

# Long-Term Treatment with Olanzapine in Hospital Conditions: Prevalence and Predictors of the Metabolic Syndrome

Irena Popović<sup>1</sup>, Dragan Ravanić<sup>2</sup>, Slobodan Janković<sup>2</sup>, Dragan Milovanović<sup>2</sup>, Marko Folić<sup>2</sup>, Albina Stanojević<sup>1</sup>, Milutin Nenadović<sup>3</sup>, Milena Ilić<sup>2</sup>

<sup>1</sup>Special Hospital for Mental Disorders Gornja Toponica, Niš, Serbia;

<sup>2</sup>University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Serbia;

<sup>3</sup>University of Priština, Faculty of Medical Sciences, Department for Psychiatry, Kosovska Mitrovica, Serbia

## SUMMARY

**Introduction** The risk of metabolic abnormalities is greatly increased in schizophrenic patients started on an atypical antipsychotic medication. Patients with psychiatric disorders exceed mortality ranges resulting from, among others, increased risk of cardiovascular events. Other factors contributing to the development of metabolic syndrome include prolonged duration of illness, increasing age, female sex and lifestyle factors.

**Objective** This cross-sectional study was taken up to assess the prevalence of the metabolic syndrome (MetS) in schizophrenic patients receiving olanzapine monotherapy for at least six months and to determine the most important risk factors associated with metabolic syndrome presence in these patients.

**Methods** A total of 93 long term hospitalized schizophrenic patients (71 men, 22 women), had a screening of the following: case-history data, psychiatric scales, anthropometric measures, blood (fasting glucose, lipid status, C-reactive protein – CRP) and urine samples (microalbuminuria).

**Results** Prevalence of MetS according to International Diabetes Federation criteria in our study was 34.4%. The multivariate analysis distinguished the following significant predictors of MetS presence (in order of appearance): data about diabetes mellitus in family history ( $p=0.002$ ), body mass index  $>25$  kg/m<sup>2</sup> ( $p=0.002$ ), hyperlipidemia in family history ( $p=0.008$ ), and elevated CRP value ( $p=0.042$ ).

**Conclusion** High rate of MetS in patients treated with olanzapine in this study exceeds MetS prevalence in general population. Among observed parameters, our study pointed to several “high risk” predictors associated with MetS presence. Regular monitoring of cardiometabolic risk factors is highly recommended. Positive heredity distress mentioned above may direct a psychiatrist to prescribe some other drug than olanzapine in the long term treatment of schizophrenia.

**Keywords:** metabolic syndrome; schizophrenia; olanzapine

## INTRODUCTION

Schizophrenia is a chronic and debilitating psychiatric illness with a worldwide prevalence of approximately 1% [1]. It is characterized by positive, negative and affective symptoms. Since the introduction of chlorpromazine in 1952, antipsychotic drugs are the mainstay of the pharmacologic treatment of psychosis and schizophrenia [2]. By blocking dopaminergic neurotransmission in subcortical areas, antipsychotics are capable of producing extrapyramidal side-effects. This propensity is more pronounced with the first-generation antipsychotics (FGA), than with the second-generation antipsychotics (SGA). Thus, during the past two decades, SGA replaced FGA as the standard treatments for schizophrenia [3]. SGA's antagonism to histamine H<sub>1</sub> and serotonin 5HT<sub>2c</sub> receptors, associated with weight gain and metabolic deregulation, enhance the prevalence of the metabolic syndrome (MetS) in patients taking this kind of medication [4]. Factors that also contribute to the development of MetS are long-term duration of illness, old age, female sex, lifestyle factors related to psy-

chotic disorder [5]. Patients suffering from psychiatric disorders have significantly increased morbidity and mortality ranges – increased risk of cardiovascular events and premature death is estimated to 10 to 25 years earlier than in general population [6]. Data in literature indicate that treatment-induced metabolic abnormalities, such as raised lipids and glucose blood levels, eventually result in abdominal obesity, may contribute to the development of diabetes mellitus type 2 and arterial hypertension, and may account for up to 60% of premature deaths of persons with serious mental illness [7].

