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Original Article / Оригинални рад

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Cigarette smoking and heavy coffee drinking affect therapeutic response to olanzapine

Утицај пушења цигерета и значајног конзумирања кафе на клинички одговор пацијената лечених оланзапином

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Cigarette smoking and heavy coffee drinking affect therapeutic response to olanzapine

Утицај пушења цигерета и значајног конзумирања кафе на клинички одговор пацијената лечених оланзапином

SUMMARY

Introduction/Objective Considering relatively complex pharmacokinetic profile of olanzapine, it is expected that certain medications and some compounds, found in food and drink, can induce or inhibit its metabolism.

Aim of study was to investigate influence of cigarette smoking and heavy coffee consumption on clinical response to olanzapine.

Methods The phase IV, open-labeled, four-weeks, prospective clinical trial, included 108 adult patients, having diagnosed schizophrenia. According to cigarette smoking (n=52) and coffee drinking (n=55) four subgroups were defined: non-smokers, non-heavy coffee consumers (group 1), non-smokers, heavy coffee consumers (group 2), smokers, non-heavy coffee consumers (group 3) and smokers and heavy coffee consumers (group 4). PANSS and GAF scales were used for therapeutic response evaluation.

Results Baseline and final GAF scores were 33.3±5.0 and 61.5±9.6, respectively, and PANSS scores were 100.7±3.9 and 85.5±5.4, respectively. The change from baseline to study end of GAF and PANSS scores were 115.1±35.7 and -19.6±3.1, respectively (group 1), 91.1±30.8 and -15.3±2.9, respectively (group 2), 76.1±29.8 and -13.4±4.4, respectively (group 3) and 64.7±29.3 and -11.3±3.22, respectively (group 4), making significant subgroup differences for both scale scores ($p<0.001$). Cigarette smoking and heavy coffee drinking significantly and independently diminished improvement in both GAF and PANSS total score ($p<0.001$). Changes of BMI from baseline significantly influenced change of PANSS total score only (p=n.s.), in a negative direction (r=-0.454, $p<0.001$).

Conclusion Smoking and heavy coffee drinking influenced effects of olanzapine in patients with schizophrenia treated in routine practice.

Keywords: schizophrenia; antipsychotic agents; coffee; tobacco use

САЖЕТАК

Увод/Циљ С обзиром на релативно сложен фармакокинетички профил оланзапина очекује се да поједини лекови и нека једињења која се налазе у храни и пићу могу индуковати или ихибирати његов метаболизам.

Циљ студије је био да се испита утицај пушења и интензивнијег конзумирања кафе на клинички одговор пацијената лечених оланзапином.

Методе рада Укључено је 108 пацијената са дијагнозом схизофреније у проспективну, интервентну, контролисану, клиничку студију IV фазе. У зависности од пушења цигарета (n=52) и интензивног конзумирања кафе (n=55), дефинисане су четири субгрупе: непушаци и особе које не пију кафу (група 1), непушачи и особе које интензивно пију кафу (група 2), пушачи и особе које не пију кафу (група 3) и пушачи и особе које интензивно пију кафу (група 4). *PANSS* и *GAF* скале су коришћене за евалуацију клиничког одговора.

Резултати Почетни и коначни резулататати GAF скале су били 33,3±5.0 односно 61.5± 9.6, а резултати PANSS скале су били 100.7 +/- 3.9 односно 85.5±5.4. Промене на GAF и PANSS скалама од почетка до краја студије су биле 115.1±35.7 односно -19.6±3.1 (група 1), 91.1±30.8 односно -15.3±2.9 (група 2), 76.1±29.8 односно -13.4± 4.4 (група 3) и 64,7±29,3 односно -11.3±3,22 (група 4), чинећи сигнификантну разлику субгрупа за обе скале ($p<0.001$). Пушење и интензивније конзумирање кафе значајно и независно су смањили побољшање исказано и у GAF и у укупним *PANSS* ($p<0,001$) скоровима. Промене *BMI* у односу на почетак истраживања значајно су утицале на промену *PANSS* укупног резултата (p= n.s.) у негативном смеру (r = -0,454, $p<0.001$).

