., 2005; Hosojima et al., 2006) and clozapine-treated patients (Monteleone et al., 2002; Kivircik et al., 2003; Sporn et al., 2005; Theisen et al., 2005) confirmed the association between use of these medications, weight gain, and increased serum leptin levels. For agents with less weight gain liability, such as high potency typicals (Hagg et al., 2001; Atmaca et al., 2003a; Atmaca et al., 2003c), sulpiride (Baptista et al., 2000), quetiapine (Atmaca et al., 2003c), or risperidone (Fitzgerald et al., 2003; McIntyre et al., 2003; Martin et al., 2004; Chiu et al., 2006), comparative trials noted modest weight gain and leptin changes, while olanzapine and clozapine exposed subjects experienced marked increases in adiposity, weight and serum leptin. A few prospective trials which examined the effect of pharmacological weight-modifying strategies using adjunctive amantadine (Graham et al., 2005a) or nizatidine (Atmaca et al., 2003b; Atmaca et al., 2004) found positive effects of the adjunctive medication, with proportional differences in leptin levels compared to those treated with antipsychotic alone. One randomized 6-week clozapine trial used the cytochrome P450 1A2 inhibitor fluvoxamine to inhibit clozapine metabolism and thereby decrease metabolite levels. The underlying hypothesis for this strategy is based on the concept that the occurrence of agranulocytosis and other clozapine related side effects such as

weight gain may be related to the formation of toxic clozapine metabolites which affect cytokine levels (Hinze-Selch et al., 2000). Despite dosing adjustments to achieve comparable serum clozapine levels between the cohorts, and nonsignificant differences in weight gain over the 6 weeks of the study, combination treatment with fluvoxamine resulted in a 94% increase in serum leptin levels compared to only 52% for clozapine monotherapy ($p=.03$).

Gender Effects

Most, but not all, cross-sectional studies found that women have higher serum leptin levels than men, even when men had greater BMI (Melkersson and Hulting, 2001; Arranz et al., 2004; Haupt et al., 2005). When studied prospectively, this gender discrepancy was gradually effaced as men demonstrated greater increases in serum leptin during several trials (Baptista et al., 2000; Hagg et al., 2001; Zhang et al., 2003). Data from for one long-term clozapine-treated study found that leptin changes were independent of gender and proportional to weight gain (Monteleone et al., 2002), but other analyses which examined both weight and fat depots still found significant effects of gender (Zhang et al., 2004). One notable exception was McIntyre's 6-month randomized adjunctive risperidone vs. olanzapine study in symptomatic bipolar patients on mood stabilizers, in which women had greater increases in serum leptin in both antipsychotic arms (McIntyre et al., 2003).

Diagnosis Effects

As the association between antipsychotic-induced weight gain and changes in serum leptin levels became firmly established, investigators sought to understand whether there were significant disease influences that modified the drug effects. One early cross-sectional analysis of 14 olanzapine-treated schizophrenia patients by Melkersson noted that 57% had elevated serum leptin levels when compared to normal leptin levels adjusted for BMI and gender (Melkersson et al., 2000), but the absence of a weight-matched control group limited the interpretation of the findings. To separate diagnosis and treatment effects, Arranz (Arranz et al., 2004) performed a cross-sectional study of 50 drug-naïve schizophrenia patients, 50 drug-free schizophrenia patients, and 50 unmatched controls. Leptin levels across all cohorts were positively correlated with age and BMI, and women had higher levels than men in all three cohorts. The antipsychotic-free patients were older and heavier than the other two 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 again limited the ability to make any definitive statements regarding the impact of treatment on leptin levels.

Other studies removed these limitations by matching schizophrenia patients with controls on the basis of gender, BMI and sometimes age. These studies indicate conclusively that, when matched appropriately with nonpsychiatric subjects, patients with schizophrenia do not exhibit greater than expected serum leptin levels regardless of antipsychotic drug exposure (Baptista et al., 2001; Eder et al., 2001; Herran et al., 2001; Hagg et al., 2001; Zhang et al., 2003; Arranz et al., 2004; Sporn et al., 2005; Haupt et al., 2005; Gergerlioglu et al., 2006; Atmaca et al., 2007). The one controlled comparative study of medication-treated bipolar patients vs. matched controls also reported no significant difference in leptin levels between the psychiatric patients and their peers (Gergerlioglu et al., 2006). Interestingly, a 6-month prospective risperidone study in autistic children noted no increase in serum leptin levels despite a mean weight gain of 5.6 kg (Martin et al., 2004). Lastly, a single 12-week prospective trial compared the effects of olanzapine, risperidone and quetiapine for levodopa psychosis in 30 Parkinson's Disease (PD) patients, using one group of PD subjects ($n=10$) treated solely with antiparkinsonian medications and another unmedicated cohort ($n=10$) as controls (Rustembegovic et al., 2006). Only olanzapine caused significant weight gain, but BMI changes were positively correlated with changes in leptin levels across all cohorts.

