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# **Chapter 4**

Olanzapine shifts the temporal relationship between the daily acrophase of serum prolactin and cortisol concentration rhythm in healthy men

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# SUMMARY

Treatment with the atypical antipsychotic drug olanzapine is frequently associated with development of obesity and insulin resistance. Treatment-induced weight gain has been suggested to be the main contributing factor of diminished insulin sensitivity. This study evaluated the effects of short-term treatment with olanzapine on 12h plasma prolactin and cortisol concentrations in healthy men. The effects of two distinct olanzapine formulations were investigated; the oral standard tablets (OST) and the orally disintegrating tablets (ODT). Recent reports indicate that treatment with the ODT formulation may be less harmful in terms of weight gain than the OST. 12 healthy men (age: 25.1+/-5.5 y) received olanzapine OST (10mg QD, 8 days), olanzapine ODT (10mg QD, 8 days) or no intervention in a randomized cross-over design. On day 8, blood samples were taken every 10min between 0000 and 1200h for determination of cortisol and prolactin concentrations. Treatment with olanzapine OST and ODT similarly increased the 12h mean PRL concentrations and the secreted PRL mass. Both drugs similarly shifted the maximal PRL concentration approximately 3-4h backwards in time. Cortisol secretions rates were lower, but the timing of the cortisol acrophase did not change. Both drugs significantly elevated HOMA index for insulin resistance. In conclusion olanzapine OST and ODT equally elevated the prolactin concentration and significantly shifted its acrophase, thus dissociating PRL and cortisol, while both formulations induced similar insulin resistance as evidenced by the elevated HOMA-IR. Notably, these alterations occurred without a measurable effect on body adiposity.

# INTRODUCTION

The use of atypical antipsychotic (AP) drugs is associated with obesity (1), diabetes mellitus (DM) (2) and dyslipidemia (3), which limits the clinical applicability of these compounds. Olanzapine is one of those drugs. Two types of olanzapine tablets are available for clinical use: standard (OST: oral standard tablets) and orally disintegrating (ODT; orally disintegrating tablets). Recent papers report that treatment with ODT might be less harmful in terms of weight gain than treatment with OST (4,5). The main difference between these compounds is that ODT dissolves instantaneously in the oral cavity upon administration allowing absorption through the sub-lingual mucosa. Olanzapine ODT is therefore absorbed more rapidly than olanzapine OST (6).

Prevalence of type 2 diabetes increases strongly with aging. In humans, glucose tolerance is among the biological processes that display a circadian and circannual (seasonal) rhythm (7), driven by the hypothalamic suprachiasmatic nucleus (SCN), the biological clock. Cues from the internal and external environment, e.g. light–dark signals, hormones and drugs, entrain and coordinate these circadian and circannual rhythms. The SCN uses the endocrine and the autonomic nervous system to organize and generate metabolic rhythms. The prevalence of type 2 diabetes increases strongly with aging and both aging (8) and type 2 diabetes (9) are associated with malfunction of the biological clock. Importantly, non-diabetic offspring of type 2 diabetic patients already exhibits defects in SCN function (10,11), which suggests that abnormal SCN function precedes metabolic dysfunction.

In the wild, obesity and insulin resistance have evolved as a strategy to survive long periods (seasons) of low food availability (12). Dopaminergic and serotoninergic neurons in the SCN appear to be critically involved in these metabolic adaptations. Specifically, phase relationships between circadian rhythms of these monoamines change at the appropriate time of year to modulate peripheral and central mechanisms controlling metabolism (12). In particular, a forward shift in time of the acrophase (i.e. maximum) of serum prolactin concentrations presages weight gain and insulin resistance in seasonally obese animals, and the prolactin concentration acrophase shifts back in preparation of summer (lean phenotype). Importantly, the time relationship with the serum corticosteroid acrophase, which does not fluctuate with season, is critical for the metabolic impact of prolactin (13).

Prolactin and cortisol have powerful metabolic effects in humans as well (14,15). Given the above facts, we hypothesized that treatment with olanzapine, which modulates dopaminergic and serotonergic neurotransmission, would phase-shift the serum prolactin versus cortisol concentration acrophase to explain its metabolic effects. We also asked whether olanzapine ODT might have less impact on circadian timing of serum prolactin and cortisol rhythms to explain its modest effect on body weight. We therefore compared the early endocrine effects of the two olanzapine formulations on prolactin and cortisol secretion in healthy men.