Закључак Пушење и интензивно конзумирање кафе утицали су на терапијске ефекте оланзапина код пацијената оболелих од схизофреније у свакодневној клиничкој пракси.

Кључне речи: схизофренија; антипсихотици; кафа; употреба дувана

INTRODUCTION

The treatment of patients with psychotic disorders changed in recent decades, mainly due to the emergence of a new group of drugs called atypical, newer or second-generation antipsychotics. They have fewer side effects, better compliance and, in some domains, improved efficacy in comparison to

conventional antipsychotic drugs [1]. Olanzapine, an atypical antipsychotic of thienobenzodiazepine structure, has a broad pharmacological profile and it acts on dopamine ($D_1/D_2/D_3/D_4$), serotonin (5-$HT_{2A/2C}$), muscarinic (M_1), histamine (H_1) and the adrenergic (α_1) receptors [2]. In clinical trials, in patients suffering from schizophrenia, or schizophrenia spectrum disorders, olanzapine has proved effective in the treatment of both positive and negative symptoms, with a low incidence of extrapyramidal symptoms [3].

Antipsychotic efficacy of olanzapine is achieved in daily doses ranging from 5-20 mg. Pharmacokinetics of olanzapine is characterized by a large volume of distribution, multiple biotransformation pathways, and a relatively long half-life, which require slowly-titrating dosing regimen [4]. Several enzymes are involved in the metabolism of olanzapine, including cytochrome P450 1A2 (CYP1A2) and 2D6 (CYP2D6), flavin-containing monooxygenase 3 (FMO3) and UDP-glucuronosyltransferase 1A4 (UGT1A4) [5-7].

Considering such relatively complex pharmacokinetic profile of olanzapine, it is expected that certain medications and some compounds, found in food and drink, can induce or inhibit its metabolism, changing the drug plasma levels. Therefore, drug interactions or genetic variability may require the use of doses that differ from those recommended ones for atypical antipsychotics [8]. For example, co-administration of olanzapine and the potent CYP1A2 inhibitors such as fluvoxamine or ciprofloxacin resulted in its higher olanzapine serum concentrations [9]. Contrary, carbamazepine, a CYP1A2 inducer causes the increase of clearance and volume of distribution of olanzapine [10]. Interethnic differences in the distribution of *CYP1A2* alleles lie behind different catalytic activity of the cytochrome in different population as shown, for example for Orientals compared with Caucasians [11].

Many patients with mental disorders are regular cigarette smokers, and their consumption of large amount of caffeine-containing drinks is widespread. Earlier investigations showed that smoking can significantly decrease olanzapine levels, up to 50%, possibly due to effects of polycyclic aromatic hydrocarbons (PAHs) presented in the tobacco smoke [12]. PAHs are potent inducers of the hepatic cytochrome P-450 (CYP) isoenzymes 1A1, 1A2, and, possibly, 2E1 [13]. Therefore, starting or quitting cigarette smoking during ongoing therapy sometimes requires adjusting of dosing regimen and the measurement of olanzapine plasma levels [14]. Similarly, heavy coffee consumption increases CYP1A2 activity, most probably due to the effects of PAHs, which are formed during roasting of coffee beans [15].

The separate effects of smoking and coffee drinking on the pharmacokinetics of psychotropic drugs, including olanzapine, are pretty well documented in the literature. The relationships between pharmacokinetics and pharmacodynamics with treatment response of antipsychotics, based on the standardized psychiatric rating scales, have been established [16]. However, little is known about consequences of patients' life-style patterns on antipsychotic therapeutic response.

