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A low TSH profile predicts olanzapine-induced weight gain and relief by adjunctive topiramate in healthy male volunteers

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ABSTRACT

Second generation antipsychotics, like olanzapine (OLZ), have become the first line drug treatment for patients with schizophrenia. However, OLZ treatment is often associated with body weight (BW) gain and metabolic derangements. Therefore, the search for prospective markers for OLZ's negative side effects as well as adjunctive treatments to inhibit these has been of major interest.

The aim of this study was to investigate in healthy male volunteers (age: 36 ± 11 years; BW: 84 ± 12 kg; BMI = 25.5 ± 2.5) whether adjunctive topiramate (TPM) administration opposes OLZ-induced weight gain over the course of 14 days treatment. In addition, we investigated behavioral, endocrine and metabolic characteristics as underlying and potentially predictive factors for weight regulation and/or metabolic derangements associated with OLZ and TPM treatment.

While adjunctive TPM indeed reduced OLZ-induced weight gain ($P < 0.05$, Mann–Whitney U), behavioral/metabolic/endocrine characteristics of OLZ treatment were not affected by TPM. Using multiple regression analysis, BW gain was the key factor explaining metabolic disturbances (e.g., plasma insulin–LDL interaction: $P < 0.01$, $R^2 = .320$), and cumulative food intake during treatment was the best denominator of BW gain ($P < 0.01$, $R^2 = .534$). Neither TPM treatment, nor its circulating levels, contributed to variation observed in ΔBW . In a second multiple regression analysis, we observed that a low baseline thyrotropin profile (TSH_{AUC}) before the start of drug treatment was associated with an increase in ΔBW over the course of drug treatment ($P < 0.05$, $R^2 = .195$). Adding TSH_{AUC} as covariate revealed that adjunctive TPM treatment did attenuate OLZ induced BW gain ($P < 0.05$, ANCOVA). Further exploration of the circulating thyroid hormones revealed that individuals with a low plasma TSH profile were also those that were most sensitive to adjunctive TPM treatment blocking OLZ-induced ΔBW gain. Others have shown that OLZ-induced BW gain is associated with improvement in brief psychiatric rating scores (BPRS); adjunctive TPM treatment may be a solution specifically for those subjects susceptible to OLZ-induced rapid weight gain who—on a therapeutic level—benefit most of OLZ treatment.

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1. Introduction

Second generation ('atypical') antipsychotics have become the first line drug treatment for patients with schizophrenia (Wallingford et al., 2008). Among these, olanzapine (OLZ) is known for its clinical efficacy (Leucht et al., 2009; Lieberman et al., 2005), but its use is strongly associated with body weight (BW) gain (Bak et al., 2014; Komossa et al., 2010), increased appetite and food

intake (Stauffer et al., 2009), and is additionally related to hyperglycemia, insulin resistance, elevated cholesterol levels, and acute hypothermia (Atmaca et al., 2003; Graham et al., 2005; Hosojima et al., 2006; Lindenmayer et al., 2003; Melkersson et al., 2000; van Marum et al., 2007).

BW gain as a result of OLZ treatment can be remarkably large and increases the risk for diabetes mellitus (DM) (Meyer, 2010). This is particularly relevant since individuals suffering from schizophrenia are already predisposed for developing DM irrespective of treatment with antipsychotic agents (Mukherjee et al., 1996). In fact, metabolic syndrome and cardiovascular diseases are important causes of morbidity and mortality among patients with severe mental illnesses (Pramyothin and Khaothiar, 2010). The search for an adjunctive treatment to reduce OLZ-induced BW gain, and

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concomitant reduction of metabolic side effects, without affecting clinical efficacy, is therefore of major interest. Not only for the health benefit on a metabolic level, but also to improve treatment compliance (McQuade et al., 2004) benefitting mental health.

Topiramate (TPM), an anticonvulsant prescribed mainly for the treatment of epilepsy and known to induce weight loss (Li et al., 2005), was found capable of diminishing olanzapine-induced weight gain in schizophrenic patients without aggravation of psychotic symptoms (Kim et al., 2006; Narula et al., 2010). Additionally, co-administration of TPM with OLZ resulted in a reduction of OLZ-induced weight gain and appetite, but also improved insulin sensitivity and favorably decreased fasting blood glucose, total cholesterol, triglycerides, high-density lipoprotein (HDL)-cholesterol and leptin levels in schizophrenic patients (Narula et al., 2010).

Although the phenomenon of severe weight gain by OLZ is well-recognized (Bak et al., 2014; Choong et al., 2012; McEvoy et al., 2005) some individuals actually lose weight during OLZ treatment (Kinon et al., 2005), which shows that not all individuals are equally prone to this adverse side effect. This individual variation in metabolic responsiveness to OLZ treatment is most likely due to OLZ's atypical receptor binding profile (Bymaster et al., 1999) and complicates the identification of responsible mechanisms of OLZ-induced weight gain. Nonetheless, a number of neuroendocrine factors related to energy homeostasis released from pineal, pituitary, gonadal, adrenal, and thyroid glands have been identified to be affected by OLZ treatment (Mann et al., 2006; Raskind et al., 2007; Starrenburg and Bogers, 2009; Vidarsdottir et al., 2010b). We therefore hypothesize that the cause of the individual variation in susceptibility to OLZ-induced weight gain (Ascher-Svanum et al., 2005; Kinon et al., 2005; Stauffer et al., 2009) may originate from inter-individual differences in responsiveness of neuroendocrine pathways to drug treatment.

The first aim of this study in healthy male volunteers was to investigate the potency of adjunctive TPM administration to reduce OLZ-induced body weight gain and related metabolic side effects. Secondly, to identify -post hoc- baseline parameters predictive of OLZ-induced BW gain and related co-morbidities. The latter is important, because the moment a specific pathway can be identified as a predictor for OLZ-induced side effects, it becomes possible to avoid/decrease the occurrence of unwanted side effects, either by (1) excluding patients that are at risk of developing negative side-effects or (2) by treating these patients with an adjuvant selected specifically to counter these unwanted side-effects.

2. Methods

2.1. Study design

This was a randomized, double-blind, placebo-controlled clinical study conducted at PRA Clinics in Zuidlaren, the Netherlands. An independent ethics committee (BEBO, Assen, the Netherlands) approved the clinical study protocol. All subjects provided written informed consent before participation. The study was conducted in accordance with the principles of the Declaration of Helsinki, and with the laws and regulations of the Netherlands and the EU. This work was performed within the framework of the Dutch Top Institute Pharma project: T2-105. EudraCT number: 2010-019664-37.