International Diabetes Federation (IDF) criteria are the most widely used in European studies (Table 1). Definition of MetS includes an assembly of disorders such as the abdominal obesity, hypercholesterolemia, hyperlipidemia, arterial hypertension and raised blood glucose levels [8].

In comparison to general population, the prevalence of MetS is increased in patients taking psychotropic agents [9, 10]. This applies not only to antipsychotics, but also to mood stabilizers and antidepressants [11, 12]. Apart from that, subjects with schizophrenia or bi-

## Correspondence to:

Irena POPOVIĆ  
Special Hospital for Mental  
Disorders Gornja Toponica  
18202 Gornja Toponica  
Serbia  
ipopovic69@yahoo.com

**Table 1.** IDF metabolic syndrome worldwide definition\*

| Parameter                       |                         | Ethnicity specific – Europids   |
|---------------------------------|-------------------------|---|
| Waist circumference             |                         | Male $\geq 94$ cm<br>Female $\geq 80$ cm  |
| ..plus any two of the following | Raised triglycerides    | $\geq 1.7$ mmol/L (150 mg/dl) or specific treatment for this lipid abnormality                                  |
|                                 | Raised blood pressure   | systolic $\geq 130$ mmHg or diastolic $\geq 85$ mmHg or treatment of previously diagnosed arterial hypertension |
|                                 | Reduced HDL cholesterol | $< 1.03$ mmol/L (40 mg/dL) in males<br>$< 1.29$ mmol/L (50 mg/dL) in females                                    |
|                                 | Raised plasma glucose   | fasting plasma glucose $\geq 5.6$ mmol/L (100 mg/dl) or previously diagnosed diabetes mellitus type 2           |

\* Consensus Statement from the International Diabetes Federation (IDF) [8]

polar disorder may be prone to metabolic deregulation regardless of any specific drug treatment, which correlates with genetic factors [13]. Furthermore, origination of metabolic disturbances via enhanced food intake, insulin resistance, further diabetes mellitus type 2 development, as well as elevated serum lipids fractions, implies a timeframe of at least three months [14]. Consequently, the authors of this cross-sectional study set the six months of previous olanzapine monotherapy treatment as time long enough to declare with high probability that MetS is caused by the actual antipsychotic consumption, considering that long term hospitalization conditions control other confounders (nutrition, concomitant therapy, physical activity).

Olanzapine is an antipsychotic agent displaying nanomolar affinity at dopamine  $D_1$ - $D_4$ , serotonergic ( $5\text{-HT}_{2,3,6}$ ), muscarinic ( $M_{1,5}$ ), adrenergic ( $\alpha_1$ ), and histaminergic ( $H_1$ ) binding sites [15]. The pharmacology may further include a glutamatergic mechanism [16]. Such profile distinguishes olanzapine from other, conventional antipsychotic agents. However, olanzapine causes MetS in 19–50% of schizophrenic patients on long-term therapy [17, 18].

## OBJECTIVE

The objectives of the present cross-sectional study were as follows:

- 1) To assess the prevalence of the metabolic syndrome (according to the IDF criteria) and its constituting components in long-term olanzapine treated patients;
- 2) To determine potential cardiometabolic risk factors in a subgroup of patients with diagnosed MetS, related to:
  - social-demographic parameters (age, sex, schizophrenia type according to International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) classification, heredity of diabetes or hyperlipidemia in family history, number of previous hospitalizations, smoking habit, duration of the illness, duration of the antipsychotic treatment, average olanzapine daily doses);
  - anthropometric parameters (waist circumference, body mass index [BMI], blood pressure);

- laboratory parameters (fasting glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, total triglycerides, microalbuminuria);
- psychiatric clinical state evaluated by Positive and Negative Syndrome Scale (PANSS) for schizophrenia [19] and Brief Psychiatric Rating Scale (BPRS) [20].

