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Original Investigation | Published: 23 November 2020

The usefulness of Olanzapine plasma concentrations in monitoring treatment efficacy and metabolic disturbances in first-episode psychosis

J. A. Arnaiz, C. Rodrigues-Silva, G. Mezquida, S. Amoretti, M. J. Cuesta, D. Fraguas, A. Lobo, A. González-Pinto, M. C. Díaz-Caneja, I. Corripio, E. Vieta, I. Baeza, A. Mané, C. García-Rizo, M. Bioque, J. Saiz, M. Bernardo, S. Mas ✉ & PEPs group

Psychopharmacology **238**, 665–676 (2021)

Abstract

Introduction

The role of Olanzapine therapeutic drug monitoring is controversial. The present study explores the associations of Olanzapine plasma concentrations with clinical response and metabolic side effects in first episode psychosis (FEP) after 2 months of treatment.

Methods

Forty-seven patients were included. Improvement in clinical symptomatology was assessed using the PANSS. Metabolic assessment included weight, blood pressure, waist circumference, blood glucose,

Results

The Olanzapine plasma concentrations after 2 months of treatment were positively correlated with weight gain (r = 0.49, p = 0.003), and a concentration > 23.28 ng/mL was identified as a positive predictor of weight gain (≥ 7%). The Olanzapine concentration to dose (C/D) ratio was positively correlated with the percentage of improvement in the total PANSS (r = 0.46, p = 0.004), and a C/D ratio > 2.12 was identified as a positive predictor of a good response (percentage of improvement > 30%) after 2 months of treatment. We also identified several factors that could alter Olanzapine pharmacokinetics: gender (p = 0.03), diagnosis (p = 0.05), smoking habit (p = 0.05), and co-medications such as valproic acid (p = 0.05) and anxiolytics (p = 0.01).

Discussion

In conclusion, our results suggest that therapeutic drug monitoring of Olanzapine could be helpful to evaluate therapeutic efficacy and metabolic dysfunction in FEP patients treated with Olanzapine.

Introduction

schizophrenia and the World Federation of Biological Psychiatry suggests it as a first-line therapeutic option (Hasan et al. 2013). Several pharmacological guidelines for schizophrenia treatment also recommend Olanzapine as one of the two non-clozapine AP trials before a trial of clozapine is considered in first-episode psychosis (FEP) patients (Keating et al. 2017). Olanzapine is effective in the acute reduction of psychopathological symptoms in FEP patients, showing relative advantages in therapeutic response in comparison to other APs with higher rates of treatment retention or longer times to drug discontinuation (Lieberman et al. 2003; Kahn et al. 2008; Green et al. 2006). Nevertheless, Olanzapine treatment is associated with a higher risk of weight gain and metabolic effects than other typical and atypical APs are (Lambert et al. 2005; Duggan et al. 2005; Fernandez-Egea et al. 2011; Arango et al. 2014); for this reason, some guidelines do not recommend Olanzapine as a first-line option (Buchanan et al. 2010; Nguyen et al. 2020).

Olanzapine exhibits large inter-individual variability in pharmacokinetics (up to 10-fold) (Polasek et al. 2018). The intrinsic and extrinsic factors that could explain this variability include ethnicity, gender, age, Olanzapine dose, co-medication, smoker status, and intrinsic inter-individual variability in drug metabolism or

Olanzapine is almost entirely eliminated by metabolism: predominantly by CYP1A2, CYP2C8, and UGT1A4 (Korprasertthaworn et al. 2015), and to a lesser extent by CYP2D6 (Callaghan et al. 1999).

Given the large inter-patient variability in plasma Olanzapine concentrations at the same dose, the monitoring of blood Olanzapine concentration can be very useful in assessing therapeutic efficacy and avoiding adverse events (Mauri et al. 2018). In order to ensure Olanzapine effectiveness and minimize adverse reactions, the consensus guidelines of the Therapeutic Drug Monitoring (TDM) group of the Arbeitsgemeinschaft fur Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) suggest that Olanzapine-treated undergo TDM and recommend Olanzapine concentrations ranging from 20 to 80 ng/mL (Hiemke et al. 2018).

However, the role of TDM is controversial both in terms of Olanzapine efficacy (Citrome et al. 2009; Fellows et al. 2003; Perry et al. 2001; Zabala et al. 2017; Lane et al. 2002; Lu et al. 2016; Mauri et al. 2005; Perry et al. 1997) and of Olanzapine-induced adverse effects (Citrome et al. 2009; Lu et al. 2016; Kelly et al. 2006; Perry et al. 2005; Skogh et al. 2002). The management of metabolic disturbances is especially relevant taking into account the

people with schizophrenia have metabolic syndrome, and the prevalence of obesity, type 2 diabetes, and hypercholesterolemia is 3 to 5 times higher in schizophrenia patients than in the general population (Pillinger et al. 2020). Moreover, people with schizophrenia compared to general population have double risk to have a diagnosis and die as a consequence of cardiovascular disease (Olfson et al. 2015). Interestingly, although antipsychotic medication has been related to the metabolic alterations observed in schizophrenia, accumulating evidence shows the presence of metabolic dysregulation in drug naïve patients with a FEP and their relatives (Garcia-Rizo et al., 2017; Fernandez-Egea et al. 2008; Garcia-Rizo et al. 2017).