# METHODS

#### **Subjects**

Twelve healthy men between 20 and 40 y were recruited through advertisements in local newspapers. The subjects were required to have a stable BMI between 20 and 27 kg/m<sup>2</sup> and a normal fasting plasma glucose concentration (<6.0 mmol/l). Subjects, who were, at present or in the past, treated with antipsychotic, antidepressant or other medications affecting the brain (e.g. dopaminergic drugs), and subjects smoking and/or abusing drugs were excluded. All subjects provided written informed consent after explanation of the study procedures and possible adverse effects of the treatment. The protocol was approved by the medical ethics committee of the Leiden University Medical Center and registered by www.controlled-trials. com (ISRCTN17632637).

#### Drugs

All subjects received olanzapine standard tablets (OST; 10 mg QD for 8 days), olanzapine orally disintegrating tablets (ODT; 10 mg QD for 8 days) or no intervention in a randomized cross over design. The drugs were taken at 0800 h except on day 8 when they were taken at 0700 h. The minimum plasma concentration ( $C_{min}$ ) of olanzapine was determined on day 8 at 0700 h. Olanzapine serum concentrations were determined by reversed phase high-performance liquid chromatography (HPLC). Detection was at 270 nm. The assay was linear from 5–60 µg/l. The detection limit was 5 µg/l. Accuracy was 103% and the reproducibility had a coefficient of variation of 3.0% at 60 µg/l and of 7.4% at 5 µg/l.

# Diet

To limit confounding by nutritional factors, subjects received a standard diet consisting of 2500 kcal/day on days 7 and 8 of each intervention period. The diet consisted of bread, fillings and drinks, prepared by the research center. The macronutrient composition of the diet was exactly the same on all occasions: 45% of energy derived from carbohydrates, 20% from proteins and 35% from fat. Intake of alcohol and caffein/thein containing beverages were not allowed, the day before and during all study occasions.

#### **Clinical protocol**

Subjects were studied three times in random order; without an intervention (control) and after treatment with olanzapine OST (10 mg QD, 8 days) or ODT (10 mg QD, 8 days). There was a time interval of at least 6 weeks between each study occasion. On day 7, after a 10 h overnight fast, body fat percentage was determined by bioelectrical impedance analysis (BIA; Bodystat 1500 MDD, Bodystat Itd, Douglas Isle of Man, UK). As of this time point, the subjects were prescribed the standard diet delineated earlier. Subjects were re-admitted to the research center at 1700 h. A cannula for blood sampling was inserted into an antecubital vein. Blood samples were

collected with S-monovette (Sarstedt, Etten-Leur, The Netherlands) from a three-way stopcock that was attached to a 0.9% NaCl infusion (20 ml/h; with 100 U heparine/500 ml) to keep the cannula from clotting. Blood samples were taken every 10 min between 0000 and 1200 h for determination of cortisol and prolactin concentrations. At 0700 h the drug was taken. Dinner and breakfast were served at 1830 and 0800 h, respectively. Subjects remained sedentary except for bathroom visits; at 2300 h lights were switched off.

#### Assays

Each tube, except the serum tubes, was immediately chilled on ice. Samples were centrifuged at 3520 rpm at 4°C for 20 min. Subsequently, plasma/serum was divided into separate aliquots and frozen at  $-80^{\circ}$ C until assays were performed. Serum insulin was measured by immunoradiometric assay (INS-IRMA; BioSource Europe S.A., Nivelles, Belgium). Blood glucose concentrations were assessed using a blood glucose analyzer (*Accu-Chek* Sensor, Roche, Mannheim, Germany). Serum cortisol concentrations were measured by radioimmunoassay (RIA) with a detection limit of 25 nmol/l (DiaSorin, Stillwater, Minnesota, USA). The intra-assay coefficient of variation (CV) ranged from 2.0–4.0%. Serum prolactin concentrations were measured with a sensitive time-resolved fluoroimmunoassay with a detection limit of 0.04 µg/l (Delfia, Wallac, Turku, Finland). The standards were calibrated against the 3rd WHO International Standard for Prolactin 84/500, 1 ng/ml = 36 mU/l. The intra-assay CV varies from 3.0% to 5.3% and the inter-assay CV was 3.4–6.2%.