## METHODS

The present study was designed as a cross-sectional, case-control study, undertaken during the year 2012, among patients hospitalized at Specialized Psychiatric Hospital Gornja Toponica, Niš, Serbia, after receiving approval from the Institutional Human Ethics Committee. It included 93 long-term hospitalized patients (71 men, 22 women), diagnosed with Schizophrenia group (F20–F29), according to diagnostic criteria from the ICD-10 [21]. Those who were receiving a single SGA agent olanzapine for a period of six months or more were enrolled in the study after obtaining written informed consent. Additional administration of benzodiazepines and/or hypnotics was allowed in therapeutic doses, but no other psychotropic drugs. Concomitant somatic medication was allowed, if necessary (antihypertensives, antidiabetics). Nutrition in hospital conditions was up to standard dietary protocols, without changes of physical activity during the study.

The IDF criteria were used to distinguish presence/absence of MetS (Table 1). According to MetS presence, patients were divided into two subgroups – those with diagnosed MetS (observed as “cases” in the study), and those without diagnosed MetS (observed as “controls” in the study).

The clinical psychiatric state of the patients was measured by PANSS for schizophrenia, and the BPRS. The following demographic characteristics were obtained using a questionnaire: age and sex, duration of illness, details of medication, duration of medical treatment, case-history of co-morbid conditions (arterial hypertension and/or diabetes mellitus type 2), as well as diabetes mellitus type 2 and hyperlipidemia in family history. The patients were fasting (overnight fast of 12–14 hours) for the purpose of blood collection for lipid blood tests and measurement of blood glucose. Venous puncture was performed for all subjects between eight and nine a.m. after a 12-hour overnight fast. Immediately after collecting blood samples, serum concentrations of total cholesterol, high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), total triglycerides and fasting glucose were determined using enzyme methods and commercial kits (Olympus Diagnostic, GmbH, Hamburg, Germany) on Olympus AU 600 automated analyzer. C-reactive protein (CRP) serum levels were determined using immunoturbidimetric method. The cut-off point for CRP elevation was set at 5 mg/L. Microalbuminuria was detected by standard spot urine albumin sample (referent value 30–300 mg/L). BMI was calculated after measuring patients' weight and height ( $\text{kg}/\text{m}^2$ ). Waist as a major marker (central adiposity) was measured in the midpoint of distance between

**Table 2.** Patient sample's structure (according to gender)

| Parameter                           | Total (n=93) | Men (n=71) | Women (n=22) | p*                 |
|-------------------------------------|--------------|------------|--------------|--------------------|
| Age (years)                         | 48.13±8.78   | 48.14±8.94 | 48.09±8.41   | 0.981              |
| Antipsychotic treatment (years)     | 4.15±2.62    | 4.39±2.77  | 3.36±1.91    | 0.107              |
| Olanzapine treatment (months)       | 8.39±2.15    | 8.51±2.23  | 8.00±1.82    | 0.288              |
| Olanzapine dose (mg pro die)        | 13.96±2.15   | 13.90±4.26 | 14.14±4.45   | 0.824              |
| Number of previous hospitalizations | 5.62±4.94    | 4.96±3.66  | 7.77±7.47    | <b>0.019</b>       |
| Illness length (years)              | 13.53±5.05   | 13.41±5.15 | 13.91±4.78   | 0.687              |
| Smoking habit                       | 90 (96.8)    | 68 (95.8)  | 22 (100.0)   | 0.933 <sup>b</sup> |
| MetS presence                       | 32 (34.4)    | 21(29.6)   | 12 (54.5)    | 0.078 <sup>b</sup> |
| F20.0**                             | 46 (49.5)    | 38 (53.5)  | 8 (36.4)     | 0.161 <sup>b</sup> |
| F20.1**                             | 20 (21.5)    | 14 (19.7)  | 6 (27.3)     | 0.553 <sup>a</sup> |
| F20.5**                             | 12 (12.9)    | 10 (14.1)  | 2 (9.1)      | 0.724 <sup>a</sup> |
| F25**                               | 5 (5.4)      | 3 (4.2)    | 2 (9.1)      | 0.588 <sup>a</sup> |
| F22**                               | 10 (10.8)    | 6 (8.5)    | 4 (18.2)     | 0.239 <sup>a</sup> |