Therefore, the aim of our study was to investigate the influence of cigarette smoking and heavy coffee consumption on clinical response to olanzapine in patients with schizophrenia. We hypothesized that these factors significantly change the therapeutic and adverse effects of the drug.

METHODS

This study was designed as a phase IV, open-labeled, prospective clinical trial in a cohort of patients with schizophrenia, which were treated with olanzapine. Recruitment of the subjects is conducted at the Psychiatric Clinic of Clinical Centre "Kragujevac", Kragujevac, Serbia, from 2014. to 2016. One hundred and eight adult patients, meeting the DSM-V diagnostic criteria [17] for schizophrenia, and having either the first episode or the disease relapse, as assessed with BPRS (Brief Psychiatric Rating Scale) [18], were enrolled in the study. There exclusion criteria were as follows: younger than 18 years of age, pregnant or lactating women, psychotropic drugs other than benzodiazepine or hypnotic agents, the presence of disabling and medically uncontrolled somatic condition(s), known contraindications for olanzapine treatment, and subject's rejection of study participation. The participation was voluntary and subjects were included in the study after providing the written informed consent. The study was approved by the Ethic Committee of the Clinical Centre Kragujevac, Serbia, decision No 01/5273.

The study included three patient visits: at the baseline, and 2 and 4 weeks after the introduction of olanzapine treatment. Baseline visit encompassed screening for subject's eligibility for the study entry and collection of all necessary study data. Written information about the gender, age, psychiatric and concomitant diseases and treatments, as well as the baseline cigarette smoking and coffee consumption habit were obtained using a detailed questionnaire.

The oral olanzapine treatment was introduced according to the recommendation described in the British National Formulary i.e. with the starting dose of 10 mg once daily. The clinical effectiveness of olanzapine treatment at the study visits was assessed using PANSS (Positive and Negative Symptoms Scale) and GAF (Global Assessment of Functioning) rating scales [19]. Olanzapine dose adjustments have been performed according to the achieved clinical response and the drug tolerability.

During the study, subjects have been be provided with a wide list of possible adverse effects that can occur during olanzapine treatment, and the patients were encouraged to write down any noxious symptom if they experience it. The patients' diaries also included the information on cigarette smoking habit and daily intake of coffee. According to the data on coffee consumption and cigarette smoking, participants have been divided in four groups: a) non-smokers, non-heavy coffee consumers (group 1), b) non-smokers, heavy coffee consumers (group 2), c) smokers, non-heavy coffee consumers (group 3) and d) smokers and heavy coffee consumers (group 4). Smoking at average two or more cigarettes per day has defined a cigarette smoker, while regular daily intake of at least three cups of coffee has defined a heavy coffee consumer.

The sample size was determined according to the expected differences in primary variable, the percent change of PANSS total score from the baseline to the end of the study, between the users (group 4) and the non-users of cigarettes and at least three cups of coffee per day (group 1). We postulated the difference for independent samples of at least 10% with the standard deviation of 10%, at alpha error of 5% and study power of 80%, for two sided, t-test. The minimum number of 20 patients per subgroup was calculated [20]. The data analysis included descriptive statistics, hypothesis testing and correlation, according to the types of the variable and data distributions, at the probability of null hypothesis of 5% or less, with two-sided approach. The analysis of primary variable was performed using general linear model with the pattern of smoking and coffee consumption (study groups) and gender as fixed factors and years of age, olanzapine dose and the percent change of body mass index (BMI) from baseline as the covariates.

Table 1. Patients' characteristics (n=108).