In Vitro and Animal Studies

While the effects in human studies are consistent, those from animal and *in vitro* studies are less clear. Hauner's assay of clozapine in mature adipose cells from human mammary tissue did not find any effects on insulin-stimulated glucose transport or leptin production (Hauner et al., 2003). A 20-day fixed dosed study using 1, 2 or 4 mg/kg/day olanzapine in female rats found that the 1 and 2 mg/kg dosages produced maximal weight gain, while the highest dose did not differ significantly from the control group exposed vehicle only. Moreover, there were no significant differences across any of the cohorts in serum leptin levels at endpoint despite differences in weight gain (Cooper et al., 2005). Conversely, Sondhi's 28-day controlled clozapine study in laboratory rats did find significantly greater weight gain ($p < .0001$) and increases in serum leptin levels ($p < .001$) in the clozapine-exposed cohort (Sondhi et al., 2006).

Genetic Studies

Genetic predictors of antipsychotic-induced weight gain and obesity have become an important topic of investigation, with three studies examining variables related to changes in leptin. The first of these studied the -2548G/A functional polymorphism in the leptin gene promoter in a Chinese cohort of schizophrenia patients treated prospectively for 10 weeks. Zhang and colleagues found a significant association between antipsychotic related weight gain and homozygosity for this polymorphism, but not with the genetic marker and baseline weight (Zhang et al., 2003). A subsequent 9-month study in 75 neuroleptic-naïve Spanish schizophrenia patients found that the 2448A polymorphism did not predict short term weight gain (over 6 months), but was associated with 9 month weight gain (Templeman et al., 2005). Most recently, 29 single nucleotide polymorphisms (SNP) from 13 candidate genes were examined in a cross-sectional study of 67 olanzapine- and 101 risperidone-treated patients, including a SNP in the leptin receptor gene (rs8179183) associated with body weight in nonpsychiatric subjects (Ruano et al., 2007). Among this group of genetic markers, the leptin receptor SNP rs8179183 was found to have the strongest association with weight, and was significantly associated with weight profiles for the risperidone cohort ($p < .001$).

Features of Weight and Leptin Changes During Antipsychotic Treatment

Weight gain with olanzapine and clozapine therapy predominantly occurs over the first 6 months of treatment, and plateaus between months 6 and 12, but leptin changes do not parallel weight changes during extended antipsychotic treatment. A prospective 10-week clozapine trial by Bromel (Bromel et al., 1998), found that leptin levels peaked early in treatment, at week 2, followed by a subsequent decrease and 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 two (Monteleone et al., 2002), and later studies (Theisen et al., 2005).

Despite these fluctuations, overall leptin levels during longer-term antipsychotic treatment are highly correlated with weight and body mass index (BMI) 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 (Hagg et al., 2001; Melkersson and Hulting, 2001; Melkersson and Dahl, 2003). Younger and thinner patients, regardless of medication, have lower serum leptin levels (Wang et al., 2006), and the association between the medication itself and leptin levels disappears when adjusted for differences in BMI (Smith et al., 2005). Once BMI is accounted for, there appear to be no other effects of antipsychotics on leptin physiology independent of their effects on adiposity.

Other Metabolic Parameters

In humans, elevated serum leptin levels are associated with certain adverse metabolic markers, particularly those associated with insulin activity, including insulin itself, and serum triglycerides (Wallace et al., 2001; Franks et al., 2005). Several antipsychotic studies measured metabolic outcomes along with serum leptin levels, but did not specifically calculate correlation coefficients between leptin and other parameters (Baptista et al., 2001; Eder et al., 2001; Atmaca et al., 2003a; Melkersson and Dahl, 2003; Graham et al., 2005a; Graham et al., 2005b; Smith et al., 2005; Sporn et al., 2005; Chiu et al., 2006; Hosojima et al., 2006; Atmaca et al., 2007). Nonetheless, in many instances leptin levels increased significantly without significant changes in serum insulin, other glycemic or lipid measures (Zhang et al., 2004; Murashita et al., 2005; Sporn et al., 2005; Chiu et al., 2006; Hosojima et al., 2006; Atmaca et al., 2007). One cross-sectional study in bipolar subjects also found no correlation between any glucose or lipid parameter and leptin levels (Gergerlioglu et al., 2006), although a small number reported significant correlations between leptin and serum insulin (Baptista et al., 2000; Melkersson et al., 2000; Melkersson and Hulting, 2001), glucose (Wang et al., 2006) and serum triglycerides (Atmaca et al., 2003c); however, most of the authors reporting significant correlations did not control for BMI.

Ghrelin

As a stimulant of weight gain, ghrelin may be a significant factor in the etiology of obesity (Tschop et al., 2000; Horvath et al., 2001; Horvath et al., 2003), and has been examined in a small number of prospective studies looking at the association between antipsychotic exposure and changes in serum ghrelin levels (Table 2). In 8 studies looking at ghrelin levels in patients taking atypical agents, 2 studies showed decreasing ghrelin levels, 3 showed increasing ghrelin levels and in the other 3 studies there were no significant change in ghrelin levels despite different degrees of weight gain.

