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Pathophysiology of drug induced weight and metabolic effects: findings from an RCT in healthy volunteers treated with olanzapine, iloperidone, or placebo

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Abstract

Second generation antipsychotics are prescribed for an increasing number of psychiatric conditions, despite variable associations with weight gain, dyslipidemia, and impaired glucose tolerance. The mechanism(s) of the apparent causal relationships between these medications and metabolic effects have been inadequately defined and are potentially confounded by genetic risk of mental illness, attendant lifestyle, and concomitant medications. Therefore, we conducted a study in which 24 healthy volunteers were randomized to olanzapine (highly weightgain liability), iloperidone (less weightgain liability), or placebo treatment for 28 days under double-blind conditions. We hypothesized that antipsychotics induce weight gain primarily through increased caloric intake, which causes secondary dyslipidemia and insulin resistance. Subjects were

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Trial registry information

Trial registry name: Assessment and comparison of metabolic changes in non-psychotic adults taking iloperidone or olanzapine or placebo.

ClinicalTrials.gov identifier:

URL: https://www.clinicaltrials.gov/ct2/show/NCT01920802

phenotyped pre- and post-treatment for body weight, adiposity by dual energy X-ray absorptiometry, energy expenditure by indirect calorimetry, food intake, oral glucose tolerance, plasma lipids, glucose, insulin, and other hormones. We found significantly increased food intake and body weight but no change in energy expenditure in olanzapine-treated subjects, with associated trends towards lipid abnormalities and insulin resistance the extent of which were presumably limited by the duration of treatment. Iloperidone treatment led to modest non-significant and placebo no weightgain, lipid increases and alterations in insulin metabolism. We conclude that second generation antipsychotic drugs, as represented by olanzapine, produce their weight and metabolic effects, predominantly, by increasing food intake which leads to weight gain that in turn induces metabolic consequences, but also through other direct effects on lipid and glucose metabolism independant of food intake and weight gain.

Keywords

Antipsychotic drugs; weight gain; obesity; glucose homeostasis; randomized clinical trial

Background

Antipsychotic drugs (APDs) are principally indicated for the treatment of schizophrenia but are increasingly used for other psychiatric disorders as well. Over 30 million prescriptions are written for these agents in the US annually (Stagnitti, 2010). While highly effective, APDs are associated with significant side effects that often limit their clinical utility and pose safety concerns. Of particular concern for the preferentially used second-generation APDs are their adverse metabolic consequences including weight gain, insulin resistance, and dyslipidemia, rates of which vary by particular drug (Bak et al., 2014). It has been hypothesized that these effects, combined with sedentary lifestyle and increased rate of smoking (Ballon et al, 2014), contribute to a 20-year shorter life span in people with schizophrenia compared to the general population (Laursen, 2011: 101–104). The majority of APDs have metabolic effects including weight gain to varying degrees, with clozapine and olanzapine having the highest reported risk, and other drugs, such as aripiprazole and ziprasidone, lower risk (Allison et al., 1999; De Hert et al., 2011)

The pathophysiology of APD-associated weightgain and metabolic alterations remains unclear and is likely multifactorial (Teff and Kim, 2011). It has not been conclusively proven that the former (weight gain) is the primary cause of the latter (disturbances in glucose and lipid metabolism). For instance, APDs provoke cell-autonomous and weight-independent effects on insulin secretion by pancreatic β cells (Manu et al., 2013), lead to a metabolically adverse adipokine profile (Sugai et al., 2012; Wampers et al., 2012) and may directly affect central nervous system regulation of hepatic glucose production (Martins et al., 2010). In addition, it is unclear whether increased caloric consumption and/or decreased energy expenditure (or both) is the basis for pharmacotherapy-induced weight gain and adiposity-related comorbidities.

Assessment of the underlying pathogenesis of APD effects on metabolism is further complicated by several characteristics of patients for whom APDs are typically prescribed.