Studies of Olanzapine TDM have mostly been of chronic schizophrenia patients, with a few exceptions (Zabala et al. 2017). Taking into account that FEP patients tend to be more sensitive to the effects of APs and more vulnerable to side effects (Fernandez-Egea et al. 2011; Arango et al. 2014), together with the importance of early treatment of these patients to improve outcomes and prevent deterioration, it is especially important to develop TDM studies in FEP patients. Therefore, the aims of the present study are to explore the associations of Olanzapine plasma concentrations with clinical response and metabolic side effects in a naturalistic

affect Olanzapine plasma concentrations.

Material and methods

This study is part of the project "Phenotype–genotype interaction: application of a predictive model in first-episode psychosis, FIS PI080208" (known as the PEPs study, from the Spanish abbreviation for first-episode psychosis). A complete description of the protocol for the PEPs study has been published previously (Bernardo et al. 2013; Bioque et al. 2016; Mas et al. 2017; Bioque et al. 2018). The 16 centers participating in the PEPs project recruited a total of 335 patients with a FEP from April 2009 to April 2012. Patients were recruited from 16 centers located throughout the Spanish territory with experience in performing and assessing diagnoses, in the use of semi-structured interviews and clinical scales, and in treating this population. The PEPs study was carried out in the context of the Center for Biomedical Network Research on Mental health (CIBERSAM), the leading scientific institution devoted to mental health research in Spain (Salagre et al. 2019; Bernardo et al. 2019). Every patient who met the inclusion criteria and was attended at these facilities during the recruitment period was invited to participate in the study on either an inpatient or outpatient basis. The inclusion criteria for patients were as follows: age between 7 and 35

week duration in the last 12 months, and speak Spanish correctly. The exclusion criteria for patients were as follows: (1) mental retardation according to the Diagnostic and Statistical Manual of mental disorders, 4th edition (DSM-IV), (2) history of head trauma with loss of consciousness, and (3) presence of an organic disease with mental repercussions.

Participants

During the recruitment period (2009–2012), 335 subjects who presented FEP were included in the PEPs study. From that initial FEP sample, 302 participants were prescribed at least one AP during the follow-up period. Of these, 234 (77.5%) participated in the pharmacogenetic and therapeutic module of the study, and 174 (74.3%) of the participants in this module provided blood samples for the determination of AP plasma level. Of these 174 FEP patients, 47 (27.0%) were treated with Olanzapine during the first 2 months of the follow-up period, and were included in the present study (age range 17–36 years). Being a naturalistic study, there were no specific guidelines for treatment, so patients received AP treatment based on the clinician's decision. Co-medications and treatment changes were based only on clinical necessity, and a flexible dose regime was allowed. Prior treatment with APs did not exceed 12 months

and informed consent was obtained from all the participants or their legal guardians.

Clinical assessment

As a measurement of AP efficacy, improvement in clinical symptomatology was assessed using the Spanish validated version of the PANSS (Peralta and Cuesta 1994), a semi-structured interview with 30 items rated on a 7-point scale. The PANSS results were collected at each visit during the PEPs study. The current study is focused on data from 2 months of follow-up. The clinical response after 2 months of Olanzapine treatment was evaluated using the percentage of improvement from baseline according to total PANSS scores: $((PANSS_{2months} - PANSS_{basal}) / PANSS_{basal}) \times 100$. For the nonparametric ROC curve analysis, response to treatment was defined as a decrease of at least 30% in the PANSS total score from baseline, based on the strong support of these criteria (Zabala et al. 2017).

Metabolic assessment

Several anthropometric and metabolic traits were measured at baseline and at 2, 6, 12, and 24 months, including body weight, blood pressure, waist circumference visit, blood glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL)

were directly analyzed by enzymatic procedures with an Automatic Chemical Analyzer. The current study is focused on data from 2 months of follow-up. The metabolic response after 2 months of Olanzapine treatment was evaluated using the percentage of change of each metabolic parameter. For the nonparametric ROC curve analysis, a threshold for weight gain of 7% was chosen to be consistent with the Olanzapine prescribing information regarding weight gain (Perry et al. 2005).

Olanzapine and desmethyl-Olanzapine determination

At 60 days after being included in the PEPs study, we collected pre-dose and fasting blood samples from patients between 08:00 and 10:00 h. Plasma was stored at − 30 °C until analysis.