Adiponectin

An important AAP metabolic effect is the induction of insulin resistance (Houseknecht et al., 2007), leading several investigators to postulate that circulating adiponectin levels might serve as a useful marker for monitoring changes of weight and insulin resistance during AAP treatment. In the 6 studies that examined adiponectin level in patients taking AAPs, four suggested no significant changes in adiponectin levels from baseline, despite the fact that most of these AAP-exposed patients exhibited weight gain during treatment. Of the remaining two trials, one showed increased adiponectin levels and the other one showed decreased adiponectin levels in patients on AAPs compared to controls. The one study that showed decreased total adiponectin also demonstrated significantly decreased high molecular weight (HMW) adiponectin in patients on olanzapine compared to those on conventional agent or control group, but none of other 5 studies examined HMW adiponectin (Table 3).

Discussion

Obesity and the metabolic syndrome are highly prevalent problems among patients with severe mental illness, and contribute to cardiovascular risk and increased mortality (McEvoy et al., 2005). Medications with significant metabolic liabilities are often eschewed as initial treatment, yet certain patients taking these antipsychotics do not necessarily gain weight or develop metabolic adverse effects. As psychiatric practice moves into an era of personalized medicine, the ability to identify risk markers, besides those related to demographic characteristics or the drug itself, will not only help clinicians to screen out patients at high risk for weight gain and metabolic changes, but potentially allow earlier access to higher risk medications for patients who do not possess vulnerability markers. The identification of biomarkers predictive of AAP-

related metabolic changes will hopefully facilitate an understanding of the mechanisms that contribute to metabolic dysfunction during treatment with antipsychotics, and possibly during exposure to other medications (e.g. protease inhibitors) with metabolic adverse effects (Mantel-Teeuwisse et al., 2001).

Driven by the public health impact of obesity, substantial progress has recently been made in the basic understanding of the regulation of appetite and body weight, including the identification of genetic polymorphisms (Basile et al., 2001; Correll and Malhotra, 2004), and other markers of obesity risk (Baptista and Beaulieu, 2002; Amamoto et al., 2006). As metabolic research has evolved in the past decade, there has been a steady accumulation of data exploring the association between peptide metabolic regulatory hormones and antipsychotic-induced weight gain and metabolic dysfunction. Overall, there is strong evidence to suggest that leptin levels are increased during longer-term antipsychotic treatment, and that they are highly correlated with weight and BMI changes. Though the increase in leptin levels often parallels significant weight gain, these changes appear to be more the result of weight gain rather than a direct impact of the antipsychotic on the leptin feedback pathway (Haupt et al., 2005). There is also conflicting evidence linking leptin increases to changes in other metabolic parameters, since virtually none of the papers reviewed examined the association between leptin and glucose-insulin measures independent of the effect of weight changes.

The data on ghrelin and adiponectin changes in patients taking antipsychotics are preliminary at best, and show conflicting results. In 8 studies looking at ghrelin levels, 2 showed decreasing ghrelin levels, 3 showed increasing ghrelin levels and in 3 studies there were no significant change in ghrelin levels despite different degrees of weight gain. It is interesting that the 3 long-term studies showed increased ghrelin level in patients on antipsychotics that experienced significant weight gain. If replicated, this implies that the negative feedback effect of ghrelin secretion is disrupted or that ghrelin secretion is enhanced by antipsychotics through certain undefined mechanisms. Though studies in the general population have found a negative association between circulating ghrelin and insulin secretion, none of the antipsychotic trials reviewed examined the association between ghrelin and other metabolic or insulin sensitivity changes independent of the effect of weight changes. With this limited body of data, one cannot make any definitive statements regarding associations between changes in serum ghrelin and those in nonweight metabolic parameters in patients taking AAPs.

Most studies suggest that adiponectin levels are not different between patients and normal controls and also do not change before and after AAP treatment. Since AAPs may have adiposity-independent effects on insulin resistance (Houseknecht et al., 2007), it is important to note the recent adiponectin data which suggest that insulin sensitivity changes in nonpsychiatric subjects correlate more closely with serum HMW adiponectin levels than with total serum adiponectin levels (Pajvani et al., 2003; Waki et al., 2003). The one antipsychotic trial reporting HMW adiponectin levels did find lower HMW adiponectin levels in patients on olanzapine compared to patients on conventional agents or controls. This is consistent with the expected differential impact of olanzapine and high potency typical antipsychotics on insulin sensitivity, but more studies are needed to determine if HMW adiponectin is sensitive to AAP-related insulin resistance changes and strongly predictive of metabolic changes in patients taking AAPs.