Data are presented as mean value ± standard deviation, or as the number of patients (frequency) with percentage.

\* p – Student's t-test value (p<0.05 bolded if significant)

<sup>a</sup> Fisher's exact p; <sup>b</sup> Pearson's  $\chi^2$  p

\*\* Diagnosis according to ICD-10 classification: F20.0 – paranoid schizophrenia; F20.1 – hebephrenic schizophrenia; F20.5 – residual schizophrenia; F25 – schizoaffective disorder; F22 – persistent delusional psychosis

the costal arc and iliac crest when the patient was standing up and at mid-expiration. Blood pressure was measured with an aneroid sphygmomanometer in an office setting. Average daily dose of olanzapine was calculated for each patient for the complete previous period of administration (mg pro die).

Excluded from the study were patients who had shown symptoms of chronic or acute infection, allergies, or any other condition known to affect the immune system for at least two weeks before the study. They were also free of using other concomitant drugs known to alter immune function.

## Statistical analyses

Simple descriptive statistics (means, standard deviations and 95% confidence interval) were generated for all continuous variables. For discrete variables number of patients and percentages are given. The difference between the two group means was analyzed by Student's t-test. The difference between the two group proportions was analyzed by Pearson's chi-squared test, and Fisher's test where appropriate. The significance level was set at p<0.05. Multivariate logistic regression was used to access predictors of MetS. Analyses were performed using SPSS for Windows, Version 18.0.

## RESULTS

The average age of the patients was 48.13±8.78 years. For the majority of patients (49.5%) clinical diagnosis (ICD-10) was the paranoid form of schizophrenia, followed by the hebephrenic form (21.5%). Permanent antipsychotic treatment with olanzapine lasted for 8.39±2.15 months, with average doses of 13.96±4.28 mg pro die, which is middle to high therapeutic range. Average duration of illness of 13.53±5.05 years and number of previous hos-

pitalizations of 5.62±4.94 suggest that this patient sample can be considered to consist of schizophrenic patients. In this regard, the fact that the vast majority of patients were smokers (over 96%) was expected. As it is shown in Table 2, there was no significant difference by sex according to the data, except for the number of previous hospitalizations, in favor of women.

The prevalence of MetS in our study group was 34.4%, women insignificantly higher than men (54.5% and 29.6%, respectively) (Table 2).

In Table 3 data were compared according to MetS presence (IDF criteria). We found statistically significant difference in favor of the subgroup with present MetS among these observed parameters: age (p=0.039), waist circumference (p<0.001), both the systolic (p=0.001) and diastolic (p<0.001) blood pressure, heredity data about diabetes mellitus type 2 (p=0.001) and hyperlipidemia (p<0.001). BMI was also significantly different in the subgroup with diagnosed MetS (p<0.001), where patients were overweight (average BMI of 27.82±4.34). Subgroup of patients without MetS was in the normal weight range of BMI (average 24.21±3.81). Presence microalbuminuria in our patient sample was also significantly higher in the subgroup with diagnosed MetS. Smoking habit, average daily dose of olanzapine, duration of olanzapine administration, as well as the illness length, did not show statistical difference regarding MetS presence.

Clinical state of patients evaluated by PANSS for schizophrenia showed average total PANSS score of 85.73± 26.13. Also, none of the PANSS subscales significantly differed according to MetS presence. The similar ratio is present for BPRS scores – average total score of 39.69±10.26, no statistically significant difference regarding the presence of MetS among patients (Table 4).