Plasma concentrations of Olanzapine and its metabolite desmethyl-Olanzapine (DMO) were measured by a simple isocratic high-performance liquid chromatography system, with UV diode array detection and selective solid-phase extraction (Dusci et al. 2002). To assure high precision and accuracy of the method, an internal standard is included in the sample preparation and quantitative evaluation. The within- and between-day precision expressed as coefficient of variation (CV)% were < 10%. The limit of quantification

external quality assessment.

Using the concentration results, we extrapolated the steady-state C_{min} using the equation $C_{min} = Ct \times e^{-ke(tmin - t)}$ as described elsewhere (Hiemke et al. 2018; Gex-Fabry et al. 2003), where Ct is the drug concentration measured at time t, t_{min} the time at C_{min} and ke the elimination rate constant ($ke = \ln 2/t_{1/2}$) (Olanzapine $t_{1/2}$ = 33 h) (Hiemke et al. 2018; Gex-Fabry et al. 2003). We computed a concentration/dose (C/D) ratio by dividing the total concentration of Olanzapine or DMO, in ng/mL, by the Olanzapine dose, in mg/day. This C/D ratio is considered an index of the total capacity to eliminate Olanzapine. Lower values are related to an increased capacity to eliminate Olanzapine (i.e., CYP inducers), whereas higher values are related to an impaired capacity to eliminate Olanzapine (i.e., CYP inhibitors).

Cytochrome genotyping

Samples were genotyped at the Santiago de Compostela node of the **Spanish National Genotyping Centre (CeGen)** using the iPLEX ADME PGx multiplex panel (Sequenom, Inc., San Diego, CA, USA). SNPs from the panel that failed in the sample or had excessive missing genotypes were also analyzed using commercially available TaqMan® assays (Applied Biosystems, Foster City,

deletion using TaqMan® Copy Number Assays. All TaqMan® analyses were carried out at the Clinical Research Center of the Extremadura University Hospital Medical School (Badajoz, Spain). The Cytochrome (CYP) allele designations refer to those defined by the Cytochrome P450 Allele Nomenclature Committee (http://www.cypalleles.ki.se/). The activity score was computed and the phenotype was extrapolated based on the genotype obtained (Gaedigk et al. 2008; Swen et al. 2012).

Statistical analysis

Data were analyzed using SPSS 20.0 (statistical analysis software, IBM, Chicago, IL, USA). Two-tailed p values < 0.05 were considered to be of statistical significance. Means and standard deviations were computed for continuous variables. The normality of continuous variables was tested using the Kolmogorov–Smirnov and Shapiro–Wilk tests, and the equality of the variance between groups was assessed using Levene's test. Olanzapine and DMO plasma concentrations together with the computed ratios were not normally distributed; therefore, the Mann–Whitney U test or Kruskal–Wallis test was conducted to compare groups. If the overall null hypothesis was rejected, pairwise tests of the differences between groups were performed via the

Olanzapine C/D ratio or Olanzapine concentrations were tested using a multiple linear regression model, following a stepwise approach using a backward method. The association between plasma concentrations or ratios and clinical improvement or metabolic profiles was analyzed using the Spearman rank correlation coefficient. In cases where significant correlations were detected, nonparametric ROC curve analysis was conducted to determine optimum breakpoints as response markers. Olanzapine doses, concentrations, and C/D ratio are given as median and interquartile ranges.

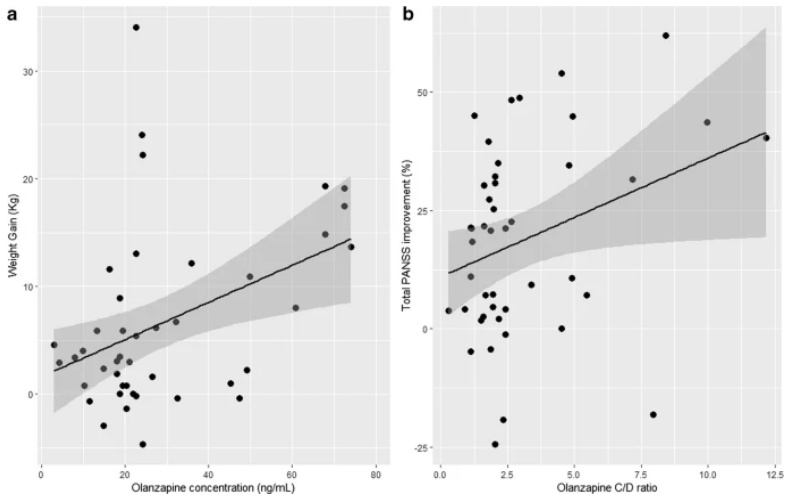
Results

Demographic, clinical, pharmacological, and metabolic data are presented in Table 1. The correlations between drug levels and clinical response or metabolic parameters are shown in Table 2. Olanzapine concentration positively correlates with weight gain after 2 months of Olanzapine treatment ($p = 0.003$), and the Olanzapine C/D ratio positively correlates with the percentage response according to total PANSS scores ($p = 0.004$) (Fig. 1).