Variable	Value
Gender (male/female)	53 (44.1) / 55 (50.9)
Age (years)	46.0±14.5 (19-78)
Residential facility (yes/no)	27 (25%) / 81 (75%)
Smokers (yes/no)	55 (50.9%) / 53 (49.1%)
Coffee drinkers (yes/no)	52 (48.1%) / 56 (51.9%)
Study group 1	33 (30.6%)
Study group 2	22 (20.4%)
Study group 3	21 (19.4%)
Study group 4	32 (29.6%)
ODT (yes/no)	15 (13.9) / 93 (86.1%)
Olanzapine dose (mg per day)	15.4±3.2 (10-20)
GAF score (baseline)	33.3±5.0 (21-43)
GAF score (end of study)	61.5±9.6 (28-80)
PANSS score (baseline)	100.7±3.9 (90-109)
PANSS score (end of study)	85.5±5.4 (73-104)
BMI (baseline) (kg/m^2)	25.1±3.2 (18.7-30.5)
BMI (end of study) (kg/m^2)	26.0±3.3 (19.3-39.7)
Glucose (mmol/L)	5.6±0.9 (3.9-9.8)
Cholesterol (mmol/L)	5.9±1.1 (3.8-9.2)
HDL-cholesterol (mmol/L)	1.4±0.3 (0.7-2.2)
LDL-cholesterol (mmol/L)	3.6±1.1 (1.5-6.5)
Triglycerides (mmol/L)	2.3±1.0 (0.6-5.9)

RESULTS

The main patients' demographic and clinical characteristics are presented in the Table 1. In general, there were similar proportion of male and female subjects, with an average age within the fifth decade of life, and about one quarter being residents of a long-term psychiatric care facility. About one half of the study patients were smokers and heavy coffee drinkers, and the study groups had similar proportion of subjects.

Among the four study groups there were significantly different therapeutic responses as measured with percent of change from baseline of GAF score ($p<0.001$, $F=5.8$, $df=10$) and PANSS total score ($p<0.001$, $F=12.9$, $df=10$) (Table 2). Cigarette smoking and heavy coffee drinking (study group as a fixed variable) significantly diminished improvement in both GAF ($p<0.001$, $F=10.0$, $df=3$) and PANSS total score ($p<0.001$, $F=16.9$), $df=10$). The percent changes of BMI from the baseline (a covariate) significantly influenced the change of PANSS total score only ($p=0.024$, $F=5.3$, $df=3$), in a negative direction (Pearson $r=-0.454$, $p<0.001$). Patients' gender (a fixed factor) and patient's age and olanzapine daily dose (the covariates) did not affect the therapeutic response as assessed with either GAF or PANSS score changes ($p>0.05$).

Table 2. The change from baseline (%).

Study group	GAF*	PANSS*
1	115.1±35.7	-19.6±3.1
2	91.1±30.8	-15.3±2.9
3	76.1±29.8	-13.4±4.4
4	64.7±29.3	-11.3±3.22

*-p<0.001, multivariable linear model

The median amount of coffee consumed per day was 4 cups (interquartile range 2, minimum 4, maximum 8). A significant correlation between the amount of coffee drinking and the change from baseline for both GAF (Spearman rho=-0.307, p=0.038) and PANSS scores (Spearman rho=0.312, p=0.035) was found. In regard to smoking, similar effects were not observed. The mean amount of tobacco smoked per day was 27 cigarettes (standard deviation 10, minimum 10 maximum 40), with no significant correlation with either GAF (Pearson r=-0.163, p=0.262) or PANSS (Pearson r=0.228, p=0.115) score changes from the baseline.

The study patients who smoked and heavily drank coffee had significantly lower serum levels of cholesterol (p=0.001, F=5.6, df=1, one-way analysis of variance), LDL-cholesterol (p<0.001, F=11.9, df=3, one-way analysis of variance) and triglycerides (p=0.020, Kruskal-Wallis test), and they had less increase in BMI (p<0.001, F=7.6, df=3, one-way analysis of variance) (Table 3). However, these habits did not significantly influence the values of HDL-cholesterol (p=0.080, F=2.3, df=3, one-way analysis of variance) and glucose (p=0.323, Kruskal-Wallis test).

Table 3. Metabolic parameters of patients according to the study groups.