For example, people with schizophrenia may encounter environmental factors predisposing them to metabolic disturbances including sedentary lifestyle, poor nutrition, and increased rates of smoking as compared to the general population (Vancampfort et al., 2012). Moreover, beyond these environmental risks, people with schizophrenia also appear to have both a heightened intrinsic risk for metabolic diseases including diabetes as well a genetic predisposition to the adverse metabolic effects of APDs (Enez Darcin et al., 2015; Henderson et al., 2015). Finally, most of these patients have had extensive prior exposure to APDs and other medications that affect weight and metabolism prior to entry into studies examining metabolic factors related to a specific drug. The combination of these potential confounds has made interpretation of APD-induced metabolic risk highly challenging within this clinical population.

A limited number of studies have attempted to control for some of these confounds by using healthy volunteers. Many, but not all, of these studies have either been uncontrolled, of limited duration and/or used clinically ineffective low doses of agents being studied (Albaugh et al., 2011; Baptista et al., 2002; Fountaine et al., 2010). Moreover, prior studies have not directly compared the differential effects of particular APDs. Therefore, we conducted a randomized, double-blind, placebo-controlled study in healthy volunteers, free of metabolic or psychiatric illness, comparing two different APDs (olanzapine, iloperidone) to placebo over a 4-week period. We chose olanzapine and iloperidone because olanzapine has been associated with the highest risk of metabolic side effects, while iloperidone has been reported to have significantly lower but detectable metabolic risk as compared to placebo (De Hert et al., 2012; Leucht et al., 2013; Musil et al., 2015). We hypothesized that subjects randomized to olanzapine would be more hyperphagic, gain more weight (and body fat), and manifest more adverse metabolic changes compared to placebo and iloperidone. Consistent with these hypotheses, we found that in healthy volunteers, olanzapine (versus placebo) led to increased caloric intake and rapid weight gain, with trends towards increased insulin resistance and hypertriglyceridemia

Methods

Subject population

Subjects were recruited through local internet advertisements. All subjects signed an informed consent (see Supplementary Information) prior to screening. Inclusion criteria included age between 18 and 35 years, BMI between 19 and 25 kg/m^2, no prior Axis I or II diagnosis, no prior psychotropic drug exposure, and no active substance abuse. Subjects were required to have fasting glucose <100 mg/dL, hemoglobin A1C (HbA1c) <5.8%, blood pressure <130/85, and could not be on a hormonal form of contraception. To rule out prior psychiatric disease, subjects were administered a Structured Clinical Interview for Diagnosis–Non-patient (SCID-NP) performed (First et al., 2002), and were assessed for psychotic symptoms with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). To assess metabolic fitness, detailed medical and family histories were taken and screening labs (including plasma glucose, lipids, HbA1c, and liver function tests) obtained after minimum 8-h fast. In addition, all subjects underwent a physical examination,

including an ECG, and female subjects had a screening pregnancy test. These studies were approved by the IRB of the New York State Psychiatric Institute.

Dosing

Subjects who met eligibility criteria were randomized using a standard block randomization scheme to olanzapine, iloperidone, or placebo in a double-blind manner. Drugs and placebo were administered for a total of 28 days. Dosages were increased gradually over 3 days. Olanzapine dosing was 2.5 mg in the evening on day one, 2.5 mg morning and evening day two, 2.5 mg in the morning and 5 mg in the evening on day three, and 5 mg morning and evening thereafter. Iloperidone was dosed at 1 mg in the evening on the first day, 2 mg morning and evening on day two, 4 mg morning and evening on day three, and 6 mg morning and evening thereafter. These doses are consistent with those in current clinical use for the treatment of schizophrenia.

Subjects were seen on each day of the dose escalation and could maintain a lower dose if there were dose-limiting side effects – of 24 study completers, this eventuality occurred in 1 subject randomized to iloperidone. All dosages, including placebo, were given as 2 pills to be taken at morning and evening at each time point to maintain the double-blind. Each capsule was formulated with riboflavin as filler. The riboflavin was used as a marker of adherence and was detected in urine by visual inspection of fluorescence under UV illumination at each clinic visit using methods described elsewhere (Ramanujam et al., 2011).