2.2. Study procedures

Study medication was administered by personnel not involved in the preparation of the medication.

Table 1
Descriptive statistics body composition and demographics.

Variable	Group	n	Mean	Stdev	Median	Min	Max
Age (year)	OLZ	15	35.3	10.0	36.0	21.0	54.0
	OLZ + TPM	15	36.1	11.5	37.0	20.0	52.0
Weight (kg)	OLZ	15	85.1	12.7	84.0	67.8	110.5
	OLZ + TPM	15	84.3	12.3	82.1	70.9	119.3
Height (cm)	OLZ	15	181.5	7.9	180.0	170.0	196.0
	OLZ + TPM	15	181.3	7.5	178.0	171.0	199.0
BMI	OLZ	15	25.7	2.7	25.1	21.7	29.8
	OLZ + TPM	15	25.5	2.5	26.0	21.8	30.1
Waist circ. (cm)	OLZ	15	87.9	7.4	87.5	75.0	98.0
	OLZ + TPM	15	88.8	10.6	86.1	73.0	110.0
Adiposity (%)	OLZ	15	17.6	5.6	18.7	8.1	27.4
	OLZ + TPM	15	18.2	6.3	17.2	7.4	29.8
Ethnicity	OLZ	European		n = 13		86.6%	
		African/European		n = 1		6.6%	
		Asian		n = 1		6.6%	
	OLZ + TPM	European		n = 12		80.0%	
		African/European		n = 2		13.3%	
		African		n = 1		6.6%	

2.3. Treatments

Thirty healthy male subjects were randomized to receive OLZ plus placebo ($n = 15$) or OLZ plus TPM ($n = 15$) over a 14-day in house treatment period. The doses were 10 mg OLZ o.d. with TPM (or placebo) at 25 mg b.i.d. during days 1–6 and 50 mg b.i.d. during days 7–14. Subjects arrived at the clinic at day-2, drug treatment started at day 1 until day 14, subjects left the clinic at day 15. Recovery from effects was assessed in a follow-up visit on day 28 after washout of all medication had occurred.

It was assumed that the trial medication of OLZ plus TPM could induce unwanted side-effects (e.g., augmented sedation), which might cause subjects to drop-out and make the results difficult/impossible to interpret. For that reason a gradual increment in dosing of TPM was chosen in this study. Drug doses were selected on the basis of prior dose-response studies (Vidarsdottir et al., 2010a), and were chosen in order to minimize side effects but retain clinically relevant therapeutic levels.

2.4. Subject grouping

Key exclusion criteria were evidence of clinically relevant pathology, history of psychiatric diseases, significant psychopathology in first grade family members, and positive screen on drugs of abuse or alcohol intake of more than 24 units of alcohol per week. Baseline body weight characteristics (Table 1) and demographics were comparable across treatment groups. Body weight was measured at day-2 (baseline), 13 and 28 at 09:00 h just before drug dosing. Standardized meals, various snacks, and non-alcoholic beverages were available ad libitum on request. All caloric intake and left-overs were carefully recorded by the staff continuously from day-2 to day 15, when subjects were in the facility.

2.5. Laboratory investigations

Blood samples for assessment of OLZ levels were taken on day 1 of treatment, 4 h after dosing at 09:00 h, at day 6 (at 09:00 h at dosing and 4 h later) and at day 13 (at 09:00 h at dosing and 4 h later). Levels of TPM were assessed only at days 6 and 13 at 09:00 h (for assessment of baseline level). Blood samples for glucose, insulin and C-peptide were taken just prior to dosing at 09:00 h and at 0.5, 1, 1.5, 2, 2.5 and 3 h after a meal tolerance test 1 h post dosage (MTT;

Ensure Plus® challenge) on days -1, 6, 14 and 28 (the prior to dosing time point on days -1 and 28 was chosen at a time similar to the time points on dosing days). For determination of glucose, insulin and C-peptide, blood samples of 4 ml per time point were taken into sodium-heparin tubes. Analysis of serum glucose, insulin, C-peptide, total cholesterol, high-density lipoprotein-bound cholesterol [HDL-cholesterol], low-density lipoprotein-bound cholesterol (LDL-cholesterol), serum triglycerides were analyzed in blood samples on days -1, 6, 14, 28 and performed according to the following methods:

Circulating levels of OLZ and TPM were measured by HPLC-MS from whole blood (0.5 ml) at the University Medical Center Groningen (Dept. of Clinical Pharmacy and Pharmacology).

Serum glucose: quantitative determination of glucose in serum was done on the ADVIA 1800Chemistry systems using a hexokinase and glucose-6-phosphate dehydrogenase enzymatic method. Normal range: 4.1–5.9 mmol/l, critical value (CV) 1.1–2.3%.

Insulin: for quantitative determination of Insulin in serum the ADVIA Centaur XP Insulin assay was used, a two-site sandwich immunoassay using direct chemiluminescent technology which uses constant amounts of two antibodies. Sensitivity and assay range was 0.5–300 mU/l. Normal range: 3.0–25.0 mU/l, CV 6.3–7.5%.

C-peptide: for quantitative determination of C-peptide in serum the IMMULITE 2000 Systems on heparinized plasma was used. Normal range: 0.9–7.1 ng/ml (0.3–2.4 nmol/l; 298–2350 pmol/l), CV within-run 1.7–2.3%.

Homeostasis model assessment of insulin resistance (HOMA-IR) was estimated as described by Matthews et al. (1985). ($\text{HOMA-IR} = \text{fasting insulin (mU/l)} \times \text{fasting plasma glucose (mmol/l)} / 22.5$). These were calculated either as absolute levels or as percent change% HOMA-IR from baseline (at day -1).

Total cholesterol: quantitative determination of total cholesterol in serum on the ADVIA 1800Chemistry systems using cholesterol esterase and cholesterol oxidase conversion followed by a Trinder endpoint method. Normal values: <5.18 mmol/l, CV 0.5–1.1%.

HDL-cholesterol: quantitative determination of HDL cholesterol in serum and plasma the on the ADVIA 1800Chemistry systems was used according to the Direct-HDL Cholesterol method that measures HDL cholesterol without prior separation, based on an enzymatic method developed by Izawa, Okada and Matsui. Normal values: >1.6 mmol/l, CV 2.1–2.5%.

LDL-cholesterol: for quantitative determination of LDL cholesterol in serum the ADVIA 1800Chemistry systems was used. Normal values <2.6 mmol/l, CV 0.5–1.1%.