Table 1 Demographic, clinical, pharmacological, and metabolic data of study subjects

correlation tests for percentage improvement in clinical response and metabolic measures with levels of Olanzapine and DMO. Italicized values are significant correlations

Fig. 1



Scatter-plot showing the positive relationship between: a Olanzapine concentration and weight gain (kg) after 2 months of treatment(r = 0.49, p = 0.003); and b Olanzapine C/D ratio and the percentage of total PANSS improvement after 2 months of treatment (r = 0.46, p = 0.004).

We dichotomized weight gain using a cut-off value of 7% to determine the Olanzapine plasma concentration threshold using ROC analysis. An Olanzapine concentration > 23.28 ng/uL (AUC = 0.77 ± 0.07; sensitivity, 0.75; specificity, 0.65) was identified as a positive predictor of weight gain. The

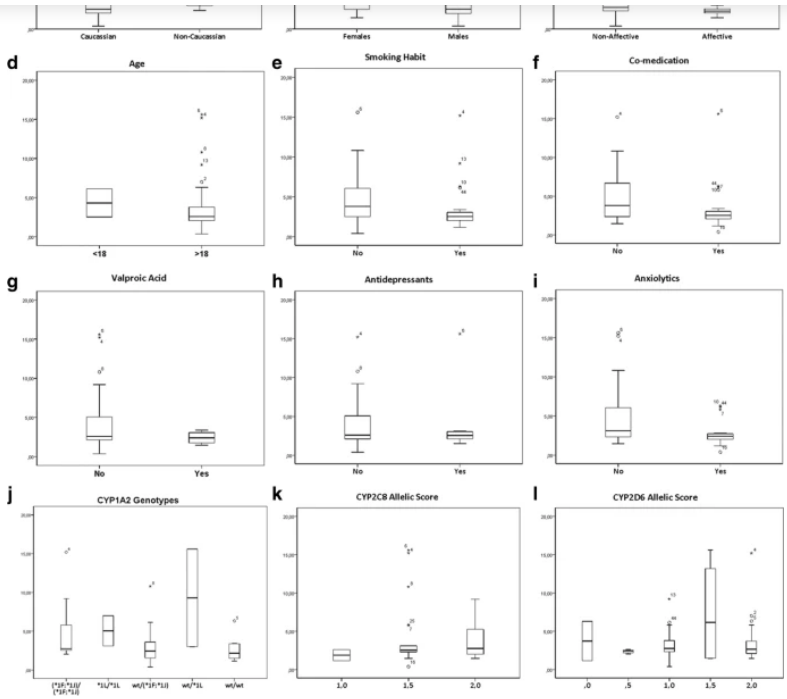
ng/mL) than in the < 7% weight gain group (N = 33, 20 ± 16 ng/mL) (U = 216, p = 0.006). Patients with ≥ 7% weight gain were treated with a significantly higher dosage (15 ± 14 vs. 10 ± 5 ng/mL, U = 315.5, p = 0.024) and presented lower baseline weight (62 ± 9 vs. 75 ± 13 kg, U = 79.0 p = 0.001) than the group of patients with < 7% weight gain.

To establish the C/D ratio threshold predictor of clinical response, > 30% response in the total PANSS score was used in the ROC analysis. A C/D ratio > 2.12 (AUC = 0.72 ± 0.08; sensitivity, 0.66; specificity, 0.62) was identified as a positive predictor of good response. Patients with a good response presented a 103% higher Olanzapine C/D ratio (N = 15, 3 ± 5) than patients with a poor response (N = 32, 2 ± 1) (U = 216, p = 0.011). Non-significant differences were found in dosage (U = 167.0, p = 0.086) and total PANSS score at baseline (U = 317 p = 0.07) between responders (dose, 5 ± 10 ng/mL; PANSS, 79 ± 19) or non-responders (dose, 10 ± 10 ng/mL; PANSS, 68 ± 24).

In order to identify those factors that alter Olanzapine pharmacokinetics, we used the Olanzapine C/D ratio. Figure 2 shows Olanzapine C/D ratio distribution, according to the variables tested: age, ethnicity, gender, diagnosis, smoking habit, co-medication (valproic acid, anxiolytics, or

was significantly higher in females (3 ± 6) than males (2 ± 1) (U = 145, p = 0.03); non-affective psychotic patients (2 ± 3) than affective (2 ± 1) (U = 161, p = 0.05); non-smokers (3 ± 3) than smokers (2 ± 1) (U = 161, p = 0.05); patients not using anxiolytics (3 ± 4) than those using anxiolytics (2 ± 1) (U = 149, p = 0.01); and patients treated with valproic acid (2 ± 3) than those not treated with valproic acid (2 ± 1) (U = 161, p = 0.05). However, when these variables were included in a linear regression model, only gender (β = − 2.44 ± 1.08, t = − 2.25, p = 0.030) and anxiolytics (β = − 1.98 ± 0.94, t = − 2.09, p = 0.042) significantly accounted in part for the variability detected in the Olanzapine C/D ratio (R^2 = 0.198). We also tested whether these variables explained the observed variability in Olanzapine plasma concentrations: they were included in a linear regression model jointly with Olanzapine dose. Only Olanzapine dose (β = 1.45 ± 0.33, t = 4.39, p < 0.001) and ethnicity (β = 20.98 ± 8.66, t = 2.42, p = 0.020) remained significant in the model (R^2 = 0.407).