# DATA ANALYSES

#### Cluster

For the detection of discrete PRL peaks, Cluster Analysis was used. This computerized pulse algorithm is largely model-free, and identifies statistically significant pulses in relation to dose-dependent measurement error in the hormone time series (16). A concentration peak is defined as a significant increase in the test peak cluster versus the test nadir cluster. We used a  $2 \times 1$  cluster configuration (2 samples in the test nadir and one in the test peak) and *t*-statistics of 2.0 for significant up- and down-strokes in PRL levels to constrain the false positive rate of peak identification to less than 5% of signal free noise. The locations and widths of all significant concentration peaks were identified, the total number of peaks was counted, and the mean interpeak interval was calculated in minutes. In addition, the following pulse parameters were determined: peak height (highest value attained within the peak), incremental peak amplitude (the difference between peak height and prepeak nadir), and area under the peak. Interpulse valleys were identified as regions embracing nadir with no intervening upstrokes. Pulsatile PRL secretion was calculated as the product of pulse mass and pulse frequency. Basal PRL secretion

was calculated as the difference between total PRL secretion estimated by the integrated area of the concentration profile and the pulsatile contribution.

#### Approximate entropy

Approximate Entropy is a scale- and model-independent statistic that assigns a non-negative number to time series data, reflecting regularity of these data (17). Higher ApEn values denote greater relative randomness of hormone patterns. Normalized ApEn (1,20%) parameters of m = 1 (test range), r = 20% (threshold) and 1000 for the number of runs were used as described previously (18). The ApEn metric evaluates the consistency of recurrent subordinate (non-pulsatile) patterns in a time series and thus yields information distinct from and complementary to deconvolution (pulse) analysis (19). Data are also presented as normalized ApEn ratios, defined by the mean ratio of absolute ApEn to that of a 1000 times randomly shuffled version of the same series. ApEn ratios close to 1.0 express highly irregular (maximum randomness) secretory patterns.

# Deconvolution analysis

Multi-parameter deconvolution analysis was used to estimate various kinetic and secretory parameters of 12 h spontaneous (nocturnal) cortisol secretion, calculated from cortisol concentration time series. Initial waveform-independent assessments of cortisol was created with Pulse 2, an automated pulse detection program. Subsequent analysis with a waveform dependent multi parameter deconvolution method was performed as described previously, using a first component half-life of 3.8 min, second component half-life of 66 min and a relative contribution of the slow component to the total elimination of 0.67.

# Circadian rhythmicity

Nyctohemeral characteristics of PRL and cortisol concentration patterns were determined using a robust curve fitting algorithm (LOWESS analysis, Systat version 11 Systat Inc, Richmond, CA (20). The acrophase is the clock time at which the fitted PRL and cortisol concentration is maximal. The amplitude of the rhythm was defined as half the difference of the zenith (maximum) and the nadir (minimum). The relative amplitude was the maximal percentage increase of the mesor (average) value.

## **Calculations and statistics**

# HOMA model

Insulin resistance was quantified by homeostasis model assessment of (HOMA-IR) as described by Matthews et al. (21) (HOMA-IR = fasting insulin (mU/I)  $\times$  fasting plasma glucose (mmol/I)/22.5).

# **Statistics**

Results are presented as mean  $\pm$  S.E.M. Data was logarithmically transformed before analysis when appropriate and analyzed using a Student's *t*-test. When the distribution of the data was not normal after logarithmic transformation they were analyzed using the Wilcoxon signed-rank test. Significance level was set at 0.05. First, the effect of treatment with olanzapine-ODT was compared with olanzapine-OST. Secondly, to evaluate the effect of treatment with olanzapine-ODT was calculated and compared with values measured in the control group. All analyses were performed using SPSS for Windows, version 12.0 (SPSS Inc., Chicago, IL).

# RESULTS

#### **Subjects**

Twelve men (age  $25.1 \pm 5.5$  y) were included in the study; two of them did not show up for the third study occasion for personal reasons. None of the participants had major side effects while they were treated with olanzapine. However, most of them felt tired during the first days of the treatment.

Parameter	Control	Ola-OST	Ola-ODT
Subjects	12	11	11
BMI (kg/m <sup>2</sup> )	$23.6\pm0.6$	$23.8\pm0.6$	$23.7 \pm 0.7$
WHR	$0.80\pm0.01$	$0.81\pm0.01$	$0.81 \pm 0.01$
Fat percentage (%)	9.6 ± 1.2	9.8 ± 1.3	$10.4 \pm 1.1$
Diastolic blood pressure (mmHg)	71 ± 2	$76 \pm 3$	$72 \pm 2$
Systolic blood pressure (mmHg)	$131 \pm 4$	$128 \pm 4$	$127 \pm 4$
Heart rate (min)	$63 \pm 4$	$68 \pm 4$	$68 \pm 4$
HOMA IR <sup>a)</sup>	1.53 ± 0.19*	$\textbf{2.18} \pm \textbf{0.25}$	$2.12\pm0.34$

**Table 1.** Clinical and biochemical measurements (in fasting condition): without intervention (control), during treatment with olanzapine standard tablets (OST) and orally disintegrating tablets (ODT).