On the contrary, the laboratory tests results (Table 5) revealed significant differences. In comparison to patients without MetS, subjects with a diagnosis of MetS had significantly higher the following measured parameters: fast-

**Table 3.** Metabolic syndrome presence related to anamnestic, anthropometric data and microalbuminuria spot urine test

| Parameter                              | MetS present (n=32) | Without MetS (n=61) | p*                           |
|--|---------------------|---------------------|------------------------------|
| Age (years)                            | 50.72±7.82          | 46.77±9.00          | <b>0.039</b>                 |
| Smoking habit                          | 32 (100.0)          | 57 (93.4)           | 0.139 <sup>b</sup>           |
| Olanzapine dose (mg/pd)                | 14.12±4.26          | 13.88±4.34          | 0.800                        |
| Olanzapine treatment (months)          | 8.31±2.07           | 8.43±2.20           | 0.810                        |
| Illness length (years)                 | 14.72±5.31          | 12.90±4.84          | 0.099                        |
| Waist circumference (cm)               | 99.06±12.34         | 86.84±11.16         | <b>&lt;0.001</b>             |
| BMI (kg/m <sup>2</sup> )               | 27.82±4.34          | 24.21±3.81          | <b>&lt;0.001</b>             |
| Systolic blood pressure (mmHg)         | 132.03±15.34        | 118.79±19.80        | <b>0.001</b>                 |
| Diastolic blood pressure (mmHg)        | 81.41±8.25          | 74.75±8.08          | <b>&lt;0.001</b>             |
| Diabetes mellitus type 2 heredity data | 12 (37.5)           | 5 (8.2)             | <b>0.001<sup>b</sup></b>     |
| Hyperlipidemia heredity data           | 10 (31.3)           | 1 (1.6)             | <b>&lt;0.001<sup>a</sup></b> |
| Microalbuminuria (>300 mg/L)           | 5 (15.6)            | 0 (0.0)             | <b>0.002<sup>a</sup></b>     |

Data are presented as mean value ± standard deviation, or as number of patients (frequency) with percentage.

\* p – Student's t-test value (p<0.05 bolded if significant)

<sup>a</sup> Fisher's exact p; <sup>b</sup> Pearson's  $\chi^2$  p

MetS – metabolic syndrome (diagnosed by IDF criteria); BMI – body mass index

**Table 4.** Psychiatric scales scores and presence of the metabolic syndrome

| Parameter                           | Total (n=93) | MetS present (n=32) | Without MetS (n=61) | p*    |
|-------------------------------------|--------------|---------------------|---------------------|-------|
| PANSS total score                   | 85.73±26.13  | 91.81±27.98         | 82.54±24.75         | 0.104 |
| PANSS positive score                | 18.71±8.21   | 20.59±10.30         | 17.72±6.77          | 0.110 |
| PANSS negative score                | 26.53±9.57   | 28.72±8.78          | 25.38±9.85          | 0.110 |
| PANSS general psychopathology score | 41.20±12.00  | 42.66±12.10         | 40.44±11.98         | 0.401 |
| BPRS total score                    | 39.69±10.26  | 40.22±12.59         | 39.41±8.90          | 0.720 |

Data are presented as mean value ± standard deviation.