Triglycerides were measured on the ADVIA 1800Chemistry systems according to the method based on the Fossati three-step enzymatic reaction with a Trinder endpoint. The single-reagent procedure quantitates the total triglycerides including the mono and diglycerides and the free glycerol. Normal value: <2.83 mmol/l.

Daily energy expenditure was calculated using the doubly-labeled water method as previously described by our group (Guidotti et al., 2013, 2016). Determination of $^2\text{H}/^1\text{H}$ and $^{18}\text{O}/^{16}\text{O}$ ratios in saliva and blood samples were performed at the ESRIG Center for Isotope Research, University of Groningen.

Thyroid hormone activity: because particular emphasis is put in this study on the role of thyroid hormones in treatment efficacy of OLZ and TPM, plasma levels of TSH, T3 and T4 were determined at several days (-1, 1, 6, 13, and 14) during the study at time points 0, 3, 5, and 7 h after drug administration at 09:00 h. Because circadian patterns of these hormones show a nocturnal rise (Brabant et al., 1992), and decline in the morning, an area under the curve (AUC) for each individual on the days of sampling was calculated (from 0 to 7 h after drug dosing) and used as the parameter for plasma thyroid hormone profile (=AUC of daily thyroid hormone levels: e.g., TSH_{AUC}). Besides the absolute AUCs also the percent change (e.g., $\text{TSH}_{\text{AUC}}(\%)$) from baseline (at day -1) was assessed.

Thyrotropin (TSH): for quantitative determination of thyroid-stimulating hormone (TSH, thyrotropin) in serum, heparinized plasma, and EDTA plasma the ADVIA Centaur XP TSH3-Ultra assay was used, a third-generation assay that employs anti-FITC monoclonal antibody covalently bound to paramagnetic particles, an FITC-labeled anti-TSH capture monoclonal antibody, and a tracer consisting of a proprietary acridinium ester and an anti-TSH mAb antibody conjugated to bovine serum albumin (BSA) for chemiluminescent detection. Normal for adults: 0.55–4.78 $\mu\text{IU/ml}$ (mIU/l); CV 5.13–6.64%.

Triiodothyronine (T3): for quantitative determination of T3 in serum the ADVIA Centaur XP systems was used. Sensitivity and assay range was 0.15–12.3 nmol/l nmol/l. Normal values 0.92–2.79 nmol/l; CV 1.84–3.44.

Thyroxine (T4): for quantitative determination of T4 in serum the ADVIA Centaur XP systems was used. Sensitivity and assay range was 3.9–387 nmol/l; normal range: 58.1–140.6 nmol/l.

Statistical analysis was performed using SPSS20.0. To test for normal distribution the Shapiro-Wilk test was performed. Within group testing was done by paired *t*-test (2-tailed) analysis, between

Fig. 1. Circulating olanzapine and topiramate levels.

(A) OLZ levels were assessed at day 1 (4 h after administration at 09:00 h), day 6 and day 13 (both 0/4 h after dosing at 09:00 h). Adjunctive TPM treatment did not affect circulating OLZ levels. A build-up of basal circulating OLZ levels can be noted at day 6 and 13, prior to drug administration at time points 6-0 and 13-0. (B) Basal TPM levels after 6 and 13 days of treatment measured at 09:00 h prior to drug administration. TPM levels increased due to the increase of dosing at day 7 of treatment from 50 mg/day (at days 1–6) to 100 mg/day (at days 7–14).

Table 2
OLZ and OLZ + TPM, group averages $\pm$ sem.

	Day	OLZ	OLZ + TPM
BW (kg)	–2	85.1 $\pm$ 12.7	84.3 $\pm$ 12.3
	13	86.6 $\pm$ 11.9 [#]	84.6 $\pm$ 13.3
	28	87.5 $\pm$ 12.4 ^{##}	85.3 $\pm$ 12.9 ^{##}
Δ BW (kg)	13	2.40 $\pm$ 0.53 [#]	1.08 $\pm$ 0.37
Adiposity (%)	13	19.65 $\pm$ 1.50	19.14 $\pm$ 1.37
Daily caloric intake (kcal)	Avg	2652 $\pm$ 105	2487 $\pm$ 114
Carbohydrate breakfast (kcal)	Avg	93.7 $\pm$ 4.9	78.8 $\pm$ 4.6 [*]
Energy expenditure (kcal/day)	6–13	2324 $\pm$ 90	2309 $\pm$ 125
HOMA-IR	–1	1.96 $\pm$ 0.23	2.12 $\pm$ 0.31
	14	3.16 $\pm$ 0.31	2.84 $\pm$ 0.38
Insulin (AUC)	–1	127 $\pm$ 22	114 $\pm$ 17
	14	154 $\pm$ 28	171 $\pm$ 32
Glucose (AUC)	–1	37.0 $\pm$ 1.2	37.6 $\pm$ 1.1
	14	39.0 $\pm$ 1.1	38.9 $\pm$ 0.7
Δ Temperature ($^{\circ}$ C)	1	–0.48 $\pm$ 0.09	–0.29 $\pm$ 0.08

Avg—daily average; AUC—area under the curve.

[#] $P < 0.05$, paired t -test compared to day-2.

^{##} $P < 0.05$, paired t -test compared to day-2 and day 13.

^{*} $P < 0.05$, oneway-ANOVA, OLZ > OLZ + TPM.

groups analyses were performed using Mann–Whitney U test, rm- or oneway-ANOVA (post hoc LSD), and analysis of covariance (ANCOVA) tests. Relations between parameters were performed either using Pearson 2-tailed correlation (R^2) or by using linear regression analyses (ANOVA). Differences were considered significant at a confidence interval of 95% and $P < 0.05$. Stepwise multiple regression analysis (stepping method criteria; Use probability of F : entry < 0.05 , removal > 0.10) was used to define which parameters best explained the variation observed in the dependent variable of interest; to avoid Type I errors, a Bonferroni adjustment was applied and significance was considered under $\alpha < 0.05/k$, in which k is the amount of independent variables meeting the entry criteria (Curtin and Schulz, 1998; Perrett et al., 2006). Graphs were illustrated using Graphpad Prism 5.0. Results are expressed as average $\pm$ sem, unless stated otherwise.

3. Results

3.1. Circulating OLZ and TPM levels

Circulating OLZ levels on day 1 at 13:00 h (i.e., 4 h after dosing at 09:00 h) increased on day 6 (both at baseline right before dosing at 09:00 h and 4 h later) and at day 13, the latter reflecting a gradual increase of circulating OLZ over time (see Fig. 1A). Basal circulating TPM levels at 09:00 h were raised on day 6 and further increased on day 13, most likely reflecting the shift from 50 mg to 100 mg TPM at day 7 till the end of treatment (see Fig. 1B). Adjunctive TPM administration did not have an effect on circulating OLZ levels as is illustrated in Fig. 1A.