As the literature on AAPs and peptide hormones evolves, ongoing metabolic research will continue to identify new peptide hormones that play important roles in regulation of food intake and body weight. Other metabolically active hormones of interest include peptide YY, resistin and the recently discovered obestatin. Peptide YY (PYY), first discovered by Tatemoto et al. (Tatemoto and Mutt, 1980) in 1980, is produced by intestinal cells in responses to the presence of food. Recently, it has been suggested that PYY counteracts the effects of ghrelin by inducing

satiety and reducing appetite and caloric intake. Endogenous levels of PYY are low in obese subjects, suggesting that low PYY activity may contribute to the pathogenesis of obesity (Batterham and Bloom, 2003). Infusion of PYY significantly decreases the cumulative 24-hour energy intake in both humans and animals. Another novel peptide, obestatin, discovered by Zhang et al. in 2005 (Zhang et al., 2005), also opposes the appetite-stimulating effects of ghrelin. Obestatin is mainly produced in stomach and treatment of rats with obestatin suppresses food intake significantly. While there is no published data on the association between these hormones and antipsychotic treatment in humans or laboratory animals, these peptides will likely be the focus of future research given their central role in regulating food intake and metabolism.

The lack of a significant association between antipsychotic use and leptin levels, independent of drug effects on adiposity, or some inconsistent results about ghrelin and adiponectin changes have been particularly instructive regarding the demands of metabolic study design. The ability to understand drug effects on metabolic hormones depends on a design that can eliminate as much as possible the impact of weight gain on glucose-insulin homeostasis and other factors that influence hormone levels. Whether changes in any metabolic hormone level are a direct result of antipsychotic exposure may require more acute exposure studies to limit the role of weight gain, as has been performed with animal models (Houseknecht et al., 2007). Ideally such research would occur in human models free of possible carry over from prior antipsychotic exposure. Candidate populations for such studies include antipsychotic naïve bipolar or first episode schizophrenia patients, and nonmentally subjects who possess metabolic risk factors that may increase the likelihood for expressing an antipsychotic effect during acute exposure.

Medications such as olanzapine and clozapine carry significant metabolic burdens, but are effective treatments for some patients who do not respond to other antipsychotics. The elucidation of mechanisms by which antipsychotic medications impact metabolic parameters remains important for quantification of patient risk, to inform the frequency and targets of metabolic monitoring during antipsychotic therapy, and to permit the development of novel agents without these limitations.

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Table 1**Summary of Published Studies on Leptin in Patients on Antipsychotics**

Study	Sample Size	Methodology	Results
1. (Bromel et al., 1998)	12 clozapine	Prospective 10-week study	> 100% increase in leptin levels by wk 2, but only 75% increase at wk 10 (n=7; p=.126).
2. (Kraus et al., 1999)	11 clozapine 8 olanzapine 13 haloperidol 12 unmedicated	Prospective 4-week study	Significant increase (40%) for olanzapine/clozapine cohorts. No changes for haloperidol or unmedicated subjects.
3. (Baptista et al., 2000)	19 sulpiride 9 obese women 13 lean women (on various antipsychotics)	Prospective 4-week sulpiride trial, and cross-sectional study comparing lean and obese women	No significant weight or leptin changes were observed after sulpiride administration in women, but significant weight gain was found in sulpiride-treated men +0.7 kg (p = 0.004), as did leptin levels (baseline: 2.77 ng/ml vs. endpoint 13.9 p=0.035). In the cross-sectional study, obese psychotic women (BMI 31.5 kg/m ²) had higher leptin levels than non-obese psychotic women (BMI = 25.5 kg/m ² ; p = 0.006). Leptin levels correlated with basal insulin levels in women (p=.001)
4. (Hinze-Selch et al., 2000)	12 clozapine 11 clozapine + fluvoxamine	Prospective 6-week study	Despite similar serum levels, combination treatment 94% increase in leptin levels vs. 52% for clozapine monotherapy.
5. (Melkersson et al., 2000)	14 olanzapine	Cross-sectional study	Median dose 12.5 mg, median exposure 4.8 months. 8 of 14 had elevated leptin levels when compared to normal leptin levels adjusted for BMI and gender. Leptin levels correlated with insulin levels (r=.57, p=.03).
6. (Baptista et al., 2001)	26 controls 26 women, various antipsychotics	Cross-sectional study, with age-, BMI-, and day of menses matched controls	Compared to controls, antipsychotic-treated women had comparable leptin and sex hormone levels.
7. (Eder et al., 2001)	10 olanzapine 10 controls	Prospective 8-week study with age-, BMI- and gender-matched controls	84% increase in leptin levels vs. 13% decrease for controls (p=.05).
8. (Hagg et al., 2001)	41 clozapine 62 typical depot 189 controls	Cross-sectional study, controls not matched	After adjustment for age, gender, smoking status and BMI, leptin levels were higher for males and females on clozapine but only males on typicals, compared to controls.
9. (Herran et al., 2001)	17 atypicals 17 typical depot 25 typical oral 59 controls	Cross-sectional study, with age-, BMI- and gender-matched controls	Leptin levels were not significantly different between patients and controls. Leptin levels correlated with BMI for both groups.
10. (Melkersson and Hulting, 2001)	14 clozapine 14 olanzapine 19 typical	Cross-sectional study	For 26% of the typical group, leptin levels were elevated (when compared with normal leptin levels adjusted for BMI and gender), and were higher among females. 21% of clozapine and 56% of olanzapine patients had elevated leptin levels (compared to normal leptin levels adjusted for BMI and gender), but no expected gender difference. Leptin and insulin levels were correlated for the olanzapine and clozapine groups (r=.67, p=.01), and for zuclopenthixol (r=.71, p=.04), but not perphenazine.
11. (Monteleone et al., 2002)	22 clozapine	Prospective 32-week study	At baseline, men heavier than women (84.0 kg vs. 69.2 kg, p<0.007), but lower plasma leptin (5.0 ng/mL vs. 14.7 ng/mL, p<0.003). Leptin levels peaked at wk 2, abruptly decreased, then rose to nearly wk 2 levels by week 32. Increases at wk 2 correlated with long-term wt gain, and were comparable for both genders based on weight gained.
12. (Atmaca et al., 2003a)	15 olanzapine 15 quetiapine 15 haloperidol	Prospective 6-week study	Mean weight gain for olanzapine, quetiapine, and haloperidol was 8.4, 3.9 and 0.5 kg, respectively (p < 0.01). Endpoint leptin levels greatest for olanzapine (p < 0.05 vs. quetiapine; p < 0.01 vs. haloperidol). After adjustment,