Assessments

Height was measured at baseline, and weight and hip/waist circumference were assessed at each visit per CDC protocol (Centers for Disease Control and Prevention, 2007). Subjects were assessed for side effects at each visit, including with the abnormal involuntary movement scale (AIMS) (Lane et al., 1985), Barnes Akathisia scale (BAS) (Barnes, 1989), and Simpson–Angus Scale (SAS) (Simpson and Angus, 1970). A score >0 at any time point would exclude further participation. Increase in body weight of ≥7% was the pre-defined threshold for discontinuation of study drug. Subjects who reached that threshold were asked to complete final assessments, and were included in the analysis. Subjects who terminated prior to 14 days of study drug were not included in the analysis.

Venous blood was collected after an overnight (>8 h) fast at baseline and at each study visit (days 3, 14, and 28), allowed to clot on ice for 30 min, and then spun in a refrigerated centrifuge. Serum was analyzed by colorimetric assay for glucose (Analox #GMRD-002A), triglyceride (Cliniqa #R85457), cholesterol (Cliniqa #R85464), HDL cholesterol (Cliniqa #R85510), and NEFA (Wako #HR Series(2) reagent); by RIA for insulin (Millipore #HI-14K), C-peptide (Millipore #HL-81HK), glucagon (Millipore #GL-32K), leptin (Millipore #HL-81HK), and adiponectin (Millipore #HADP-66HK); by ELISA for cortisol (MP Biomedicals #07M21602), growth hormone (ALPCO Diagnostics, #25-HGHHU-E01), TNF-α (R&D Systems #HSTA00D), and IL-6 (R&D Systems #HS600B). A 2-h, 75 g oral glucose tolerance test (OGTT) was also conducted at baseline, day 3, day 14, and day 28 of the study.

Dual energy X-ray absorptiometry (DXA) to assess body composition was performed on day 3 and at day 28. Coefficient of variation for detection of fat in our facility is ~3.1% (Gallagher et al., 2010).

Resting energy expenditure (REE) was determined by hood calorimetry (Leibel et al., 1995), using a Viasys Vmax Encore Metabolic Cart as previously described (Schadewaldt et al., 2013).

An assessment of food intake was conducted at baseline, day 14, and day 28, on the same days as the OGTT. After the OGTT, subjects were then asked not to eat or drink anything except for water for five hours, after which subjects presented to the Eating Behavior Laboratory of the NY State Psychiatric Institute for a standardized, laboratory lunch meal. The basic protocol for this meal has been used by us for many years (Gianini et al., 2015). The laboratory lunch meal consisted of an array of 25 common high and low calorie foods (e.g. grilled chicken, fried chicken, macaroni and cheese, canned tuna, salad, fruit, cookies, condiments, and drinks) placed on a table. Prior and subsequent to the meal, participants were asked to complete 100 mm visual analog rating scales indicating hunger, fullness, and desire to eat. Participants were instructed: “This is your lunch for the day. Eat as much or as little as you would like.” They were alone in the room during the meal, observed via a one-way, closed circuit TV. Participants had up to 60 min to eat their meal and were asked to indicate when they were done with the meal by ringing a bell on the table. Immediately post-meal, while still seated at the table, participants were asked to estimate total calories consumed. Gram weight and kcal were calculated for all food consumed, as well as macronutrient composition of the meal including grams of carbohydrate, protein and fat.

Statistical analyses

This investigation was designed as a proof-of-concept study, therefore we focused the analysis on subjects ($N = 24$) who either completed 28 days of drug exposure, or for whom the trial was terminated early for reaching the safety threshold for weight. To further enhance our power to detect differences associated with weight gain, we stratified subjects by those who did or did not gain at least 5% of their body weight over the course of the study.

Statistical significance for the main effect on weight gain was determined by repeated-measures analysis of variance (ANOVA, $\alpha = 0.05$) between baseline and day 28 followed by a paired samples t-test, as were the three treatment group effects on body weight and fat gain, hunger ratings, test meal caloric intake, and plasma measurements. Two-tailed t-tests were used for pairwise comparisons. Statistical tests were conducted using SPSS (version 18.0, IBM, Armonk, NY) and Statistica 10.0; graphs were made with GraphPad Prism (version 6.0h for Mac OSX, GraphPad Software, La Jolla, CA) with error bars indicating standard error of the mean (SEM).