3.2. General effects of OLZ and adjunctive TPM treatment

Pre-treatment body weight (at day-2) was 85.1 ± 12.7 kg for the OLZ group and 84.3 ± 12.3 kg for the OLZ + TPM group (Table 2). Fig. 2a shows the changes in body weight (Δ BW) over the course of treatment. Within group analyses revealed that the OLZ-treated subjects gained weight over 13 days of treatment ($P = 0.023$; $t_{14} = -2.562$, paired t -test), whereas OLZ + TPM treated subjects did not significantly increase weight over 13 days of treatment compared to their initial body weight ($P = 0.538$; $t_{14} = -0.631$, paired

Fig. 2. Delta body weight.

(A) Body weight changes (Δ BW) over the course of 14 day drug treatment with OLZ or OLZ + TPM, and fourteen days after treatment termination on day 28. BWs were measured at day-2, day 13, and day 28. OLZ treated subjects showed an increase in BW after 13 days of treatment compared to initial BW ($*P < 0.05$; paired t -test). Compared to day-2 both groups showed increased BW at day 28 ($**P < 0.01$, $*P < 0.05$; paired t -test). (B) Subjects segregated into tertiles ($n = 10$) based on body weight gain over 13 days of drug treatment. Subjects were classified as: gained body weight (Gain), remained a stable body weight (Stable), or lost body weight (Lose). This segregation illustrates the variation in Δ BW responses between these groups ($P < 0.001$, rm-ANOVA post hoc LSD) irrespective of treatment. Compared to the Stable group the Gain and Lose group showed respectively increased or decreased body weights at day 13 and 28 ($*P < 0.05$, $**P < 0.01$, oneway-ANOVA post hoc LSD). (C) Subjects treated with OLZ versus those treated with OLZ + TPM were differently distributed over the three Δ BW groups (mean rank: 18.83/12.17; $P < 0.05$, Mann–Whitney U). Specifically, the Gain group consisted predominantly of OLZ-treated subjects (OLZ/TPM: 7/3), whereas the Lose group by large constituted of OLZ + TPM treated subjects (2/8). The Stable group showed an equal distribution of subjects from both treatment groups (6/4). This segregation reveals that TPM does attenuate OLZ-induced weight gain, but not in every individual.

t -test). Additionally, at day 28 (i.e., 14 days after treatment termination), body weights were increased in both experimental groups, compared to their initial body weight (day-2) (OLZ: $P < 0.01$, $t_{14} = -4.522$; OLZ + TPM: $P < 0.05$, $t_{14} = -2.895$) and compared to day 13 of treatment (OLZ: $P < 0.01$, $t_{14} = -3.514$; OLZ + TPM: $P < 0.05$, $t_{14} = -2.369$).

As displayed in Table 2, no main effects were found of adjunctive TPM treatment on adiposity, daily caloric intake, daily energy expenditure (assessed by DLW analysis or activity-scores), HOMA-IR, glucose_{AUC}, insulin_{AUC}, and temperature response. However, a between groups treatment effect of TPM was found on the amount of carbohydrate intake during breakfast over the course of drug treatment ($P < 0.05$, $F_{1,29} = 4.855$, oneway-ANOVA), which was significantly elevated in the OLZ-treated subjects compared to the OLZ + TPM treated subjects.

To explore the variation in body weight gain, we segregated the ΔBW s over the 13-day treatment period into tertiles ($n = 10$ each) of “Gain”, “Stable” and “Lose” irrespective of treatment (Fig. 2B), similar to Ascher-Svanum et al. (2005). We observed that subjects treated with OLZ vs those treated with OLZ + TPM were unevenly distributed over the three ΔBW groups (mean rank: 18.83/12.17; $P < 0.05$, Mann–Whitney U). The Gain group consisted of significantly more OLZ-treated than OLZ + TPM treated subjects, whereas the Lose group consisted predominantly of OLZ + TPM treated subjects (see panel 2C). While the segregation was done according to ΔBW on day 13, repeated measures ANOVA revealed that ΔBW profiles differed significantly between all three groups over the entire period up to day 28 ($F_{4,54} = 23.289$, $P < 0.001$; rm-ANOVA post hoc LSD), 14 days after drug treatment was terminated (Fig. 2B).

3.3. Multiple regression analyses

To investigate independent variables related to ΔBW fluctuation (i.e., plasma OLZ/TPM levels, OLZ-induced hypothermia, energy intake/expenditure/excess, age, TSH_{AUC}/T3_{AUC}/T4_{AUC}), we performed a stepwise multiple regression analysis. Total cumulative food intake (FI) during treatment was the most important factor explaining the variation of ΔBW on day 13 of treatment ($P < 0.001$, $F_{1,27} = 30.945$, ANOVA, $R^2 = .534$), and addition of morning plasma OLZ levels taken at day 13 of treatment improved this relation considerably ($P < 0.001$, $F_{2,26} = 22.622$, ANOVA, $R^2 = .635$). Further analysis revealed that the variation in total FI was best explained by the circulating OLZ levels at day 13 at 4 h after drug administration ($P < 0.01$, $F_{1,27} = 9.515$, ANOVA; $R^2 = .261$) and the model was improved by the temperature response after drug administration at the first day of treatment ($P < 0.01$, $F_{2,26} = 8.215$, ANOVA; $R^2 = .387$). Remarkably, both circulating OLZ levels on day 13 at 4 h ($F_{1,29} = 10.169$, $P < 0.01$, ANOVA; $R^2 = .266$) and ΔT_{AUC} at day 1 ($F_{1,29} = 8.060$, $P < 0.01$, ANOVA; $R^2 = .230$) were negatively correlated to total FI. This implies that both higher circulating OLZ levels and a larger (initial) hypothermic response are associated with lower food intake.