\* p – Student's t test value (p<0.05 bolded if significant)

**Table 5.** Metabolic syndrome in relation to laboratory test results

| Parameter                | Total (n=93) | MetS present (n=32) | Without MetS (n=61) | p*               |
|--------------------------|--------------|---------------------|---------------------|------------------|
| Fasting glucose (mmol/l) | 4.97±1.20    | 5.39±1.29           | 4.75±1.09           | <b>0.014</b>     |
| Triglycerides (mmol/l)   | 2.00±1.10    | 2.47±1.25           | 1.76±0.93           | <b>0.003</b>     |
| HDL-cholesterol (mmol/l) | 1.27±0.25    | 1.14±0.26           | 1.33±0.22           | <b>&lt;0.001</b> |
| CRP (mg/L)               | 6.31±3.92    | 7.13±4.79           | 5.89±3.33           | 0.147            |
| LDL-cholesterol (mmol/L) | 3.06±0.77    | 3.14±0.78           | 3.02±0.78           | 0.488            |
| Cholesterol (mmol/L)     | 5.27±0.98    | 5.43±1.06           | 5.18±0.94           | 0.265            |

Data are presented as mean value ± standard deviation.

\* p – Student's t-test value (p<0.05 bolded if significant)

**Table 6.** Multivariate analysis of metabolic syndrome risk factors

| Risk factor                  | OR     | 95% CI      |             | p*           |
|------------------------------|--------|-------------|-------------|--------------|
|                              |        | Lower limit | Upper limit |              |
| Age (years)                  | 1.095  | 0.998       | 1.202       | 0.056        |
| Enhanced CRP value (>5 mg/L) | 4.555  | 1.057       | 19.627      | <b>0.042</b> |
| BMI (kg/m <sup>2</sup> )     | 1.328  | 1.105       | 1.597       | <b>0.002</b> |
| DM type 2 heredity data      | 14.134 | 2.724       | 73.348      | <b>0.002</b> |
| Microalbuminuria (>300 mg/L) | 1.208  | 0.000       | 0.000       | 0.999        |
| Hyperlipidemia heredity data | 53.134 | 2.768       | 1019.916    | <b>0.008</b> |

Hosmer–Lemeshow goodness-of-fit test  $\chi^2=5.847$ ; df=8; p=0.664; p<0.05 significance bolded; DM – diabetes mellitus

ing glucose (p=0.014), total triglycerides (p=0.003) and significantly lower HDL-c levels (p<0.001). Interestingly, CRP plasma levels did not differ significantly according to Mets presence, while all the ranges were above the cutoff point of 5 mg/L: total average of 6.31±3.92, subgroup with

MetS 7.13±4.79, subgroup without MetS 5.89±3.33. In addition, the LDL-c ranges as well as total cholesterol ranges did not show statistically significant difference in regard to the presence of MetS.

The multivariate logistic regression was done with the aim to reveal factors associated with MetS (in addition to its constituting variables by the IDF criteria) in our sample of patients (Table 6). We chose risk factors which are easy to handle in everyday clinical work. Among them, we found several statistically significant parameters, marked as strong predictors in this patient sample, in order of appearance: case history data about diabetes mellitus type 2 in family history (p=0.002); BMI (p=0.002); case history data about hyperlipidemia in family history (p=0.008); enhanced CRP levels (over the cutoff point of 5 mg/L) (p=0.042).

The age of the patients was close to being a significant predictor (p=0.056), while microalbuminuria did not present itself as a significant risk factor in our study (p=0.999).

## DISCUSSION

According to data provided by meta-analysis, the overall rate of MetS in schizophrenia and related disorders is 32.5% [22]. A European study showed prevalence of the metabolic syndrome in patients with schizophrenia treated with antipsychotics to be 36% (IDF criteria) [9]. In our study group treated with olanzapine prevalence of MetS was similar (34.4%). Such high prevalence of MetS in this population reaches as much as twice the prevalence of general population: in European countries it varies from 5.9% in men and 2.1% in women in France [23], to 15.7% in men and 14.2% in women in Finland [24]. Kagal et al. [25] described comparable results in 2012 on a sample of 80 patients with a diagnosis of schizophrenia and treated with a single SGA for three months, where prevalence of MetS was found to be 35%. In the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) study, the authors identified 88% of patients with dyslipidemia, 62% of patients with arterial hypertension and 38% of patients with diabetes who were not properly diagnosed and had received no treatment for their physical disorders [26].