Parameter	Group 1	Group 2	Group 3	Group 4	*p*
Cholesterol (mmol/L)[1]	6.4±1.2	5.9±0.7	5.7±1.1	5.4±0.9	0.001
HDL-cholesterol (mmol/L)	1.3±0.4	1.5±0.2	1.4±0.3	1.4±0.4	0.080
LDL-cholesterol (mmol/L)	4.4±1.1	3.6±0.8	3.4±0.9	2.3±0.9	<0.001
Glucose (mmol/L)*	5.8 (1.1)	5.6 (0.4)	5.5 (0.9)	5.6 (0.6)	0.323
Triglycerides (mmol/L)*	3.3 (2.2)	2.5 (0.7)	2.0 (1.1)	1.9 (0.5)	0.020
BMI change†	5.2±3.3	2.9±1.8	3.2±2.6	1.7±3.3	<0.001

*-median (interquartile range), †-percent from baseline

DISCUSSION

The results of our study show that the beneficial clinical response to olanzapine treatment is significantly decreased in patients who were smokers and heavy coffee consumers in comparison with the abstinents. The effect of these life-style habits was synergistic, and it was more pronounced for tobacco than for coffee consumptions. Different types of data distributions (skewed vs. normal) for coffee drinking and cigarette smoking could explain the observed difference in correlation analysis regarding the dose response. Weight gain had some predictive significance for positive olanzapine response. The cigarette smoking and heavy coffee intake decreased some adverse metabolic effects after initiation of olanzapine treatment. Gender, age and olanzapine dose did not significantly influence the effects of either tobacco use or coffee drinking. As we are aware, there were no studies with similar design as our study had.

Our results are in accordance with the fundamental knowledge in the field. Nicotine and caffeine have mainly beneficial effects in people with schizophrenia. They induce changes of the brain neurotransmitters, causing an improvement of disease symptoms such as the feeling of well-being (e.g. dopamine release) or cognition (e.g. nicotine receptors activation), with positive behavioral consequences (e.g. better structuring of daily activities), but also alleviating some of the side effects

of drug treatment (e.g. drowsiness, extrapyramidal symptoms, dry mouth) [21-23] . On the other hand, it is known that cigarette smoking and heavy coffee consumption strongly induce olanzapine-metabolizing cytochromes and decrease its plasma levels [15,24-26]. At the same time, caffeine from coffee competitively inhibits olanzapine metabolism, as they share CYP1A2 as a common metabolizing enzyme [27,28]. In our study, the proposed inducing effect seems to overcome expected beneficial effects of nicotine and caffeine, as well as the metabolism inhibition by caffeine, resulting in diminished therapeutic response by almost one tenth to more than a quarter, depending on the rating assessment method.

It is well known that olanzapine has very profound metabolic adverse effects inducing dyslipidemia, glucose intolerance and weight gain [29]. In our study, smokers and heavy coffee drinkers had significantly lower serum levels of cholesterol and triglycerides, but also lower increase in BMI without significant influence on glucose concentrations. The decrease of olanzapine blood concentration, most probably due to PAHs from cigarette smoke and coffee, could be considered a probable mechanism. In addition, there is a possibility that other factors, not identified in our research, could modulate the metabolic status of our patients. The patient's individual properties could cause particular metabolic patterns [30], as described in a case of olanzapine induced dyslipidemia and hyperglycemia without increase in weigh [31].

The results of our study should be interpreted considering several limitations. Moderate sample size and short study duration could decrease the power for identification of other important factors, which could have the effects of a lesser magnitude or be delayed, or could induce a compensatory response later in the course of treatment. In addition, we did not measure olanzapine blood concentration, thus only assumption about exact mechanism of smoking and heavy coffee drinking on the drug's pharmacokinetics, based on current, theoretical knowledge in the field, could be made. Finally, we did not perform analysis of genetic polymorphism, which could affect pharmacokinetics and pharmacodynamics of olanzapine and, consequently, modulate its efficacy and safety. Therefore, to confirm our findings, additional studies are necessary.