Results

Seventy subjects agreed to participate in the study; 30 subjects met criteria for eligibility and were randomized. 24 subjects completed the study and are included in the analysis.

Demographic characteristics between the drug groups did not differ statistically; descriptive statistics are presented in Table 1. Forty subjects terminated prior to randomization for unspecified reasons or being lost to follow-up. Of the 30 remaining participants, two were withdrawn from the study for violating inclusion criteria (taking hormonal birth control). One subject was found not to be taking the study medication at day 7 and was excluded from the analysis. Three subjects were discontinued within the first 14 days after randomization due to apparent adverse effects (one placebo-treated subject with new-onset abnormal finger movement at day 4; one olanzapine-treated subject for diarrhea at day 4; and one olanzapine-treated subject for drowsiness at day 8) and were not included in the analysis. Four subjects reached the predetermined withdrawal criterion of 7% increase in body weight (all in the olanzapine group) by day 21. Though they stopped study drug early, they completed full follow-up assessments and are included in the analysis without extrapolation for shorter duration of medication exposure. A complete list of adverse events is given in Table 2.

We observed a significant interaction between weight gain and drug treatment, ($F(2, 21) = 4.62$, $p = 0.002$), with olanzapine-treated subjects gaining an average of 3.2 kg (4.5 ± 1.4% of initial weight, $p = 0.022$ from baseline) of weight during the 4-week protocol (Figure 1(a) and Table 3). Weight gain from baseline in the placebo-treated (0.6 ± 0.7% of initial weight) and iloperidone-treated (1.1 ± 1.7% of initial weight) subjects was not statistically significant. In addition, when compared by ANOVA, olanzapine ($p = 0.002$) but not iloperidone ($p = 0.61$) treatment induced greater percentage body weight gain than placebo.

We assessed the frequency with which subjects achieved a clinically significant weight gain, defined a priori as a 5% increase from baseline, over the 4-week period. This criterion was met in 5/7 (71%) of olanzapine, 2/7 (29%) iloperidone, and 0/10 (0%) of the placebo treated subjects (Figure 1(b)). In addition, the safety end point of 7% increase in baseline body weight was achieved by 4/7 (57%) of olanzapine-treated subjects, but none in the placebo or iloperidone groups.

Weight gain is a function of net positive balance of energy intake over expenditure. Using a test meal paradigm, we assessed caloric intake at days 14 and 28 of treatment and found increased consumption (versus pre-treatment) in the olanzapine-treated group with no change observed in placeboand iloperidone-treated groups (not shown and Figure 2(a)). This approximate 25% increase in caloric intake (+268 ± 77 kcal, $p = 0.01$) relative to baseline during a single meal in the olanzapine group was not associated with increased consumption of any specific macronutrient: carbohydrate (+22 ± 11 g, $p = 0.09$), protein (+14 ± 11 g, $p = 0.23$) or fat (+13 ± 7 g, $p = 0.09$) intake were all increased. Selfreported, pre-meal hunger (measured by VAS) significantly increased between the baseline and day 28 meals in the olanzapine (82 ± 17 mm vs. 89 ± 11 mm, $p = 0.045$), and tended to increase in placebo (78 ± 16 mm vs. 88 ± 10 mm, $p = 0.07$) but not iloperidone-treated subjects (84 ± 18 mm vs. 86 ± 19 mm, $p = 0.64$).

We also measured REE by indirect calorimetry at baseline (off drug or placebo) and at end-of-treatment. REE did not change from baseline in olanzapine-treated subjects (+6.4 ± 8%, $p = 0.46$), iloperidone-treated (–4.2 ± 4.7%, $p = 0.42$), or in placebo-treated (+3.9 ± 2.3%, $p =$

0.13) subjects. Respiratory quotient (RQ) was similarly unaffected in all groups, suggesting unchanged metabolic substrate oxidation. These results suggest that olanzapine associated weight gain was due primarily to excess caloric intake.