Data are presented as means  $\pm$  S.E.M. Abbreviations: BMI: body mass index; HOMA-IR: homeostasis model assessment; WHR: waist hip ratio. There were no significant differences between Olanzapine-OST and Olanzapine-ODT. \**P* = 0.005 (one tailed), control versus treatment,

<sup>a</sup> Homeostasis model assessment (HOMA) was used to estimate insulin resistance from fasting insulin and glucose concentrations. The following equation was used: HOMA-IR = fasting insulin (mU/I) × fasting glucose (mmol/I)/22.5.

# **Olanzapine concentration**

Minimum plasma olanzapine concentration ( $C_{min}$ ) were 13.5 ± 1.3 µg/l and 15.4 ± 1.45 µg/l after treatment with olanzapine ODT and OST, respectively and did not differ between groups (P = 0.18).

## Metabolic profile and anthropometric variables in fasting condition

Table 1 summarizes anthropometric measurements and metabolic profiles in fasting conditions. There were no differences in BMI, WHR or fat percentage between treatment conditions. Treatment with olanzapine ODT and OST significantly increased HOMA-IR to a similar extent.

#### Effect of olanzapine ODT and OST on 12 h cortisol and prolactin concentrations and secretory parameters

Treatment with olanzapine ODT and OST decreased 12 h mean cortisol concentration and cortisol secretion rate as compared with the control group, where ODT and OST had similar effects. Olanzapine tended to decrease the number of the cortisol secretory bursts (P = 0.06) and thus to increase the mean intersecretory burst interval (P = 0.06) (data not shown).

Treatment with olanzapine ODT and OST similarly increased the 12 h mean PRL concentrations (Figure 1, Table 2). The two formulations of olanzapine delayed the PRL acrophase equally and significantly versus the maximum serum cortisol concentration (Figure 1, Table 3).



**Figure 1. Serum** PRL and cortisol concentration time series from 0000 to 1200 h. Data are presented as mean  $\pm$  S.E.M. Olanzapine ODT and OST significantly shifted the maximal serum PRL concentration approximately 3–4 h backwards.

Table 2. Mean serum cortiso	ol and prolactin concentratio	ons and secretory parameters du	ring treatment
with olanzapine standard ta	blets (OST) and orally disinte	egrating tablets (ODT).	

Parameter	Control	Ola-OST	Ola-ODT
Cortisol secretion rate (nmol/l/12 h)	2769 ± 170 *	2327 ± 317	$2164\pm102$
Mean cortisol (nmol/l)	236 ± 11.9 †	172 ± 17.9	$180 \pm 9.3$
Cortisol ApEn (1,20%)	0.83 ± 0.04 ‡	$0.67 \pm 0.04$	$0.68\pm0.03$
PRL secretion rate ( $\mu$ g/l/12 h)	1021 ± 114 ¶	$1304 \pm 141$	1764 ± 179
Mean PRL (µg/l)	7.8 ± 1.7 #	15.4 ± 2.8	$16.4 \pm 3.9$
PRL ApEn (1,20%)	$1.01 \pm 0.05$	$1.07 \pm 0.07$	$1.10\pm0.06$

Data are presented as mean ± S.E.M. There were no significant differences between olanzapine-OST and olanzapine-ODT.

\*P = 0.001, Control versus treatment (two tailed); †P = 0.003, Control versus treatment (two tailed);

P = 0.016, Control versus treatment (two tailed); P < 0.0001, Control versus treatment (two tailed); P = 0.032, Control versus treatment (two tailed).

Table 3. Acrophase of serum prolactin and cortisol concentration time series.

Parameters	Control	Ola-OST	Ola-ODT
Prolactin (clock hours)	$5.88 \pm 0.58^{*}$	$9.86\pm0.89$	$9.09 \pm 1.46$
Cortisol (clock hours)	$8.52 \pm 0.16$	$8.92\pm0.41$	$8.45\pm0.33$

Time of maximal serum concentration was estimated with LOWESS fitting. Data are presented as mean (clock hours)  $\pm$  S.E.M (hours).

There were no significant differences between Olanzapine-OST and Olanzapine-ODT. \*P = 0.028, Control versus treatment (two tailed).