CONCLUSION

Our study showed that cigarette smoking and heavy coffee drinking, frequent habits of patients with schizophrenia who were treated in clinical routine practice, affect the clinical response to olanzapine. In those patients, therapeutic drug monitoring of olanzapine treatment and appropriate adjustment of dosing regimen could be advisable.

NOTE

This paper is a part of doctoral thesis "Effect of Polymorphism and Induction of Gene of Metabolising Enzymes on Clinical Response of Patients Treated with Olanzapine" by Branimir Radmanović.

REFERENCES

1. Grundmann M, Kacirova I, Urinovska R. Therapeutic drug monitoring of atypical antipsychotic drugs. Acta Pharm. 2014; 64(4): 387–401.
2. Bishara D, Olofinjana O, Sparshatt A, Kapur S, Taylor D, Patel MX. Olanzapine: a systematic review and meta-regression of the relationships between dose, plasma concentration, receptor occupancy, and response. J Clin Psychopharmacol. 2013; 33(3): 329–35.
3. Zhang JP, Gallego JA, Robinson DG, Malhotra AK, Kane JM, Correll CU. Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: a systematic review and meta-analysis. Int J Neuropsychopharmacol. 2013; 16(6): 1205–18.
4. Nakajima S, Uchida H, Bies RR, Caravaggio F, Suzuki T, Plitman E et al. Dopamine D2/3 receptor occupancy following dose reduction is predictable with minimal plasma antipsychotic concentrations: an open-label clinical trial. Schizophr Bull Schizophr Bul. 2016; 42(1): 212–9.
5. Czerwensky F, Leucht S, Steimer W. CYP1A2*1D and *1F polymorphisms have a significant impact on olanzapine serum concentrations. Ther Drug Monit. 2015; 37(2): 152–60.
6. Zanger UM, Raimundo S, Eichelbaum M. Cytochrome P450 2D6: overview and update on pharmacology, genetics, biochemistry. Naunyn Schmiedebergs Arch Pharmacol. 2004; 369(1): 23–37.
7. Linnet K. Glucuronidation of olanzapine by cDNA-expressed human UDP-glucuronosyltransferases and human liver microsomes. Hum Psychopharmacol. 2002; 17: 233–8.
8. Spina E, de Leon J. Clinically relevant interactions between newer antidepressants and second-generation antipsychotics. Expert Opin Drug Metab Toxicol. 2014; 10(5): 721–46.
9. Spina E, de Leon J. Metabolic drug interactions with newer antipsychotics: a comparative review. Basic Clin Pharmacol Toxicol. 2007; 100(1): 4–22.
10. Lucas RA, Gilfillan DJ, Bergstrom RF. A pharmacokinetic interaction between carbamazepine and olanzapine: observations on possible mechanism. Eur J Clin Pharmacol. 1998; 54: 639–43.
11. Wu TH, Chiu CC, Shen WW, Lin FW, Wang LH, Chen HY, et al. Pharmacokinetics of olanzapine in Chinese male schizophrenic patients with various smoking behaviors. Prog Neuropsychopharmacol Biol Psychiatry. 2008; 32: 1889–1893.
12. Carrillo JA, Herráiz AG, Ramos SI, Gervasini G, Vizcaíno S, Benítez J. Role of the smoking-induced cytochrome P450 (CYP)1A2 and polymorphic CYP2D6 in steady-state concentration of olanzapine. J Clin Psychopharmacol. 2003; 23: 119–27.
13. Hisamuddin IM, Yang VW. Genetic polymorphisms of human flavin-containing monooxygenase 3: implications for drug metabolism and clinical perspectives. Pharmacogenomics. 2007; 8(6): 635–43.
14. Lyon ER. A review of the effects of nicotine on schizophrenia and antipsychotic medications. Psychiatr Serv. 1999; 50(10): 1346–50.
15. Djordjevic N, Ghotbi R, Jankovic S, Aklillu E. Induction of CYP1A2 by heavy coffee consumption is associated with the CYP1A2 −163C>A polymorphism. Eur J Clin Pharmacol. 2010; 66(7): 697–703.
16. Pilla Reddy V, Kozielska M, Suleiman AA, Johnson M, Vermeulen A, Liu J, et al. Pharmacokinetic-pharmacodynamic modeling of antipsychotic drugs in patients with schizophrenia. Part I: the use of PANSS total score and clinical utility. Schizophr Res. 2013; 146(1–3): 144–52.
17. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5 th ed. Arlington, VA: American Psychiatric Association; 2013.
18. Overall JE, Gorham DR: The Brief Psychiatric Scale. Psychological Reports. 1962; 10: 799–812.
19. Perkins DO, Stroup TS, Lieberman JA. Psychotic disorders measures. In: Handbook of Psychiatric Measures. Washington DC: American Psychiatric Association, 2000: p. 485–513.
20. Dupont WD, Plummer WD. Power and sample size calculations: a review and computer program. Control Clin Trials. 1990; 11: 116-28.
21. Winterer G. Why do patients with schizophrenia smoke? Curr Opin Psychiatry. 2010; 23(2): 112–9.
22. Ferchiou A, Szöke A, Laguerre A, Méary A, Leboyer M, Schürhoff F. Exploring the relationships between tobacco smoking and schizophrenia in first-degree relatives. Psychiatry Res. 2012; 200(2–3): 674–8.
23. Adolfo AB, AhnAllen CG, Tidey JW. Effects of smoking cues on caffeine urges in heavy smokers and caffeine consumers with and without schizophrenia. Schizophr Res. 2009; 107(2–3): 192–7.
24. Chiu CC, Lu ML, Huang MC, Chen KP. Heavy smoking, reduced olanzapine levels, and treatment effects: a case report. Ther Drug Monit. 2004; 26(5): 579–81.
25. Batail JM, Langrée B, Robert G, Bleher S, Verdier MC, Bellissant E, et al. Use of very-high-dose olanzapine in treatment-resistant schizophrenia. Schizophr Res. 2014; 159(2–3): 411–4.
26. Djordjevic N, Ghotbi R, Bertilsson L, Jankovic S, Aklillu E. Induction of CYP1A2 by heavy coffee consumption in Serbs and Swedes. Eur J Clin Pharmacol. 2008; 64(4):3 81–5.