Increased body weight was associated with a tendency towards increased total fat mass in olanzapine-treated subjects (+11.4% ± 5.3, $p = 0.077$), as measured by DXA (Table 3 and Figure 2(b)). Interestingly, iloperidone-treated subjects, despite unchanged body weight, showed a similar trend to increased total fat mass (Table 3 and Figure 2(b)). Fat mass gain was associated with a trend towards increased plasma leptin in olanzapine and iloperidone groups (Table 3). This was expected given the strong positive correlation typically observed between plasma leptin concentrations and adipose mass (Rosenbaum et al., 1997). Surprisingly, however, olanzapine treatment was also associated with a tendency to increased levels of adiponectin, an insulin-sensitizing adipokine generally inversely correlated with adiposity (Table 3).

While we did not observe any change in oral glucose tolerance, olanzapine treatment was associated with trends towards increased fasting C-peptide, as well as increased HOMA-IR (Table 3). This reduction in apparent insulin sensitivity was also reflected in trends towards increased plasma triglyceride in olanzapine-treated subjects (Table 3). Neither placebo nor iloperidone-treated participants showed significant alterations in glucose or lipid parameters. Other possible hormonal contributors to systemic glucose and lipid homeostasis, including glucagon and growth hormone, were unchanged, but we did observe higher levels of the inflammatory cytokine TNFα in olanzapine-treated subjects as well as a reduction in cortisol levels (Table 3).

Discussion

Large comparative effectiveness trials (CATIE, EUFEST) of APDs in schizophrenia patients have revealed significant weight gain and associated metabolic abnormalities with all tested APDs, albeit to varying degrees (Gothelf et al., 2002). These differences mirror clinical experience with these drugs, but despite decades of research, the pathophysiology underlying these disturbances remains unknown. It has been suggested that lifestyle-related and genetic/developmental factors intrinsic to schizophrenia may be responsible for these adverse metabolic profiles, independent of APD use. To eliminate this potential confound, we studied the metabolic effects of short-term (4-week) olanzapine exposure in metaolically and psychiatrically healthy volunteers. We found that olanzapine treatment caused substantial rapid weight gain; iloperidone administration was associated with mild weight gain, and placebo treatment expectedly did not induce any weight increase.

Gains in body weight (~4.5%) and fat mass (~11.4%) in olanzapine-treated subjects were associated with increased caloric consumption, likely due to greater appetite as predicted from rodent studies (Baptista et al., 1998), but no significant change in energy expenditure. The caloric excess observed during the single meal multi-item buffet in olanzapine-treated subjects (268 kcal) is consistent with the increase in total body fat (1.42 kg mean fat increase × 9.4 kcal/g fat = 13,381 kcal excess / 28 days = 478 kcal excess per day) (Racette et al., 2006). Associated with the olanzapine-induced increase in body weight and adipose mass

was the development of an unfavorable lipid profile, characterized by a trend towards increased plasma triglycerides and total/LDL cholesterol. An important question is the extent to which this change in adiposity can account for the dyslipidemia associated with olanzapine administration, and to what extent these changes are due directly to the drug itself. It is likely both mechanisms contribute. Although the increase in plasma TG correlated with change in truncal and total adipose mass in olanzapine-treated subjects (r = 0.39, p = 0.03 for truncal fat; r = 0.42, p = 0.03 for total fat), we did not observe a similar relationship for either total or LDL cholesterol.

Olanzapine has been reported to induce early changes in glucose homeostasis (unrelated to changes in fat mass or body composition), leading to the suggestion that olanzapine may exert weight-independent effects on pancreatic β-cells (Simpson et al., 2012), adipose and other insulin-sensitive tissues (Sugai et al., 2012), or even central nervous system mediators of glucose homeostasis (Martins et al., 2010). For instance, Albaugh et al. (2011), found impaired glucose tolerance after a brief exposure (3 days) to olanzapine, similar to that seen in insulin clamp studies, prior to significant weight gain (Teff et al., 2013). While we did not observe significant changes in systemic glucose homeostasis – glucose disposal was unchanged after an oral glucose load – we did observe a trend towards increased insulin resistance, as reflected by non- significant trends towards increased C-peptide and higher HOMA-IR in olanzapine-treated subjects. Counter-regulatory hormones to insulin action were either not changed (GH, glucagon) or directionally opposite (decreased circulating cortisol concentration) from increased insulin resistance, the latter confirming earlier observations with olanzapine treatment (Baptista et al., 2007). These data suggest short-term protection from impaired glucose homeostasis reflecting adequate β-cell reserve, and/or the protective effect of elevated circulating adiponectin (despite increased fat mass) seen in olanzapine-treated volunteers, which would be predicted to improve hepatic insulin sensitivity (Pajvani and Scherer, 2003). However, this finding may be due to the limited duration of the treatment period of the study; longer exposure would likely lead to dysregulated glucose homeostasis as a result of increased peripheral insulin resistance exacerbated by progressive impairments of beta cell function, consistent with the increased incidence of T2D in olanzapine-treated patients.