Despite the fact that our results didn't find statistical variance associated with MetS presence in parameters such as olanzapine treatment duration, daily dose of olanzapine, smoking habit, length of illness, Park et al. [27] noticed lifestyle factors that correlate with MetS – smoking habit, illness length and antipsychotic administration length. Otherwise, significantly marked variables associated with MetS were older age, waist circumference, overweight (BMI>25) and elevated blood pressure. Straker et al. [28], on a similar patient sample size receiving different SGA agents, also reported abdominal obesity with the highest sensitivity for MetS presence. Combining abdominal obesity and elevated fasting blood glucose they found 100% sensitivity, calculated with positive predictive value test. Frequent screening of waist circumference and blood pressure in patients receiving SGAs, like olanzapine, is an inexpensive as well as a sensitive method. Variations in these values during SGA treatment should further alert us to collect blood samples for lipid profile and fasting glucose levels.

In our study, patients with diagnosed MetS were overweight (average BMI of  $27.82 \pm 4.34$ ), in comparison with the subgroup without MetS, which were in normal weight range (average BMI of  $24.21 \pm 3.81$ ). Baptista and Kin [14] have also found high correlation of BMI and metabolic disturbances during the SGA treatment. In a cross sectional study of Mackin et al. [17], the relationship between obesity and elevated glucose levels was statistically more significant with SGA than with FGA treated subjects. Our results showed significant difference of waist circumference among the subgroups with/without MetS, but both subgroups of patients had values above those set by the IDF criteria.

Our data about fasting glucose levels, although significantly higher in favor of the subgroup with MetS, didn't show elevated values over the cutoff point of 5.6 mmol/L. In literature there is evidence that olanzapine has greater potency for glucose disturbances than other SGA agents

[29]. A recent systematic review and meta-analysis concluded that all SGAs (excluding aripiprazole, ziprasidone and amisulpride, for which there were insufficient data to be included in the analysis) were associated with a 30% increased risk of diabetes as compared to FGAs in people with schizophrenia [30].

Also, HDL-c levels were within the normal range despite the statistical significance in favor of MetS presence. Triglyceride levels were above the cutoff point of 1.7 mmol/L, with the average total of  $2.00 \pm 1.10$ , for the subgroup with MetS the average was  $2.47 \pm 1.25$ , and for the subgroup without MetS the average was  $1.76 \pm 0.93$ , with high statistical significance ( $p=0.003$ ). Atmaca et al. [31] found significant rise of plasma triglycerides after six weeks of olanzapine treatment. LDL-c and cholesterol ranges were on the upper limit of normal ranges, with no statistical difference among observed subgroups.

Absence of the positive correlation between the symptom severity and metabolic disturbances, especially weight gain, in our study could be discussed in relation to long time antipsychotic treatment and persistence of chronic schizophrenic symptoms, illustrated by PANSS and BPRS scores (average total PANSS  $85.73 \pm 26.13$ , average BPRS  $39.69 \pm 10.26$ ). In literature, there is clear evidence in short term monitoring (between two and four months), that weight gain is strongly related to significant decrease of psychiatric scales scores [32].

Using multivariate logistic regression analysis, where the presence of MetS was a dependent variable, we found significant odds ratios for positive data about diabetes mellitus type 2 and hyperlipidemia in family history, as well as for the BMI. De Leon et al. [13] marked genetic factors that are competent for direct lipid abnormalities associated with SGA administration.

CRP values over the cutoff point of 5 mg/L were a significant predictor in our study group. Inflammation of the visceral adipose tissue in the pathophysiology of MetS is well established in literature [33]. Both subgroups of our patient sample (with/without MetS –  $7.13 \pm 4.79$  vs.  $5.89 \pm 3.33$ , respectively), as well as the average total ranges of CRP ( $6.31 \pm 3.92$ ), were above the cutoff point of 5 mg/L.