Fig. 2



Box plots showing the impact of the following covariates on Olanzapine C/D ratio: **a** ethnicity; **b** sex; **c** diagnosis; **d** age; **e** smoking habit; **f** co-medication; **g** valproic acid; **h** antidepressants; **i** anxiolytics; **j** *CYP1A2* genotype; **k** *CYP2C8* allelic score; **l** *CYP2D6* allelic score. The bars represented the upper and lower quartiles, the mean (lines in the bars) and the 95% confidence intervals from data

Discussion

The aim of the present study was to explore the roles of Olanzapine plasma concentration in response outcomes, including both clinical response and metabolic disturbances in FEP patients treated with Olanzapine for 2 months. The Olanzapine plasma concentrations were positively correlated with weight gain, and a concentration >

was positively correlated with the percentage of improvement in the total PANSS score, and a C/D ratio > 2.12 was identified as a positive predictor of a good response (percentage of improvement in total PANSS score > 30%). We also identified several factors that could alter Olanzapine pharmacokinetics: sex, diagnosis, smoking habit, and co-medications (anxiolytics and valproic acid). However, only gender and co-medication with anxiolytics explained some (a small percentage) of the observed variability in the Olanzapine C/D ratio. Moreover, the observed variability in Olanzapine plasma concentrations was mainly attributable to dosage and ethnicity.

The relationship between Olanzapine concentrations and metabolic disturbances, mainly weight gain, remains highly controversial. Several studies have found no significant relationship between Olanzapine levels and weight gain (Citrome et al. 2009; Kelly et al. 2006; Lu et al. 2013, 2018). One study reported an Olanzapine concentration threshold of 20.6 ng/uL above which it was associated with significant weight gain (> 7%) during Olanzapine therapy (Perry et al. 2005). In our study, we found a significant correlation between Olanzapine concentration and weight gain, and a threshold of 23.28 ng/mL was the best predictor of significant weight gain (> 7%). Although this threshold is significantly higher than

may be accounted for by differences in study design. While Perry et al.'s (Perry et al. 2005) was a retrospective study of chronically ill patients, ours was a longitudinal study, under naturalistic settings, including FEP patients with less than a year of AP treatment. In addition, differences in age, sex, and monitoring period should be noted, as the Perry et al. (Perry et al. 2005) study was performed with older patients (36.0 ± 8.8 years), mainly male (78%) and follow-up was for only 6 weeks. One of the main explanations for the lack of drug concentration-effect relationship is the use of retrospective analysis of flexible–dose studies or of TDM databases from clinical routine (Hiemke 2019). In case of flexible doses, the presence of non-responders (that will receive high doses resulting in high drug concentrations in blood) and the presence of placebo responders (that will be treated with lower doses) could mask the concentration-effect relationship or even could result in negative correlations (Hiemke 2019).

Several studies reported negative correlations between DMO levels, or the DMO C/D or Olanzapine /DMO ratios and metabolic dysfunction (Lu et al. 2013, 2018; Melkersson & Dahl, 2003 and Melkersson et al, 2000). DMO concentrations > 5.63 ng/mL or a DMO C/D ratio > 0.35 ng/mL has been associated with a reduced risk of metabolic disturbances (Lu et al. 2018). In our study, we

The role of TDM in the determination of clinical response is similarly still controversial. While several studies found no significant correlations between Olanzapine plasma concentrations and clinical improvement (Citrome et al. 2009; Fellows et al. 2003; Perry et al. 2001; Zabala et al. 2017), others did detect such associations (Lane et al. 2002; Lu et al. 2016; Mauri et al. 2005; Perry et al. 1997). According to these latter studies, there is an increased probability of response with Olanzapine plasma concentrations ranging from 22.7 to 23.2 ng/mL (Fellows et al. 2003; Perry et al. 2001; Lu et al. 2016) for chronic schizophrenia patients, or 34.3 ng/mL for FEP patients (Zabala et al. 2017). Several studies reported a curvilinear relationship between OLZ concentrations and improved symptoms (Zabala et al. 2017; Mauri et al. 2005; Perry et al. 1997). In our study, our data did not fit the quadratic model (maybe because none of the patients was over the therapeutic range (> 80 ng/mL)), and we did not detect significant correlations between OLZ plasma concentrations and clinical improvement. However, when OLZ levels were normalized using dosage, determined as the OLZ C/D ratio, we detected a significant correlation with the percentage of response according to total PANSS scores. Lower C/D ratio could reflect impaired drug clearance, drug interactions, or lack of adherence. We could

study. Using ROC analysis, we identified an Olanzapine C/D ratio threshold of 2.12 as a predictor: greater values indicated a good response. We are unable to compare this threshold with previous studies as they focused exclusively on Olanzapine plasma concentrations and C/D ratios were not computed.