In a second analysis, we explored potential factors contributing to the variation in the change (i.e., compared to day-1) of meal-induced excursions of plasma insulin (Δ Insulin) and glucose (Δ Glucose) levels as well as its HOMA-index (Δ HOMA), which we considered to be dependent variables mostly reflecting OLZ's adverse metabolic side effects (see Table 3). Whereas variation in Δ HOMA at day 14 could not be explained by any of the parameters included in the model, variation in Δ HOMA at day 6 was to some extent explained by ΔBW ($P < 0.01$, $F_{1,27} = 10.599$, ANOVA; $R^2 = .282$). Δ Insulin at day 14 was best explained by ΔBW too ($P < 0.05$, $F_{1,27} = 7.110$, ANOVA; $R^2 = .208$), but was strengthened by addition of morning LDL levels ($P < 0.01$, $F_{2,26} = 6.114$, ANOVA; $R^2 = .320$). The latter is consistent with the observed positive relation between increased LDL levels and the increase in insulin response after 14 days of drug treatment ($P < 0.01$, $F_{1,29} = 5.707$, ANOVA; $R^2 = .169$). Unlike the variation in Δ HOMA and Δ Insulin, the variation in Δ Glucose was not explained by any parameter during treatment, except for its own baseline response at day-1 (i.e., which is indicative of the stability of glucose regulation through insulin secretion). The figures of the meal-induced excursions

(HOMA, glucose, insulin, and C-peptide) can be found in the Appendix (A1).

In a third analysis, we explored whether any of these factors before the start of drug treatment could contribute to explain the variation in ΔBW . We only added baseline parameters in the stepwise multiple regression analyses (see Table 3). The model revealed that the TSH_{AUC} at day-1 best explained the variation in ΔBW ($P < 0.05$, $F_{1,27} = 6.551$, ANOVA; $R^2 = .195$), but the model improved considerably in combination with baseline levels of free fatty acids ($P < 0.01$, $F_{2,26} = 8.726$, ANOVA; $R^2 = .313$).

3.4. Thyroid axis

Besides circulating OLZ levels, also the relative increase of the TSH response (TSH_{AUC}(%)) at day 13 ($P < 0.001$, $F_{2,26} = 24.684$, ANOVA; $R^2 = .655$), but not the TSH_{AUC} at day 13 per se, contributed to the relation between food intake and ΔBW . We also observed that TSH_{AUC}(%) on day 13 was not normally, but bimodally distributed ($P < 0.01$, $df_{30} = .914$, Shapiro–Wilk), we therefor decided to put the thyroid axis under closer inspection. We found that the total data set of basal circulating TSH at day-1 was also bimodally distributed ($P < 0.01$, $df_{30} = .897$, Shapiro–Wilk) with subjects having either a high or low level of TSH at day-1 (see Fig. 3A). On day-1, the magnitude of the TSH_{AUC} was highly correlated to the basal plasma TSH concentration at $t = 0$ (09:00 h day-1: $P < 0.001$, $r = .783$, Pearson 2-tailed). This shows that basal circulating TSH levels correspond with the TSH_{AUC} measured over 7 h (Fig. 3B). Due to this finding we decided to group the subjects accordingly into high ($> 2.0 \mu\text{IU/ml}$ TSH) and low ($< 2.0 \mu\text{IU/ml}$ TSH) TSH subgroups. The OLZ and OLZ + TPM subgroups each with a high TSH at day-1 had continuously high TSH_{AUC} profiles during the study period compared to the low TSH groups ($P < 0.01$, $F_{5,130} = 3.350$; rm-ANOVA, Fig. 3C). Inspection of the relative change of the TSH_{AUC}(%) during treatment revealed that the TSH_{AUC}(%) only increased in the OLZ-low TSH and OLZ + TPM-low TSH subgroups ($P < 0.01$, $F_{5,130} = 3.374$; rm-ANOVA, Fig. 3D).

The T3_{AUC} profiles were not affected by TPM treatment, and baseline levels were unlike the TSH_{AUC} normally distributed (Fig. 3C). Nevertheless, when segregated according to “high TSH” and “low TSH” profound elevations in T3_{AUC}(%) profiles during treatment were found in the low TSH_{AUC} subgroups compared to both high TSH subgroups ($P < 0.01$, $F_{5,130} = 3.917$, rmANOVA). In particular the OLZ-low TSH subgroup showed a higher T3_{AUC} compared to the OLZ-high TSH_{AUC} subgroup at day 13 ($P < 0.05$, $F_{3,29} = 2.428$, post hoc LSD) and day 14 ($P < 0.05$, $F_{3,29} = 2.375$, post hoc LSD, see Fig. 3E). The relative change of T3_{AUC}(%) during treatment (Fig. 3F) was only increased in the low TSH_{AUC} subgroups ($P < 0.01$, $F_{5,130} = 3.574$, rmANOVA). Within-group analyses did not reveal a change in relative T3 levels in the high TSH_{AUC} groups, whereas in the low TSH_{AUC} groups (and particular when treated with OLZ alone) within-group effects of relatively increased T3 values were observed. T4_{AUC} profiles, segregated accordingly on low or high TSH_{AUC} at day-1, did not reveal differences between groups (see Appendix A2).

Even though TSH_{AUC} profiles at day-1 were not significantly different between treatment groups (Fig. 3A: OLZ = 6.40 ± 0.92 AUC; OLZ + TPM = 5.27 ± 0.76 AUC), adding the TSH_{AUC} profiles at day-1 as a covariate into the ANOVA analysis resulted in a difference in ΔBW at day 13 between OLZ and OLZ + TPM ($P < 0.05$, $F_{1,27} = 4.484$, ANCOVA). Inspection of ΔBW in the high and low TSH_{AUC} subgroups (see Fig. 4A) revealed that only subjects with a low baseline TSH_{AUC} gained weight on OLZ, whereas subjects with a high baseline TSH_{AUC} did not gain weight ($P < 0.001$, $F_{1,29} = 28.455$, oneway-ANOVA). Adjunctive TPM treatment reduced ΔBW in the subjects based on a low TSH profile (O + T-low TSH) compared to the OLZ-low TSH subjects. Repeated measures analyses revealed

Table 3

Multiple regression analyses showing stepwise parameters explain variation of the dependent variable.

Dependent	Δ BW (kg)			Δ HOMA			Δ Insulin (AUC)			Δ Glucose (AUC)			Food intake (kcal)		
	Ind.	F	P	Ind.	F	P	Ind.	F	P	Ind.	F	P	Ind.	F	P
1 ($F_{1,27}$)	TSH	6.551	0.016	Δ BW	10.599	0.003	Δ BW	7.11	0.013	Gluc	22.857	0	OLZ	9.515	0.005
2 ($F_{2,26}$)	FFA	8.726	0.001				LDL	6.114	0.007	Cpep	14.925	0	Temp	8.215	0.002

Dependent variables: Δ BW(kg) at day 13; Δ HOMA at day 6; Δ Insulin response (AUC, area under the curve) at day 14; Δ Glucose response (AUC) at day 14; food intake—total cumulative food intake during 14 day treatment.