#### Effect of olanzapine ODT and OST on regularity of plasma cortisol and prolactin concentration time series

ApEn (1,20%) and ApEn ratios of plasma cortisol concentration time series were significantly lower after treatment with olanzapine ODT and OST as compared to no treatment, indicating that the cortisol release process became more regular. The effect of treatment with olanzapine ODT and OST did not differ in this respect (Table 2). The regularity of the 12 h PRL concentration time series was similar in all groups (Table 2).

# DISCUSSION

Here we show that 8 days of treatment with olanzapine phase-shifts the serum prolactin versus the cortisol concentration acrophase in healthy men, in a manner reminiscent of the circadian adaptations that presage weight gain and insulin resistance in seasonally obese animals. In particular, the acrophase of serum prolactin concentrations occurs almost 4 h later during olanzapine treatment, whereas the serum cortisol concentration peak is not affected. Also, olanzapine inhibits cortisol secretion (particularly pulsatile release), whereas it clearly elevates serum prolactin concentrations. Both drug formulations exert similar endocrine effects. HOMA-IR was significantly higher after treatment with both ODT and OST as compared to the control group. Notably, these endocrine and metabolic effects occur without measurable effects on body weight and body fat mass.

Elevation of PRL concentrations is frequently observed during chronic treatment with AP drugs, and it is one of the most consistent endocrine corollaries of intervention with AP drugs in healthy subjects in experimental settings (22). As far as we know, this is the first study to demonstrate that an antipsychotic drug shifts the serum PRL versus cortisol acrophase in humans. Similar endocrine changes coordinate seasonal adaptation of the reproductive and metabolic phenotype in a variety of vertebrate species (12). Indeed, phase shifts of peak prolactin and/or corticosteroid release coincide with seasonal reproductive and metabolic adaptations in animals (23-25). Interestingly, simulation of the circadian rhythms of endogenous corticosterone and prolactin by daily injections of the hormones at times corresponding to the peak levels found in 3-week-old Sprague-Dawley rats, reverses age-related increases in insulin resistance and body fat in 5–6-month-old animals (26), indicating that these hormones are also involved in the pathophysiology of age-related changes in energy metabolism in non-seasonal subjects. It is unknown if phase relationships of circadian hormone rhythms are involved in the pathogenesis of obesity and insulin resistance in humans. However, the biological clock, which drives circadian hormone rhythms, goes awry in human aging (8) and type 2 diabetes mellitus (9). Furthermore, both prolactin and cortisol clearly exert metabolic effects in man, as illustrated by the obese, insulin resistant phenotype of patients with prolactinoma (27) and Cushings syndrome (28). Thus, although human physiology is not marked by seasonal changes as overt as those occurring in some rodents, we speculate that the endocrine changes observed here are among those explaining the adverse metabolic sequelae of olanzapine treatment.

The reduction of serum cortisol levels observed here is in keeping with findings in other studies, where olanzapine acutely reduced cortisol concentrations in healthy men (29) and in schizophrenic patients (30). Quetiapine, another atypical AP drug, significantly diminishes (nocturnal) urinary cortisol excretion (31) and acutely lowers serum cortisol concentrations 150–240 min after administration in healthy men (32).

Dopaminergic and serotonergic neural circuits are likely to be involved in the apparent neuroendocrine effects of olanzapine. The drug blocks various monoamine receptors, including dopamine  $D_2$  and serotonin (5-hydroxytryptamine, 5-HT) 5-HT<sub>2A</sub>/5-HT<sub>2C</sub> receptors. Dopamine inhibits prolactin synthesis and secretion through activation of dopamine  $D_2$  receptors at the lactotroph cell membrane (33). Thus, olanzapine consistently elevates serum prolactin levels, probably through its  $D_2R$  antagonistic qualities (22). The reduction of serum cortisol levels observed here is in keeping with findings in other studies, where olanzapine acutely reduced cortisol concentrations in healthy men (29) and in schizophrenic patients (30). Quetiapine, another atypical AP drug, significantly diminishes (nocturnal) urinary cortisol excretion (31) and acutely lowers serum cortisol concentrations 150–240 min after administration in healthy men (32). AP drugs probably inhibit cortisol release by blocking serotonin 5-HT<sub>2A</sub>/5-HT<sub>2C</sub> receptors and/or dopamine  $D_1/D_2$  receptors, which stimulate CRH secretion (34-36). CRH stimulates the activity of the adrenocorticotropic hormone (ACTH)/glucocorticoid rhythm ensemble. Administration of a 5-HT<sub>2C</sub> receptor antagonist blocks depolarization of CRH neurons induced by the