Study	Sample Size	Methodology	Results
			significant differences in leptin levels persisted ($p < 0.05$ adjusted for BMI; $p < 0.05$ adjusted for age).
13. (Atmaca et al., 2003b)	18 olanzapine + nizatidine 18 olanzapine	Prospective 8-week double-blind study. Groups balanced for age-, gender and BMI.	Nizatidine + olanzapine group had 9% BMI decrease, compared to 2% increase in BMI for the monotherapy cohort ($p < .05$). Leptin levels decreased 40% in the nizatidine group, but rose 17% in the monotherapy cohort.
14. (Atmaca et al., 2003c)	14 quetiapine 14 olanzapine 14 risperidone 14 clozapine 11 unmedicated	Prospective, randomized 6-week study.	Comparable BMI, age and leptin at baseline. At endpoint, the leptin increases were: 37% quetiapine, 84% olanzapine, 14% risperidone, 77% clozapine, but -18% for controls. The differences were significant for olanzapine vs. quetiapine, risperidone and controls, and clozapine vs. risperidone and controls. Leptin levels also correlated with serum triglyceride values for all groups ($r = .58$, $p < .05$).
15. (Fitzgerald et al., 2003)	10 risperidone 12 olanzapine	Prospective 3-month study	At baseline, mean duration of drug exposure was 8.2 months. Over 3 month follow-up mean BMI increase was 2.5%, mean leptin increase was 15.6% ($p = .06$). There was a positive correlation with changes in LH ($r = .48$, $p < .05$).
16. (Hauner et al., 2003)	5 clozapine	<i>In vitro</i> assay in mature adipose cells	No significant effects were seen on basal or insulin-stimulated glucose transport, IL-6 production or leptin levels.
17. (Kivircik et al., 2003)	19 clozapine	Prospective 10-week study	BMI increased significantly (4.9%, $p = .001$), and fat mass increased 10.3% ($p = .001$). Leptin levels increased 10.4%, but this result was not significant. The change in leptin levels correlated with the change in body fat mass, but did not correlate with serum insulin values.
18. (McIntyre et al., 2003)	Adjunctive treatment with: 11 risperidone 10 olanzapine	Prospective 6-month study in bipolar patients on stable lithium or valproate	Mean doses were 2.88 mg/d for risperidone and 12.69 mg/d for olanzapine. Mean weight increases were much less for risperidone (5.9 kg) than olanzapine (11.3 kg, $p = .001$), and so were leptin changes (risperidone +45%, olanzapine +76%). Endpoint leptin levels were significantly higher for the olanzapine cohort ($p = .001$). For both medications the mean increases in leptin were greater for women than men.
19. (Melkersson and Dahl, 2003)	18 clozapine 16 olanzapine	Cross-sectional study	Mean duration of drug exposure was 5.3 years. Leptin levels above normal range (when compared to normal leptin levels adjusted for BMI and gender) were seen in 13% of olanzapine and 22% of clozapine treated subjects. Leptin levels inversely correlated with serum N-desmethyl-olanzapine levels, but not clozapine, olanzapine or N-desmethyloclozapine levels.
20. (Zhang et al., 2003)	Cross-sectional: 128 schizophrenia 38 controls Prospective: 30 schizophrenia (risperidone, chlorpromazine) 22 controls	Cross-sectional and 10-week prospective studies with age- and gender- matched controls	Schizophrenia patients had mean increases of 6.2% in weight, 38.5 in abdominal subcutaneous fat, and 40.0% in intra-abdominal fat. There were no significant differences in the distribution of allele and genotypes either between the patients and controls, or between gender groups. The -2548AA genotype was significantly associated with weight gain (OR = 1.941; 95% CI: 1.175 – 3.207; $p = 0.006$), but did not predict baseline weight in patients or controls.
21. (Atmaca et al., 2004)	14 quetiapine + nizatidine 14 quetiapine	Prospective 8-week double-blind study. Groups balanced for age-, gender and BMI.	Nizatidine + quetiapine group had 1.85% BMI decrease, compared to 2.2% increase in BMI for the monotherapy cohort ($p > .05$). Leptin levels decreased 7% in the nizatidine group, but rose 11% in the monotherapy cohort ($p > .05$). Changes in leptin levels correlated with BMI changes in both groups ($r = 0.56$, $p < .05$).