There is an established literature that proposes that people with schizophrenia have inherent risk for abnormal glucose metabolism/T2D and dyslipidemia, while at the same time a protection against Type 1 Diabetes, independent of treatment with APDs (Juvonen et al., 2007; Spelman et al., 2007). Such differences might be conveyed by shared genetic influences on brain and islet functions (Ballon et al., 2014). The trend towards insulin resistance and dyslipidemia in healthy olanzapine-treated volunteers, in the context of acute weight gain, suggests that drug-induced changes in glucose metabolism are at least partly independent of preexisting genetic and/or metabolic risk in schizophrenia.

There are several important limitations to this pilot study. Our statistical power for making direct drug-specific comparisons was constrained by the small sample size (n = 7–10 per group) and relatively short, 4-week exposure of healthy volunteers to APD. Longer exposure may have resulted in greater deviation from baseline values for olanzapine and/or iloperidone-treated subjects, but may also have clouded interpretation for mechanism of

weight gain by inducing secondary or compensatory responses. For instance, regression analyses including all subjects showed a strong correlation between changes in body weight measured by scale and those computed from the DXA data ($r^2 = 0.81$, $p < 0.0001$), but we observed no significant correlation of changes in body weight by scale or DXA with change in total body fat. Therefore, while these regression analyses support the overall accuracy of the DXA measurements, the small changes in body fat detected here are at the limits of performance of the DXA instruments employed (Gallagher et al., 2010; Rosenbaum et al., 1996). Nevertheless, the trends observed suggest that both olanzapine and iloperidone may have effects on "partitioning" of stored calories in favor of fat storage that may either not change body weight or change it subtly due to the high density of lipid calories.

Additionally, our measures of insulin sensitivity were indirect as opposed to measurement by hyperinsulinemic-euglycemic clamps, which might have detected larger between-group differences. Our conclusions are also limited to olanzapine and iloperidone (as an example of an APD thought to confer less metabolic risk) treatment, and may not necessarily apply to other APDs. Finally, our study was performed in lean, young volunteers; it cannot be assumed that these results will extrapolate directly to older or overweight/obese adults, or patients with schizophrenia, especially in regards to magnitude of metabolic effects. Despite these limitations, our data show that olanzapine induces rapid, substantive weight gain in healthy volunteers, with associated metabolic liabilities, independent of underlying psychiatric disease. Future studies to elucidate the molecular mechanisms of both short and long-term APD-induced metabolic changes are needed to counteract these adverse effects and for the development of drugs with fewer metabolic side effects and improved safety profiles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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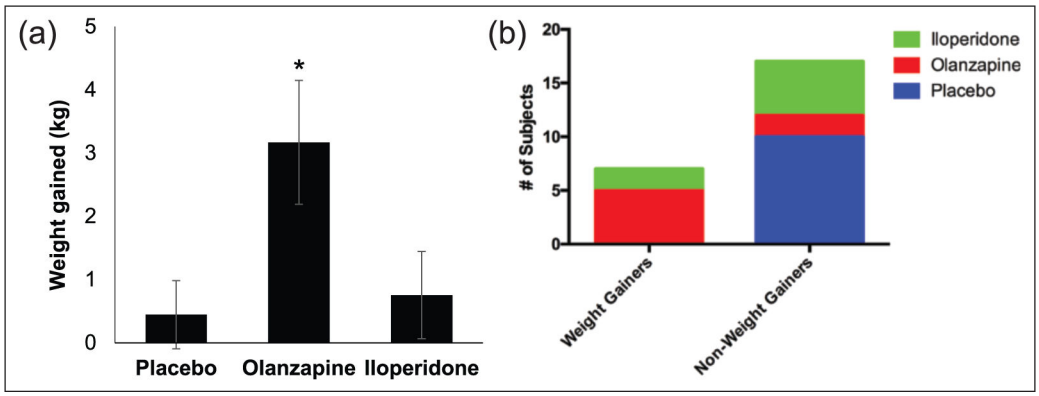

Figure 1.