Independent variables (Ind): TSH—TSH_{AUC} day-1; FFA—free fatty acid levels day-1; LDL: low density lipids levels day-1; Gluc—glucose response (AUC) at day-1; Cpep: C-peptide response (AUC) at day-1; OLZ—circulating OLZ levels at day 13–4 h; Temp: AUC of temperature response at day-1.

Fig. 3. Group segregation based on low or high baseline thyrotropin levels.

(A) Average basal TSH levels at day-1 are comparable in both the OLZ and OLZ + TPM treated group ($P=0.187$, $F_{1,29}=1.846$, oneway-ANOVA), but TSH levels are bimodally distributed over the total group ($P<0.01$, $df_{30}=897$, Shapiro–Wilk). Dividing subjects into high (>2 U/ml) and low (<2 U/ml) TSH subgroups shows a clear difference in basal TSH levels (** $P<0.001$, $F_{1,29}=30.526$, oneway-ANOVA). (B) TSH levels are continuously higher during day-1 in the high TSH subgroups compared to the low TSH subgroups (* $P<0.01$, $F_{9,78}=27.190$, rm-ANOVA post hoc LSD). (C) Thyrotropin (TSH) levels of OLZ and OLZ + TPM treated individuals expressed as AUC (area under the curve). Subjects were divided into high or low TSH subgroups according to the assessed at day-1 and were different over time (* $P<0.01$, rm-ANOVA). Adjunctive TPM did not affect TSH_{AUC} profiles during treatment. (D) Percentage change of TSH_{AUC} levels relative to day-1 (TSH_{AUC}(%)). During treatment TSH level increase relatively more in the low TSH subgroups compared to the high-TSH subgroups (* $P<0.05$, rm-ANOVA); between groups an increase was observed at day 13 and 14 in low TSH subgroups compared to the high TSH subgroups (# $P<0.05$, oneway-ANOVA post hoc LSD). (E) Triiodothyronine (T3) AUCs divided on the basis of high/low-TSH subgroups indicated in Panel A revealed an increase of T3-AUC values during treatment in the low-TSH subgroups (* $P<0.01$, rm-ANOVA). (F) T3_{AUC}(%) levels were increased during treatment only in the low-TSH subgroups (* $P<0.01$, rm-ANOVA). Within groups increases compared to day-1 of T3_{AUC} values (both AUC and %) were found at day 6, 13, and 14 (* $P<0.05$, ## $P<0.01$, paired *t*-test).

Fig. 4. Body weight distribution based on baseline TSH profiles.

(A) Segregation of subjects into OLZ or OLZ + TPM groups with high or low baseline daily TSH profiles. The high TSH profiles in both treatment groups were not associated with increased ΔBW . In contrast, subjects with a low baseline TSH profile increased ΔBW when treated with OLZ, but not when treated with OLZ + TPM ($\#P < 0.05$, post hoc LSD). At day 28, the OLZ-low TSH group increased ΔBW compared to all other groups ($\#P < 0.05$, post hoc LSD). (B) Segregation of individuals with either high or low TSH levels over the gain, stable and lose BW groups revealed that subjects in the Gain group consisted predominantly low-TSH subjects treated only with OLZ. Remarkably, also the Lose group consisted predominantly of subjects with low baseline TSH levels, but who were adjunctively treated with TPM ($P < 0.01$, Mann–Whitney U). No difference in rank distribution was observed for the high-TSH subgroups.

that ΔBW in the OLZ-low TSH subgroup was higher compared to all other groups ($P < 0.05$, $F_{6,52} = 2.710$, rm-ANOVA post hoc LSD). Specifically at day 13 ΔBW was increased in OLZ-low TSH compared to the OLZ-high TSH ($P < 0.05$) and the O + T-low TSH subgroups ($P < 0.05$, $F_{3,29} = 3.052$, ANOVA post hoc LSD); at day 28 of the study OLZ-low TSH subjects still had increased ΔBW s compared to all other groups ($P < 0.05$, $F_{3,29} = 3.232$, ANOVA post hoc LSD).

Ranking the TSH profiles over the ΔBW based tertiles (Fig. 4B) revealed that the “Gain” group consisted predominantly of OLZ-low TSH subjects, whereas the “Lose” group consisted largely of OLZ + TPM-low TSH subjects (mean rank: 11.50/5.67; $P < 0.01$, Mann–Whitney U). Subjects belonging to the high TSH subgroups did not differ in group distribution (mean rank: 7.83/8.25; $P = 0.838$).

As mentioned above, there was a positive correlation in the OLZ treated group between ΔBW (kg) at day 13 and the relative increase of $TSH_{AUC}(\%)$ at day 13 ($R^2 = 0.542$), which was absent in the TPM treated group. A similar, but weaker, correlation between ΔBW (kg) and the $T3_{AUC}(\%)$ at day 13 was observed exclusively in the OLZ treated group ($R^2 = 0.289$; $P < 0.05$, $F_{1,13} = 5.289$, ANOVA), meaning that in the OLZ treated subjects weight gain was related to an increase in both TSH_{AUC} and $T3_{AUC}$. Furthermore, increased $T3_{AUC}$ levels during treatment were directly correlated to increased TSH_{AUC} levels ($R^2 = 0.289$; $P < 0.01$, $F_{1,29} = 2.62$, ANOVA).

3.5. Temperature regulation.

The overall pattern of body temperature responses revealed that at the first day of treatment OLZ caused a hypothermic response, which was lost on the last day of treatment (see Fig. 5A). At day 1 compared to day-1, a within-group decrease in body temperature (ΔT ($^{\circ}C$)) was observed in both the OLZ ($P < 0.01$, $t_{14} = 4.927$) and the OLZ + TPM treated group ($P < 0.05$, $t_{14} = 2.851$, paired t -test); but not a between-group difference ($P = 0.117$, $F_{1,28} = 2.622$, oneway-ANOVA).

Within-group analyses of the ΔBW tertiles showed a decrease in ΔT at day 1 in the Gain ($P < 0.01$, $t_9 = 5.195$, paired t -test) and Lose ($P < 0.05$, $t_9 = 3.052$, paired t -test) group, but not in the Stable group. This resulted in a quadratic correlation between ΔT and ΔBW ($P < 0.05$, $F_{2,28} = 4.129$, ANOVA), revealing a U-shaped relation based on individuals losing and gaining weight having a more prominent hypothermic response compared to subjects with a relatively stable body weight during drug treatment (see Fig. 5B).