A recent meta-analysis by Pillinger already highlighted a historical aspect of psychiatric pharmacology, the association between clinical improvement and weight gain (Pillinger et al. 2020). Indeed, another recent article reviews the existing literature regarding symptomatology and weight under olanzapine treatment while suggesting the role of the gut-brain axis as a possible pathway underlying both conditions (Garcia-Rizo 2020).

As for the variables affecting Olanzapine pharmacokinetics, our results seem to be consistent with those obtained in chronic patients. Women seem to have higher Olanzapine concentrations than men (Seeman 2004), although the exact mechanism behind this is unknown. Clearance of Olanzapine in women appears to be slower than in men (Bigos et al. 2008) and this may be explained to a certain extent by the ability of feminine sex steroids to inhibit CYP3A4 activity (Laine et al. 2003). Smokers treated with Olanzapine showed

this may be due to the induction of CYP1A2 activity (Gex-Fabry et al. 2003). Valproic acid has been shown to reduce Olanzapine concentrations, and this interaction involves a presystemic mechanism (Tveito et al. 2019). The combination of Olanzapine and valproic acid is regularly prescribed in the treatment of bipolar or schizoaffective disorders (Vieta et al. 2018), and this could explain the observed differences in Olanzapine C/D ratios between affective and non-affective FEP patients in our study. None of the genes involved in Olanzapine metabolism included in the present study (*CYP1A2*, *CYP2C8*, and *CYP2D6*) seems to affect Olanzapine pharmacokinetics significantly. The small sample size of our study and the complex Olanzapine metabolism including several pathways could explain the lack of any significant association.

In conclusion, our results show significant correlations of Olanzapine concentrations or Olanzapine C/D ratios with weight gain and clinical improvement after 2 months of treatment. This suggests that TDM of Olanzapine could be helpful to evaluate the therapeutic efficacy and metabolic dysfunction in FEP patients treated with Olanzapine. Moreover, TDM could be useful to identify non-compliance and thus prevent relapse and patient deterioration, which are especially relevant in FEP patients.

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Acknowledgements

080208, PI10/00,283 and PI14/00,612)—Instituto de Salud Carlos III—Fondo Europeo de Desarrollo Regional (FEDER)-Unión Europea; the Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM); and by the CERCA Programme / the Government of Catalonia, Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2017SGR1562; 2017SGR1355; 2017SGR881). Dr. Vieta thanks the support of the Spanish Ministry of Science, Innovation and Universities (PI15/00283) integrated into the Plan Nacional de I+D+I y cofinanciado por el ISCIII-Subdirección General de Evaluación y el Fondo Europeo de Desarrollo Regional (FEDER); CIBERSAM; and the Comissionat per a Universitats i Recerca del DIUE de la Generalitat de Catalunya to the Bipolar Disorders Group (2017 SGR 1365) and the project SLT006/17/00357, from PERIS 2016-2020 (Departament de Salut). CERCA Programme/Generalitat de Catalunya.

PEPs Group: Torra, Mercè (Pharmacology and Toxicology Department, CDB, Hospital Clínic de Barcelona, Barcelona, Spain); Llerena, Adrian (CICAB Clinical Research Center, Extremadura University Hospital and Medical School, Servicio Extremeño de Salud, Badajoz, Spain. CIBERSAM, Spain); Anmella, Gerard and Colomer, Lluc (Hospital Clinic of Barceo Neuroscience Institute, ; IDIBAPS; CIBERSAM, Barcelona, Spain); Moreno,

Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), School of Medicine, Universidad Complutense, Madrid, Spain; CIBERSAM, Madrid, Spain); Alonso Solís, Anna and Grasa, Eva (Biomedical Research Institute Sant Pau (IIB-SANT PAU), Hospital de la Santa Creu i Sant Pau; Universitat Autònoma de Barcelona (UAB), Barcelona, Spain. Mental Health Networking Biomedical Research Centre, CIBERSAM); Lopez, Puri and García, Sainza (Department of Psychiatry, Hospital Universitario de Alava, Vitoria, Spain; Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Spain); De-la-Cámara, Concepción (Hospital Clínico Universitario and Instituto de Investigación Sanitaria (IIS) Aragón, Zaragoza. Department of Medicine and Psychiatry; Universidad de Zaragoza; CIBERSAM, Spain); Saz, Pedro (Department of Medicine and Psychiatry, Zaragoza University; Instituto de Investigación Sanitaria Aragón (IIS Aragón), Zaragoza); Moltó, Maria Dolores Department of Genetics, University of Valencia, Campus of Burjassot, Valencia, Spain. CIBERSAM; Biomedical Research Institute INCLIVA, Valencia, Spain; Hernandez Viadel, Miguel (Department of Psychiatry, Cinical Hospital of Valencia, Valencia, Spain. CIBERSAM, Spain; Biomedical Research Institute INCLIVA, Valencia, Spain) ; Casanovas, Francesc and SanAgustin, David (Hospital del Mar