Olanzapine induces significant weight gain in healthy volunteers. (a) Subjects randomized to the olanzapine group exhibited significant weight gain ($p = 0.018$); placebo-treated ($p = 0.43$) and iloperidone-treated ($p = 0.32$) participants did not show any change from baseline measurement. (b) Clinically significant weight gain, defined as having gained ≥5% of initial body weight during the 28-day medication exposure, was observed in 5/7 (71%) of subjects randomized to olanzapine versus 2/7 (29%) and 0/10 in iloperidone and placebo-treated subjects, respectively.

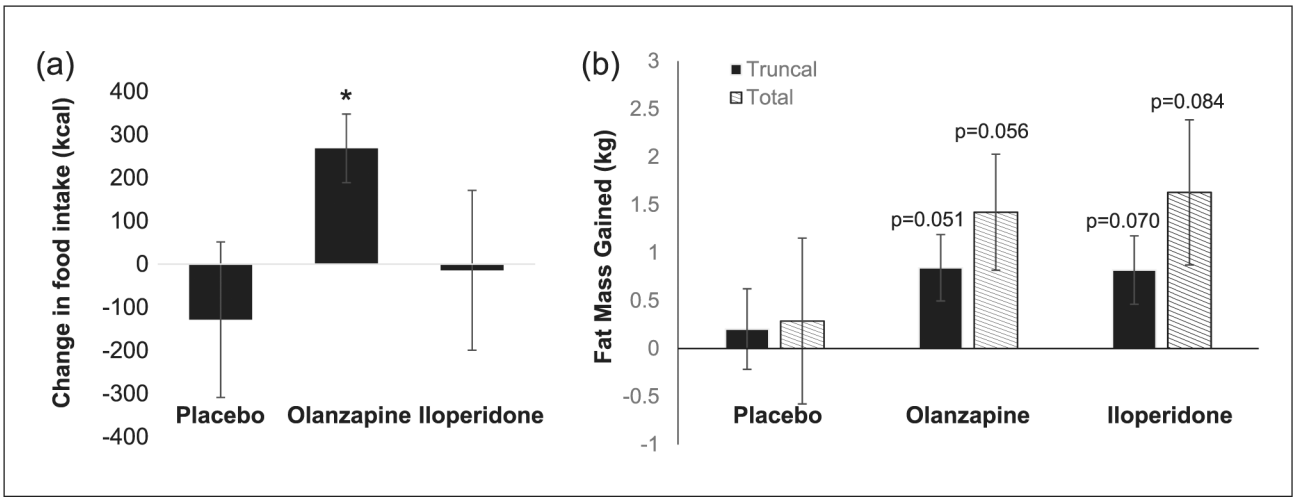

Figure 2.

Olanzapine-induced weight gain is associated with increased caloric intake, and a tendency towards increased fat mass. (a) After 28 days of treatment, olanzapine-treated subjects showed increased caloric intake in a standardized, laboratory lunch meal (+267 kcal), whereas placeboand iloperidone-treated participants showed no change from baseline measurements. (b) Total fat mass, as assessed by DXA, was unchanged by placebo treatment, but subjects randomized to olanzapine and iloperidone groups tended towards increased truncal fat mass, as well as total adiposity from baseline measurements.

Table 1.

Subject demographics.

	Placebo	Olanzapine	Iloperidone
Sex	9 male, 1 female	5 male, 2 female	4 male, 3 female
Age (years)	25.8 ± 1.5	26.7 ± 2.0	27.3 ± 1.6
Race	4 Black, 4 White, 2 Other	5 Black, 1 White, 1 Other	5 Black, 1 White, 1 Other
Education (years)	14.9	16.4	13.9
Starting BMI	22.7 ± 0.5	22.7 ± 0.3	23.6 ± 0.6

Table 2.