Based on the TSH_{AUC} profiles at day-1, within group analyses revealed that ΔT (Fig. 5C) was decreased at day 1 compared to day-1 in the OLZ-low TSH ($P < 0.01$, $t_8 = 5.143$, paired t -test) and OLZ + TPM-low TSH subgroups ($P < 0.05$, $t_9 = 2.466$, paired t -test), but not in the high TSH subgroups (due to high within group variation). A trend was observed for a lower ΔT in the OLZ-high TSH group ($P = 0.071$, $t_5 = 2.281$, paired t -test). Additionally, a negative correlation was observed between ΔT (day 1) and the relative increase of $T3_{AUC}(\%)$ at day 14 ($P < 0.05$, $r = -0.375$; Pearson 2-tailed). This reveals that individuals with a strong hypothermic response at day 1 have a relatively higher $T3_{AUC}$ at day 14 of treatment, which may be related to a thermoregulatory adaptive response.

4. Discussion

The most important findings in the present study are that (1) OLZ-induced body weight gain can be attenuated by the co-administration of TPM. (2) Induction of metabolic derangements (including increased meal-induced Δ insulin, HOMA, and morning plasma LDL) are primarily driven by OLZ-induced body weight gain, yet also body weight-independent effects of OLZ (irrespective of TPM treatment) exist. (3) Low basal TSH levels (i.e., already before the start of treatment) are found in subjects with relatively high body weight gain as a consequence of OLZ treatment, and (4) TPM appears to be especially effective in attenuating OLZ-induced weight gain in those subjects with a low basal TSH level. Although this study was carried out in healthy volunteers, this might potentially offer the use of basal TSH levels in drug naïve/free patients as a predictor for OLZ-treatment outcome, as well as a marker to consider implementation of adjunctive TPM treatment.

Distribution of all subjects into three equally sized BW groups of Gain, Stable, and Lose, according to Ascher-Svanum et al. (2005) (see Fig. 2C), revealed that the Gain group consisted of significantly more OLZ-treated than OLZ + TPM-treated subjects (7/10), whereas the Lose group predominantly consisted of OLZ + TPM-treated subjects (8/10). This is in line with the idea that OLZ induces weight gain indeed can be attenuated with adjunctive TPM. Multiple regression analyses revealed that increases in body weight during treatment most strongly explained the observed increases in HOMA, and meal-induced insulin excursion irrespective of treatment. Nonetheless, the BW Stable group surprisingly displayed the highest HOMA-IR during treatment and already had increased insulin

Fig. 5. Temperature responses.

(A) Δ Temperature of OLZ and OLZ + TPM treated groups; both groups showed a temperature decrease at day 1 of treatment compared to day-1. The hypothermic response was absent after 13 days of treatment. (B) Δ Temperature response based on body weight gain tertiles revealed that both the Gain and the Lose group decreased Δ temperature at day 1 compared to day-1, whereas temperature was not affected in the Stable group. (C) Δ Temperature responses of subgroups based on TSH profiles at day-1. Only the OLZ-low and TPM-low TSH-AUC groups showed a within-group reduction of Δ temperature at day 1 compared to day-1 of treatment (* $P < 0.05$, ** $P < 0.01$, paired t -test).

and C-peptide responses prior to treatment (see Appendix A1), which persisted throughout the duration of the study. This suggests that there is a subset of individuals not responsive to OLZ-induced weight gain, but vulnerable to OLZ-related metabolic disturbances. Thus, although OLZ-induced bodyweight gain is undoubtedly a primary factor driving metabolic disturbances, these data indicate that there are also metabolic disturbances by OLZ treatment (without or in combination with TPM) that are not per se driven by body weight gain.

Important for considering these results is the notion that neither the variation in circulating levels of OLZ or TPM, nor the -lack of- pharmacodynamical interaction could directly explain the observed variation in body weight gain and metabolic derangements. Interestingly, there was a negative correlation of circulating OLZ levels with total food intake irrespective of adjunctive TPM treatment, suggesting that high levels of OLZ would dampen weight gain by inhibition of food intake. Although we did not keep records of this, the included subjects frequently complained of sedation and sometimes nausea, and it may be speculated that higher circulating OLZ levels may have decreased the motivation to eat due to increased sedation or nausea. Circulating OLZ levels were also correlated with hypothermia, however, only in the subjects with adjunctive TPM treatment. While the use of OLZ has previously been associated with the induction of hypothermia before (Blass and Chuen, 2004; Evers et al., 2010; Kreuzer et al., 2012), our data hint toward the idea that TPM actually could worsen OLZ-induced hypothermia (Morrison et al., 1999), rather than that it would cause a relief of it. A finally important observation in our study was that the degree of the hypothermic response following OLZ treatment at day 1 was positively correlated to total food intake during treatment irrespective of TPM treatment, meaning that the initial hypothermic response to OLZ may be a marker for successive OLZ-induced hyperphagia and potentially body weight gain. Because the hypothermic response was most pronounced in both the 'Gain' and 'Lose' BW groups, whereas it was absent in the 'Stable' group, there are probably complex interactions (positive and negative) between OLZs and TPMs effects on sedation, hypothermia, and food intake that collectively determine body weight changes during treatment with these compounds.

An even earlier predictor of OLZ-induced weight gain (and the responsiveness to adjunctive TPM administration to counteract the obesogenic effects of OLZ treatment) was the basal TSH_{AUC} profile of subjects before treatment. The basal TSH levels prior to treatment within our subjects were within the normal range for adults: 0.55–4.78 μ IU/ml (mIU/l), but these levels were not normally distributed. In fact, it is noteworthy that there is an almost 10-fold difference within this normal range. The latter explains why total TSH did not increase above the normal range, because only those

individuals with low basal TSH levels increased TSH during treatment and this increase of TSH never exceeded the outer limits of the normal range. Overall our data complies with the theory that the bimodal distribution of circulating TSH levels may be related to an individual difference in the regulation of TSH secretion, which is linked to a differential vulnerability to develop metabolic and affective disorders (Loosen, 1985). Interestingly, the increase of TSH levels within the normal range is related to increases in dyslipidemia (Asvold et al., 2013) and may be linked to the increased insulin response accompanied by elevated LDL levels observed mainly in those subjects gaining weight. The latter also supports the notion that increased cholesteryl-ester trafficking from HDL to LDL is related to low -but normal- thyroid functioning in diabetes mellitus type II (Triolo et al., 2013).