## CONCLUSION

High rate of MetS in patients treated with olanzapine that we found in this study (34.4%) significantly exceeds MetS prevalence in general population. Among observed parameters, our study pointed to several cardiometabolic "high risk" predictors associated with MetS presence: heredity of diabetes and hyperlipidemia in family history, overweight, and enhanced CRP ranges. Since the risk of various cardiovascular events significantly increases in patients with MetS, regular monitoring of cardiometabolic risk factors in patients on long-term olanzapine treatment is highly recommended. Positive heredity distress mentioned above may direct a psychiatrist to prescribe some other drug than olanzapine in the long-term treatment of schizophrenia.

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## Дугорочно лечење оланзапином у болничким условима: преваленција и предиктори метаболичког синдрома

Ирена Поповић<sup>1</sup>, Драган Раванић<sup>2</sup>, Слободан Јанковић<sup>2</sup>, Драган Миловановић<sup>2</sup>, Марко Фолић<sup>2</sup>, Албина Станојевић<sup>1</sup>, Милутин Ненадовић<sup>3</sup>, Милена Илић<sup>2</sup>

<sup>1</sup> Специјална болница за психијатријске болести „Горња Топоница“, Ниш, Србија;

<sup>2</sup> Универзитет у Крагујевцу, Факултет медицинских наука, Крагујевац, Србија;

<sup>3</sup> Универзитет у Приштини, Медицински факултет, Катедра за психијатрију, Косовска Митровица, Србија

### КРАТАК САДРЖАЈ

**Увод** Ризик од метаболичких поремећаја знатно је већи код особа оболелих од шизофренија који се лече нетипичним антипсихотичима. Код ових болесника генерално је већа стопа смртности у односу на општу популацију, што укључује и повећану смртност од кардиоваскуларних обољења. Други фактори који доприносе развоју метаболичког синдрома (МетС) су: трајање болести, старост, женски пол и лоше животне навике.

**Циљ рада** Ова студија је урађена ради утврђивања преваленције МетС код шизофрених болесника који дуго бораве у болници и лече се оланзапином дуже од шест месеци (монотерапија), као и факторе – предикторе који су у позитивној корелацији са постојањем МетС према критеријумима Међународне федерације за дијабетес (*IDF*).

**Методе рада** Укупно 93 испитаника (71 мушкарац и 22 жене) оболела од шизофреније, који су дуже време били хоспитализовани у Специјалној болници за психијатријске болести „Горња Топоница“ код Ниша и који су били на монотерапији оланзапином најмање шест месеци без престанка, подвргнуто је основном прегледу који је укључивао: про-

цену према психијатријским скалама, антропометријска мерења, социодемографску анкету и лабораторијске анализе.

**Резултати** Преваленција МетС на посматраном узорку испитаника, мерено критеријумима *IDF*, била је 34,4%. Фактори ризика који су се у нашем истраживању мултиваријантном анализом издвојили као значајни предиктори МетС су (по реду значајности): позитивна анамнеза о дијабетесу тип 2 у ужој породици ( $p=0,002$ ), индекс телесне масе већи од  $25 \text{ kg/m}^2$  ( $p=0,002$ ), позитивна анамнеза о хиперлипидемији у ужој породици ( $p=0,008$ ) и повишени нивои С-реактивног протеина ( $p=0,042$ ).

**Закључак** Преваленција МетС у нашем истраживању значајно превазилази преваленцију овог поремећаја у општој популацији. Међу посматраним варијаблама ова студија издваја неколико предиктора „високог ризика“ удружених с постојањем МетС код болесника на дугорочном лечењу оланзапином. Код постојања генетског оптерећења за дијабетес мелитус тип 2, односно хиперлипидемију, боље је одлучити се за други антипсихотик безбеднијег метаболичког профила.

**Кључне речи:** метаболички синдром; шизофренија; оланзапин

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