Study	Sample Size	Methodology	Results
22. (Martin et al., 2004)	45 risperidone	Prospective 6-month study in children/adolescents with autism	Mean weight gain was 5.6 kg at 6 months. Leptin levels at endpoint decreased 0.6 ng/ml from baseline of 6.5 ng/ml. Leptin changes at month 2 did not predict future weight gain trajectory.
23. (Zhang et al., 2004)	30 risperidone 15 chlorpromazine 1 quetiapine 38 controls	Prospective 10-week study, with age- and gender-matched controls	Medications were based on treating physician's discretion. Male patients had 9.4% BMI increase and female patients 6.7% increase. Leptin increased 324% in males, and 117% in females, but there were no significant changes in insulin values. In the schizophrenia patients, gender and subcutaneous fat correlated with baseline leptin levels, but only gender was significant after 10 weeks. There were no significant correlations for the control group.
24. (Cooper et al., 2005)	Olanzapine: 14 4 mg/kg 14 2 mg/kg 14 1 mg/kg 14 placebo (vehicle)	Randomized fixed dose 20-day study in female rats	Rapid onset of weight gain occurred in the 1 and 2 mg/kg groups, which was significantly greater than vehicle and 4 mg/kg, but no difference between 4 mg/kg and vehicle. There were no significant differences in serum leptin changes between any drug cohort and vehicle.
25. (Ebenbichler et al., 2005)	14 olanzapine 14 controls	Prospective study, mean duration 10 weeks, age- and gender-matched controls	In the patients, weight increased 4.5%, but there was a 63% increase in serum leptin, and sOB-R concentrations declined 18%. In the controls (followed for 8 weeks only), weight increased 0.8%, but both leptin and sOB-R levels decreased.
26. (Graham et al., 2005a)	12 olanzapine + amantadine 9 olanzapine	Prospective 12-week double-blind study	Mean BMI change - 0.07 kg/m ² for the amantadine combination group vs. + 1.24 kg/m ² for the olanzapine only group. No changes in leptin reported but values not given.
27. (Graham et al., 2005b)	9 olanzapine	Prospective 12-week study	Mean increase of 7.3% in weight, but median leptin levels did not change (values not reported), and there was no relationship between change in leptin levels and change in body fat or body weight.
28. (Haupt et al., 2005)	27 olanzapine 24 risperidone 21 typicals 124 controls	Cross-sectional study, with a subset of controls matched for BMI, age and gender.	A significant effect of BMI on leptin levels was found, ($p < 0.0001$), with only limited interactions between BMI and treatment group ($p = 0.016$) and subject group ($p = .058$). No effects or interactions were seen for cortisol, fasting insulin or glucose, smoking status, age or ethnicity with BMI/group analyses. A significant three-way interaction between BMI, subject group, and gender was found ($p < .0001$), but no differences in plasma leptin levels were observed when comparing matched male patients vs. male controls, or female patients vs. female controls. The addition of fasting insulin, glucose or cortisol did not improve the prediction of leptin levels in the statistical model.
29. (Murashita et al., 2005)	7 olanzapine	Prospective 6-month study	Although the BMI increase was not significant (+ 2.94%, $p = .17$), there was a 9.9% increase in body fat ($p = .012$) and 29% increase in serum leptin ($p = .28$). There were no significant changes in glucose or lipid parameters.
30. (Smith et al., 2005)	53 olanzapine 49 clozapine 50 risperidone 52 typicals	Cross-sectional study based on prior MD treatment choice	Groups had comparable BMI (range 28.5 - 30.6 kg/m ² ; $p = .159$), age (range 39.1 - 42.3; $p = .299$), and duration of current antipsychotic exposure (range 6.1 - 8.3 months; $p = .184$). After BMI and race adjustment, there were no significant between-group differences in serum leptin levels.
31. (Sporn et al., 2005)	23 clozapine 1 haloperidol 21 controls	Cross-sectional study, with age-, gender-matched controls. Clozapine group followed 6 weeks.	Mean age of schizophrenia patients 14.3 yrs, controls 13.4 yrs ($p = .14$) and mean BMI 21.6 vs. 21.3 kg/m ² respectively ($p = .77$). There was no significant difference in baseline leptin between patients and controls. After 6 weeks of clozapine treatment there was a mean increase of 7.4% in