27. Tassaneeyakul W, Birkett DJ, McManus ME, Tassaneeyakul W, Veronese ME, Andersson T, et al. Caffeine metabolism by human hepatic cytochromes P450: contributions of 1A2, 2E1 and 3A isoforms. Biochem Pharmacol. 1994; 47(10): 1767–76.
28. Raaska K, Raitasuo V, Laitila J, Neuvonen PJ. Effect of caffeine-containing versus decaffeinated coffee on serum clozapine concentrations in hospitalised patients. Basic Clin Pharmacol Toxicol. 2004; 94(1): 13–8.
29. Rojo LE, Gaspar PA, Silva H, Risco L, Arena P, Cubillos-Robles K, et al. Metabolic syndrome and obesity among users of second generation antipsychotics: A global challenge for modern psychopharmacology. Pharmacol Res. 2015; 101: 74–85.
30. Chukhin E, Terevnikov V, Takala P, Hakko H, Putkonen H, Räsänen P, et al. Is there an interrelationship between the effects of antipsychotics on psychopathology and on metabolism? Nord J Psychiatry. 2016; 70(3): 190–4.
31. Pawelczyk T, Pawelczyk A, Rabe-Jablonska J. Olanzapine-induced triglyceride and aminotransferase elevations without weight gain or hyperglycemia normalized after switching to aripiprazole. J Psychiatr Pract. 2014; 20(4): 301–7.