(Department of Child and Adolescent Psychiatry and Psychology, Clínic Institute of Neurosciences, Hospital Clínic de Barcelona, 2017SGR881, University of Barcelona, CIBERSAM, IDIBAPS, Barcelona, Spain); Contreras, Fernando and Saiz, Cristina (Psychiatric Service, Bellvitge Universitary Hospital, IDIBELL, University of Barcelona, CIBERSAM); Bobes, Julio and García-Portilla, María Paz (Área de Psiquiatría, Universidad de Oviedo, Hospital Universitario Central de Asturias (HUCA); Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Spain; Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Spain); Gutierrez Fraile, Miguel (Araba University Hospital, Bioaraba Research Institute, Psychiatry, Vitoria, Spain; University of the Basque Country (UPV/EHU), Department of Neurosciences; CIBERSAM); Zabala Rabadán, Arantzazu (UPV/EHU, Department of Neurosciences; CIBERSAM; BioCruces Health Research Institute, Vizcaya, Spain.); Rodríguez-Jimenez, Roberto (Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), Madrid, Spain; CIBERSAM; CogPsy Group, Universidad Complutense de Madrid (UCM), Madrid, Spain); Fares-Otero, Natalia E. (Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), Madrid, Spain); Usall, Judith (Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), Madrid, Spain); Butjosa, Anna (Research and Development

Sant Joan de Déu, Esplugues de Llobregat, Barcelona, Catalonia); Sarró, Salvador and Pomarol-Clotet, Edith (FIDMAG Germanes Hospitalàries Research Foundation , Barcelona, Spain. Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM); Ibañez. Angela (Department of Psychiatry, Hospital Universitario Ramón y Cajal, IRYCIS, Universidad de Alcalá, Madrid, Spain; Biomedical Research Networking Center for Mental Health (CIBERSAM). Madrid ,Spain); Ribeiro, Marta (Department of Psychiatry, Complejo Hospitalario de Navarra, Pamplona, Spain. IdiSNA, Navarra Institute for Health Research, Pamplona, Spain); Balanzá-Martínez, Vicent (Teaching Unit of Psychiatry and Psychological Medicine. Department of Medicine, Universitat de València. CIBERSAM. Hospital Clínico Universitario de Valencia. INCLIVA).

Author information

J. A. Arnaiz

Present address: Department of Basic Clinical Practice, University of Barcelona (UB), Casanova 143, E-08036, Barcelona, Spain

C. Rodrigues-Silva

Present address: Department of Pharmacology, Institute of Biological Sciences, Federal University of Goiás, Goiânia, GO, Brazil

Department, Hospital Clínic de Barcelona (HCB), Barcelona, Spain

J. A. Arnaiz

Department of Basic Clinical Practice, University of Barcelona (UB), Casanova 143, E-08036, Barcelona, Spain

G. Mezquida & S. Mas

Barcelona Clínic Schizophrenia Unit, Neuroscience Institute, HCB, Barcelona, Catalunya, Spain

G. Mezquida & S. Amoretti

Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid, Spain

G. Mezquida, S. Amoretti, A. Lobo, A. González-Pinto, I. Corripio, A. Mané, C. García-Rizo, M. Bioque, J. Saiz, M. Bernardo & S. Mas

Institut d'investigacions Biomèdiques August Pi i Sunyer (IDIBAPs), Barcelona, Spain

G. Mezquida, S. Amoretti, C. García-Rizo, M. Bioque, M. Bernardo & S. Mas

Departmentof Psychiatry, Complejo Hospitalario de Navarra, Instituto de Investigaciones Sanitarias de Navarra (IdiSNa), Pamplona, Spain

M. J. Cuesta

Institute of Psychiatry and Mental Health, Hospital Clínico San Carlos, IdISSC,

D. Fraguas

Department of Medicine and Psychiatry, Zaragoza University, Instituto de Investigación Sanitaria Aragón (IIS Aragón), Zaragoza, Spain

A. Lobo

Hospital Universitario Araba, Servicio de Psiquiatria, UPV/EHU, Bioaraba, Spain

A. González-Pinto

Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañon, CIBERSAM, IiSGM, School of Medicine, Universidad Complutense, Madrid, Spain

M. C. Díaz-Caneja

Psychiatry Department, Institut d'Investigació Biomèdica-Sant Pau (IIB-SANT PAU), Hospital de la Santa Creu i Sant Pau; Universitat Autònoma de Barcelona (UAB), Barcelona, Spain

I. Corripio

Hospital Clinic, Institute of Neuroscience, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain

E. Vieta

Department of Child and Adolescent Psychiatry and Psychology, Clínic Institute of Neurosciences, Hospital Clínic de Barcelona, 2017SGR881, University of