Study	Sample Size	Methodology	Results
			BMI ($p<.0001$) and 19% in serum leptin ($p=.003$), but no significant change in serum insulin.
32. (Templeman et al., 2005)	73 first-episode drug-naïve patients in a Caucasian cohort in Spain	Prospective 9-month study with genetic markers. Antipsychotic treatment was by MD choice.	The – 759T allele of the 5HT _{2C} receptor promoter region was not associated with baseline BMI, but was associated with higher baseline leptin levels. This polymorphism was also associated with significantly less weight gain. The – 2548 leptin gene polymorphism was not associated with short-term (6 week, 3 month) weight gain, but was significantly associated with 9-month weight gain.
33. (Theisen et al., 2005)	11 clozapine	Prospective 10-week study	Mean BMI increase was 5.2% ($p<.05$), and mean increase in serum leptin was 63.9% ($p<.05$). Leptin levels peaked early in treatment (week two level 13.8 ng/ml), and were unchanged at endpoint (13.6 ng/ml).
34. (Chiu et al., 2006)	13 olanzapine 13 risperidone	Prospective randomized 2-week study in Taiwan	There were no significant differences in BMI increase ($+0.3 \text{ kg/m}^2$ for both groups). Olanzapine was associated with greater serum leptin increases (olanzapine + 13.5%, risperidone + 3.3%), but the between group $p>.05$. There were no significant changes in serum insulin.
35. (Gergerlioglu et al., 2006)	Mood stabilizer + antipsychotic: 9 olanzapine 12 risperidone 10 quetiapine 30 mood stabilizer (no antipsychotic) 45 controls	Cross-sectional study in bipolar patients with age-, gender- and BMI matched controls	No difference in leptin levels between patients and controls. Bipolar patients were divided into 3 cohorts on the basis of medications: antipsychotics only, mood stabilizers only, and combination treatment, with higher leptin levels associated with antipsychotic usage, but not with any glucose or lipid parameter.
36. (Hosojima et al., 2006)	13 olanzapine	Prospective 4-week study	Weight increased 3.0% ($p=0.01$), and serum leptin increased 43.8% ($p=0.02$). Smoking status did not correlate with leptin changes.
37. (Rustembegovic et al., 2006)	10 olanzapine 10 risperidone 10 quetiapine 10 antiparkinsonian medications only 8 controls	Prospective 12-week study in Parkinson's Disease patients and controls	Only olanzapine treatment caused significant increases in serum leptin levels ($p<0.02$). There was a positive association between serum leptin levels and BMI.
38. (Wang et al., 2006)	87 clozapine 122 typicals 99 combination	Cross-sectional study	Subjects divided into 4 cohorts: nonobese normoglycemic subjects (control group), normoglycemic obese, impaired glucose tolerance (IGT) and type 2 DM. The control group was younger, and had significantly lower serum leptin than each of the other 3 cohorts ($p<.001$ for each comparison). This was true when analyzed among males separately. In a multiple linear regression model with fasting glucose as the dependent outcome variable, serum leptin remained in the model ($\beta=.045$, $p=.049$).
39. (Atmaca et al., 2007)	21 olanzapine 21 controls	Cross-sectional study, with age-, gender-matched controls. Olanzapine group followed 6 weeks.	At baseline, mean leptin levels were not significantly different between cohorts after adjustment for BMI and age. At the end of 6 weeks, there was a significant increase in both BMI ($+10.9\%$, $p<.05$) and serum leptin ($+103.4\%$, $p<.01$) in the olanzapine cohort, and a significant decrease in serum nitric oxide (-23.4% , $p<.05$). There was also a significant negative correlation between changes in leptin and nitric oxide levels ($r = 0.73$, $p< 0.01$).
40. (Ruano et al., 2007)	67 olanzapine 101 risperidone	Cross-sectional study examining weight profiles and genetic polymorphisms	Weight profiles in risperidone treated patients were associated with a single nucleotide polymorphism (SNP: rs8179183) in the leptin receptor gene ($p<.001$). This SNP was the largest association among all genetic markers studies in both drug groups. This SNP in the leptin receptor was previously found to be associated with body

Study	Sample Size	Methodology	Results
			weight in a sample of 1873 Caucasian nonpsychiatric subjects.