In general, TSH is secreted from the adeno-pituitary and stimulates the secretion of T4 and T3 from the thyroid gland. The thyroid gland produces mainly T4 and a major part of circulating T3 is formed by the conversion of T4 into T3 by tissue specific deiodinases. In this study we were unable to discriminate between T3 secreted directly from the thyroid gland or extrathyroidal T3 synthesized from T4 using iodinases type I (liver, kidneys), type II (neuronal, pituitary, BAT), or reverse T3 formed from T4 by iodinase type III present in almost all tissue types (Roti et al., 2000). Therefore we can also not discriminate whether the increase in T3 levels is a direct consequence of increased TSH secretion, or an indirect effect of increased T4 to T3 conversion. Increased T3 levels are related to the increase of energy expenditure through the stimulation of lipolysis by increasing LDL receptor expression (Brenta et al., 2007), which speculatively may relate to an additionally observed positive correlation between Δ BW and circulating LDL levels at day 14 of treatment (Appendix Table A1). More thorough examination of OLZ on thyroid functioning and the possible effects of OLZ on T4 conversion and deiodinase expression is therefore warranted.

Pre-existing differences in TSH patterns between individuals could be a consequence of a difference in dopaminergic tone to inhibit TSH secretion at the level of the adeno-pituitary (Shupnik, 2000). Thus, we speculate that the dopaminergic suppression of TSH secretion is chronically higher in individuals with a low basal TSH_{AUC}—e.g., due to higher D2 receptor density- and therefore we only observe an increase of TSH and T3 levels in these specific individuals. High basal circulating TSH levels may be a consequence of low D2-receptor expression at the level of the adeno-pituitary and as a consequence Thyrotropin Releasing Hormone (TRH) is the dominant pathway stimulating TSH secretion. The effect of OLZ could be that it removes the brake on TSH secretion, through D2-receptor inhibition, and consequently increases circulating TSH levels specifically in those individuals in which the dopaminergic inhibition of TSH secretion is potentiated under normal conditions.

This hypothesis is further supported by the combined data of [Larsen et al. \(2004\)](#) demonstrating a negative correlation between basal TSH and mania, and the work of [Lee et al. \(2005\)](#) and [Pearlson et al. \(1995\)](#), who respectively demonstrated a positive correlation between neuroticism, mania and central D2-receptor densities. Furthermore, [Rao et al. \(1984\)](#) found that dopamine was elevated in the sera of schizophrenic patients, whereas the daily levels of TSH were decreased. [Frey et al. \(2007\)](#) observed that TSH is bimodally distributed and negatively correlated to neuroticism. [Langer et al. \(1986\)](#) showing that patients with a 'blunted' TSH response to intravenous TRH administration had a better improvement of the brief psychiatric rating scale (BPRS) due to treatment with a neuroleptic agent, compared to subjects with a relatively high TSH response. Altogether these data demonstrate that the usefulness of a TSH test in clinical psychiatric practice ([Loosen et al., 1987](#)) deserves new attention in the search for personalized medication, especially in a disease like schizophrenia that consists of multiple disease phenotypes related to dopaminergic signaling (e.g., positive vs negative symptoms).

As mentioned earlier, others ([Basson et al., 2001](#); [Kinon et al., 2005](#)) have already reported that only a sub-population of schizophrenic patients is susceptible to OLZ-induced rapid weight gain, and additionally found that OLZ-induced weight gain is associated with an improvement of the BPRS scale. Altogether it suggests that weight gain is a predictor for treatment responsiveness and therapeutic efficacy. Unfortunately, body weight gain is also a major threat to treatment compliance. Therefore our observation that specifically subjects susceptible for weight gain—characterized by low TSH levels—are also responsive to adjunctive TPM treatment is of key importance: i.e., blocking weight gain and protecting HOMA-IR and insulin levels, and possibly improving treatment compliance within a group responsive to the psychiatric benefits of OLZ treatment.

4.1. Perspectives and limitations

In this study we found that basal TSH_{AUC} in healthy drug naive subjects predicted the variation in Δ BW after 13 days of OLZ treatment the best, but also basal TSH levels per se were predictive for the Δ BW after 13 days of treatment. As is shown in [Fig. 1B](#) the difference in TSH levels between high- or low-TSH individuals is stable throughout the 7 h we measured. As a result the resolution of the TSH_{AUC} is higher and therefore gave more statistical power. For clinical purpose, however, it may be more convenient to only measure basal overnight fasted TSH levels. Our data suggests that basal TSH levels are directly related to daily TSH_{AUC} profiles, and therefore should be a valid measure for the prediction of OLZ-induced weight gain. A comparable study focusing on the relation between basal TSH levels and OLZ-induced weight gain and metabolic disturbances should therefore be performed in a larger sample for a longer period and above all in the patient population.

The lack of power due to small group size is possibly also present in the effect of TPM to attenuate OLZ-induced body weight gain. Nonetheless, we did observe that TPM does reduce the amount of weight gain due to OLZ treatment. The effectiveness of TPM as an adjunctive treatment to OLZ has extensively been studied by [Vieta et al. \(2004\)](#), who reported that the beneficial effects of adjunctive TPM treatment was optimal when titrated to app. 300 mg/day, and concomitantly reducing OLZ dosing below 10 mg/day ([Vieta et al., 2004](#)). The idea that adjunctive TPM treatment allows for a reduction in OLZ dosing without losing treatment efficacy is important, given the potentially negative side effects of OLZ (i.e., hypothermia and sedation) at high doses. We did not find an interaction between pharmacodynamics of OLZ and TPM at the concentration used in this study, but interactions at higher dosages should not be ruled out. Precaution and well-adjusted titration of drug dosages should

be advised in the use of adjunctive TPM treatment, as was shown in a case study where OLZ and adjunctive TPM treatment could lead to acute hyperthermia in high ambient temperatures ([Strawn et al., 2008](#)). Additionally, [Vieta et al. \(2004\)](#) reported an improvement of the BPRS score in subjects co-treated with TPM ([Vieta et al., 2004](#)). This results in two questions that have to be addressed in future studies: (1) does adjunctive TPM treatment have additive clinical efficacy to OLZ treatment, (2) is TPM predominantly effective in inhibiting OLZ-induced weight gain in individuals most responsive to OLZ's antipsychotic actions. Finally, the hypothesis that neuroendocrine challenges are predictive of antipsychotic treatment outcome, and could therefore be part of clinical psychiatric diagnosis, is of great relevance and deserves further exploration.

Conflict of interest

The authors declare to have no conflict of interest relevant to the data presented in this article.

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Contributors

S.S.E collected data, performed analyses, set up hypotheses and wrote the manuscript. A.v.V. set up the study and managed on site treatment protocols plus reviewed/edited the manuscript. B.v.V. managed on site study and data collection. A.J.W.S helped setting up and supervised the study. G.v.D. set up and analyzed energy metabolic studies, helped analyzing the data and setting up hypotheses plus reviewed/edited the manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.psyneuen.2015.12.024>.

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