Adverse events.

	Placebo	Olanzapine	Iloperidone
Fatigue	2	6	6
>7% body weight gain	0	4	0
Headache	3	0	0
Gastrointestinal	0	2	2
Dizziness	0	0	2
Musculoskeletal	2	0	0
Dry Mouth	0	0	1
Anxiety	1	0	0
Anorgasmia	0	0	2
Tachycardia	0	0	1
Elevated transaminases	0	2	0
Anhidrosis	0	0	1

Table 3.

Change from baseline in body weight/adiposity and metabolic parameters.

	Placebo	Olanzapine	Iloperidone
Body weight (kg)	+0.4 ± 0.5	+3.2 ± 1.0*	+0.8 ± 0.7
	$p = 0.43$	$p = 0.02$	$p = 0.32$
Body weight (%)	+0.6 ± 0.7	+4.5 ± 1.4*	+1.1 ± 1.7
	$p = 0.36$	$p = 0.02$	$p = 0.33$
Fat mass (kg)	+0.3 ± 0.9	+1.4 ± 0.6	+1.6 ± 0.8
	$p = 0.68$	$p = 0.056$	$p = 0.084$
Fat mass (%)	+7.2 ± 6.8	+11.4 ± 5.4	+10.3 ± 7.4
	$p = 0.28$	$p = 0.077$	$p = 0.10$
Adiponectin (μg/mL)	+0.62 ± 0.68	+0.94 ± 0.48	+1.57 ± 0.76
	$p = 0.38$	$p = 0.07$	$p = 0.17$
Leptin (ng/dL)	+1.16 ± 1.15	+2.47 ± 1.17	+1.76 ± 0.8
	$p = 0.34$	$p = 0.07$	$p = 0.20$
Insulin (μU/mL)	+0.28 ± 0.76	+2.54 ± 1.78	+0.88 ± 2.17
	$p = 0.72$	$p = 0.21$	$p = 0.70$
C-peptide (ng/mL)	+0.06 ± 0.06	+0.28 ± 0.12	+0.01 ± 0.10
	$p = 0.36$	$p = 0.07$	$p = 0.25$
HOMA-IR	+0.02 ± 0.13	+0.84 ± 0.41	+0.4 ± 0.56
	$p = 0.90$	$p = 0.09$	$p = 0.44$
Glucagon (pg/mL)	−2.45 ± 6.97	−2.11 ± 8.32	+1.50 ± 8.29
	$p = 0.74$	$p = 0.81$	$p = 1.0$
NEFA (μq/L)	+0.07 ± 0.11	−0.10 ± 0.08	−0.18 ± 0.10
	$p = 0.54$	$p = 0.27$	$p = 0.62$
Triglycerides (mg/dL)	+2.87 ± 6.59	+37.99 ± 17.62	+9.11 ± 4.94
	$p = 0.67$	$p = 0.07$	$p = 0.31$
Cholesterol (mg/dL)	+0.28 ± 7.92	+21.44 ± 12.29	+14.7 ± 12.86
	$p = 0.97$	$p = 0.13$	$p = 0.49$
LDL Cholesterol (mg/dL)	+0.26 ± 5.88	+10.13 ± 9.54	+6.49 ± 11.27
	$p = 0.97$	$p = 0.32$	$p = 0.88$

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	Placebo	Olanzapine	Iloperidone
Cortisol (μg/dL)	+0.05 ± 0.84	−3.9 ± 1.36*	+0.60 ± 2.01
	$p = 0.95$	$p = 0.03$	$p = 0.88$
Growth Hormone (ng/mL)	+0.63 ± 0.89	+0.14 ± 0.23	+0.89 ± 0.87
	$p = 0.53$	$p = 0.56$	$p = 0.36$
TNFα (pg/mL)	+0.19 ± 0.18	+0.31 ± 0.11*	+0.15 ± 0.19
	$p = 0.32$	$p = 0.04$	$p = 0.64$
IL-6 (pg/mL)	−0.06 ± 0.17	+0.08 ± 0.13	−0.21 ± 0.32
	$p = 0.73$	$p = 0.56$	$p = 0.56$