 $5-HT_{2C}$  receptor agonist m-chlorophenylpiperazine (m-CPP) (35), corroborating the importance of the  $5-HT_{2C}$  receptor activation for CRH secretion. Accordingly, olanzapine blocked ACTH and cortisol release induced by the  $5-HT_{2C}$  receptor agonist m-CPP in male schizophrenic patients (37). The ApEn ratio of the cortisol concentration time series, reflecting enhanced regularity of the secretion process, was reduced by olanzapine in the present study, which is consistent with diminished feed forward drive of cortisol release. In aggregate, this data clearly indicates that the D<sub>2</sub> and  $5-HT_{2C}$  receptor antagonistic properties of olanzapine are likely to be involved in the endocrine effects of the drug reported here.

Interestingly, both dopaminergic and serotoninergic neural circuits partake in the control of fuel flux and energy balance (38,39). Indeed, treatment with bromocriptine mesylate, a sympatholytic dopamine  $D_2$  receptor agonist with serotonin-modulating activity (40), favorably alters metabolism in obese animals and humans. In seasonally obese animals, it resets diurnal hormone rhythms (41,42) and reverts obesity and insulin resistance (42,43). Treatment with bromocriptine also improves glycemic control in obese type 2 diabetic patients (44) and reduces diurnal insulin and glucose concentrations in obese (non-diabetic) women (45). Similarly, the 5-HT<sub>2C</sub> receptor agonist mCPP ameliorates glucose intolerance and insulin resistance in genetic and diet induced obese animal models (46) and serotonergic agents induce weight loss and reinforce insulin action in obese humans with type 2 diabetes mellitus (47,48). Our data suggests that prolactin and cortisol may be endocrine messengers linking central regulatory pathways with peripheral tissues involved in the control of energy metabolism.

It seems important to emphasize that other mechanisms may contribute to the (long-term) metabolic side effects of atypical antipsychotic compounds. Indeed, olanzapine ODT and OST had similar effects on (timing of) plasma prolactin and cortisol concentration profiles and insulin sensitivity. Thus, the present endocrine effects do not explain the apparent differences in long-term metabolic sequelae between both formulations. Also, distinct atypical antipsychotics considerably differ in terms of metabolic side effects. These compounds also vary with respect to their affinity for a range of (other) monoamine receptors. Histamine and adrenergic receptors, for example, are involved in the control of energy balance and glucose metabolism via neuroendocrine mechanisms that are largely unknown (49,50). It is very likely that antagonism of these receptors contributes to the adverse metabolic sequelae of antipsychotic treatment. Differences in affinity for any of these receptors between compounds may explain their diversity in terms of metabolic side effects. Also, the impact of olanzapine treatment on prolactin and cortisol rhythmicity in the long-term in schizophrenic patients remains to be determined to definitely establish their role in the pathogenesis of obesity and diabetes in these patients.

If indeed the impact of olanzapine on the timing of the acrophase of endogenous serum hormone levels is involved in the pathophysiology of its adverse metabolic effects, the timing of drug administration may need careful evaluation. In this study, olanzapine was taken at 0800 h every day. Although the plasma half life of olanzapine is 31 h (51), it is conceivable that some of its effects on hormone release primarily occur in the first hours after administration, when plasma levels are highest. Indeed, peak serum prolactin levels occurred around 1000 h (approximately 4 h later than in drug free conditions), a few hours after drug intake. It may be worthwhile to evaluate if, for example, *ante noctem* intake has less metabolic effects because it promotes nocturnal instead of day-time prolactin release.

We believe that our findings warrant evaluation of the effects of other antipsychotic drugs on circadian hormone release to determine if these compounds similarly phase shift the timing of serum hormone concentration rhythms.  $D_2$  and 5-HT<sub>2C</sub> receptor antagonism are key pharmacological features of virtually all antipsychotics, but the receptor affinity profiles vary considerably among agents (52), perhaps explaining their differential potential to induce weight gain and diabetes mellitus (53).

In conclusion, short-term olanzapine treatment elevates serum prolactin levels and shifts the timing of the maximum serum prolactin versus cortisol concentration in healthy men, while it induces insulin resistance without measurable effects on body weight and fat mass. As similar endocrine changes presage weight gain and insulin resistance in a variety of obese animal models, we speculate that the endocrine effects of olanzapine reported here are involved in the pathogenesis of its adverse metabolic side effects.

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