I. Baeza

Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain

A. Mané

Autonomous university of Barcelona (UAB), Barcelona, Spain

A. Mané

Barcelona Clínic Schizophrenia Unit, Neuroscience Institute, Hospital Clínic of Barcelona, Barcelona, Spain

C. García-Rizo, M. Bioque & M. Bernardo

Department of Medicine, Barcelona, UB, Spain

C. García-Rizo, M. Bioque & M. Bernardo

Department of Psychiatry, Hospital Universitario Ramón y Cajal, IRYCIS, Universidad de Alcalá, Madrid, Spain

J. Saiz

Consortia

PEPs group

Mercè Torra, Adrian Llerena, Gerard Anmella, Lluc Colomer, Carmen Moreno, Manuel Durán-Cutilla, Anna Alonso Solís, Eva Grasa, Puri Lopez, Sainza García, Concepción De-la-Cámara, Zaragoza Aragón, Pedro Saz, Maria Dolores Moltó, Miguel Hernandez Viadel, Francesc Casanovas, David SanAgustin, Josefina Castro-Fornieles, Elena de la Serna, Fernando Contreras, Cristina Saiz, Julio Bobes, María Paz García-Portilla, Miguel Gutierrez Fraile, Arantzazu Zabala Rabadán, Roberto Rodríguez-Jimenez, Natalia E. Fares-Otero, Judith Usall, Anna

Contributions

The results presented here are part of a broader project, the PEPs study. Bernardo M is the coordinator of the PEPs study. Saiz J is the coordinator of the pharmacogenetic's module. Cuesta MJ, Fraguas D, Lobo A, González-Pinto A, Díaz-Canjea MC, Corripio I, Vieta E, Baeza I, Mané A, and García-Rizo C are the coordinators of their research centers and participated in the recruitment and assessment of the sample. Bioque M, Mezquida G, and Amoretti S participated in the coordination of the sample shipment, the maintenance of the PEPs database and in the recruitment, and assessment of the sample. Arnaiz JA and Rodrigues-Silva C designed and performed the statistical analysis under the supervision of Mas S and wrote the first draft of the manuscript. Authors listed in the PEPs group acronym participated in the recruitment and assessment of the sample. Llerena A was responsible of the TaqMan® analyses and Torra M performed the drug plasma determinations All the authors, including the PEPs group authors listed in the acronym, contributed to the final draft of the manuscript.

Corresponding author

Correspondence to S. Mas.

C. De-la-Camara received financial support to attend scientific meetings from Janssen-Cilag, Almirall, Eli Lilly, Lundbeck, Rovi, Esteve, Novartis, and Astrazeneca. E. Vieta has received grants and served as consultant, advisor or CME speaker for the following entities: Abbott, Allergan, Angelini, Dainippon Sumitomo Pharma, Janssen, Lundbeck, Novartis, Otsuka, Richter, Sage, Sanofi-Aventis, and Takeda. M. Bernardo has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of ABBiotics, Adamed, Angelini, Casen Recordati, Eli Lilly, Janssen-Cilag, Lundbeck, Otsuka, Takeda, and Somatics and has obtained research funding from the Ministry of Education, Culture and Sport, the Spanish Ministry of Economy, Industry and Competitiveness (CIBERSAM), by the Government of Catalonia, Secretaria d'Universitats i Recerca del Departament d'Economia i Coneixement (2017SGR1355), Foundation European Group for Research In Schizophrenia (EGRIS), and the 7th Framework Program of the European Union.

M. Bioque has received honoraria from talks and consultancy of Adamed, has received honoraria from consultancy of Ferrer, has received research support and honoraria from talks and consultancy of Janssen-Cilag, has received honoraria from talks and consultancy of Lundbeck, has received

Jiménez has been a consultant for, spoken in activities of, or received grants from: Instituto de Salud Carlos III, Fondo de Investigación Sanitaria (FIS), Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid Regional Government (S2010/ BMD-2422 AGES), JanssenCilag, Lundbeck, Otsuka, Pfizer, Ferrer, Juste, Takeda, Exeltis, Angelini, and Casen-Recordati. V Balanzá-Martínez has been a consultant, advisor or Continuing Medical Education (CME) speaker over the last 3 years for the following entities: Angelini; Ferrer; Lundbeck; Nutrición Médica; and Otsuka. All other authors declare that they have no conflict of interest.

Additional information

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Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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About this article

Cite this article

Arnaiz, J.A., Rodrigues-Silva, C., Mezquida, G. *et al.* The usefulness of Olanzapine plasma concentrations in

Received	Accepted	Published
23 July 2020	10 November 2020	23 November 2020

Issue Date

March 2021

DOI

https://doi.org/10.1007/s00213-020-05715-5

Keywords

Olanzapine **Therapeutic drug monitoring**

Pharmacokinetics **First-episode psychosis**

Drug level **Efficacy** **Weight gain**