Table 2

Summary of Published Studies on Ghrelin in Patients on Antipsychotics

Study	Sample Size	Methodology	Results
(Togo et al., 2004a)	19 olanzapine 15 risperidone 18 control	Cross-sectional study in patients on antipsychotics for 4 weeks or more with age- and BMI-matched controls	Significant lower ghrelin level in antipsychotic groups compared to controls. No BMI differences among three groups.
(Birkas Kovats et al., 2005)	15 olanzapine 15 risperidone 15 clozapine 15 quetiapine 75 controls	Prospective 1-year study	80% of patients become overweight or obese. Ghrelin level was significantly higher in patients than in controls.
(Palik et al., 2005)	14 olanzapine 15 risperidone 15 clozapine 12 quetiapine 75 controls	Prospective 1-year study in psychotic pts with age- and gender-matched controls	Patients had significantly higher baseline BMI. Ghrelin was significantly higher in patients than in controls, but no differences among the atypicals. Ghrelin had significant negative correlation with BMI & fasting glucose.
(Murashita et al., 2005)	7 olanzapine	Prospective 6-month study	Compared to baseline, ghrelin level and percent body fat were significantly increased at 6 month
(Theisen et al., 2005)	12 clozapine	Prospective 10-month study	Compared to baseline, BMI increased significantly, but no significant difference in ghrelin levels at 6 months.
(Himmerich et al., 2005)	29 antidepressant 6 clozapine 17 other atypical antipsychotics	Prospective 1-week study	Clozapine and olanzapine induced significant weight gain, but ghrelin levels did not differ significantly between those who did or did not gain weight.
(Sporn et al., 2005)	24 clozapine 23 controls	Prospective 6-week study in childhood onset schizophrenia with age-, gender- and BMI-matched controls	BMI, but not ghrelin levels, increased significantly at week 6. Increased BMI was significantly correlated with decreased ghrelin.
(Hosojima et al., 2006)	13 olanzapine	Prospective 4-week study	At week 4, ghrelin levels were significantly decreased and body weight was significantly increased compared to baseline.

Table 3**Summary of Published Studies on Adiponectin in Patients on Antipsychotics**

Study	Sample Size	Methodology	Results
(Togo et al., 2004b)	18 olanzapine 15 risperidone 17 control	Cross-sectional study in patients on antipsychotics for 4 weeks or more with age- and BMI-matched controls	Significantly higher adiponectin levels in those on atypicals vs. controls. Adiponectin levels negatively correlated with higher BMI in patients on olanzapine, but not risperidone.
(Richards et al., 2006)	9 olanzapine 9 conventional agents 16 controls	Cross-sectional study with gender- and BMI-matching across the three groups. Olanzapine cohort significantly younger.	Both total and HMW Adiponectin levels were significantly lower in the olanzapine cohort than for conventional and controls. No significant difference between typical and control groups. In another human vitro study with 7-day olanzapine exposure had no effect on adiponectin
(Murashita et al., 2005)	7 olanzapine	Prospective 6-month study	Compared to baseline, no significant change in adiponectin levels although body fat significantly increased at month 6.
(Murashita et al., 2007)	15 risperidone 25 controls	Cross-sectional study in patients treated with risperidone and gender, age-matched controls.	Compared to controls, BMI, glucose and TG were significantly higher, but there were no differences in adiponectin levels.
(Sporn et al., 2005)	24 clozapine 23 controls	Prospective 6-week study in childhood onset schizophrenia with age-, gender- and BMI-matched controls	BMI increased significantly by week 6, but no change in adiponectin levels. Increased BMI was inversely correlated with adiponectin levels in clozapine patients.
(Hosojima et al., 2006)	13 olanzapine	Prospective 4-week study	Compared to baseline, adiponectin levels were not significantly different, although body weight was significantly increased.

Table 4

Summary of Leptin, Ghrelin and Adiponectin Properties and Changes During Antipsychotic Trials

Hormone(1 st Published Citation)	Secretion and function	Plasma level change	Effect of atypical antipsychotics	Comments
Leptin (Zhang et al., 1994)	Secreted by adipocytes. Stimulates central receptors that inhibit appetite. Increases metabolic rate and energy expenditure.	Levels increased after food intake and in obese patients, and decreased during fasting and malnutrition.	Consistent increases related to AAP-associated weight gain.	Leptin increases are the result of weight gain rather than a direct impact of AAPs on leptin physiology
Ghrelin (Kojima et al., 1999)	Secreted by upper GI tract. Stimulates appetite and food intake, inhibits energy expenditure and promotes adiposity.	Levels increased before feeding, during starvation and weight loss. Levels decreased in obese patients.	Inconsistent, but 3 long-term studies showed levels increased in patients on AAPs with weight gain.	AAP exposure may enhance ghrelin secretion, or disrupt the negative feedback of weight gain on ghrelin secretion.
Adiponectin (Nakano et al., 1996)	Secreted by adipocytes. Increases metabolic rate and insulin sensitivity..	Levels decreased in obese, diabetes patients, and increased levels seen after weight reduction	Most studies show no baseline differences between patients on AAPs and controls, or before and after AAP treatment.	No evidence to show adiponectin changes in patients on AAPs based on limited studies. HMW adiponectin could be more sensitive