

## PHARMACOLOGICAL AND DISORDER ASSOCIATED CARDIOVASCULAR CHANGES IN PATIENTS WITH PSYCHOSIS. A COMPARISON BETWEEN OLANZAPINE AND RISPERIDONE

LIANA DEHELEAN<sup>1#\*</sup>, MINODORA ANDOR<sup>2#</sup>, ANA MARIA ROMOȘAN<sup>3#</sup>, MINODORA MARINELA MANEA<sup>4#</sup>, RADU ȘTEFAN ROMOȘAN<sup>1</sup>, ION PAPA VĂ<sup>1</sup>, ANA CRISTINA BREDICEAN<sup>1</sup>, VALENTINA OANA BUDA<sup>5</sup>, MIRELA CLEOPATRA TOMESCU<sup>2</sup>

<sup>1</sup>Psychiatry, Neurosciences Department, "Victor Babeș" University of Medicine and Pharmacy, 2 E. Murgu Square, Timișoara, Romania

<sup>2</sup>Medical Semiology II, Internal Medicine I Department, "Victor Babeș" University of Medicine and Pharmacy, 2 E. Murgu Square, Timișoara, Romania

<sup>3</sup>"Victor Babeș" University of Medicine and Pharmacy, 2 E. Murgu Square, Timișoara, Romania

<sup>4</sup>Psychology, Medical Education Department, "Iuliu Hațieganu" University of Medicine and Pharmacy, 8. V. Babeș Street, Cluj-Napoca, Romania

<sup>5</sup>Pharmacology and Clinical Pharmacology, 2<sup>nd</sup> Department, "Victor Babeș" University of Medicine and Pharmacy, 2 E. Murgu Square, Timișoara, Romania

\*corresponding author: [lianadeh@umft.ro](mailto:lianadeh@umft.ro)

#These authors contributed equally to this work and thus share first authorship.

Manuscript received: March 2017

### Abstract

Patients receiving antipsychotic medication present a high risk of cardiovascular complications due either to medication or to the disorder itself. This study compares the cardiovascular risk factors and echocardiographic parameters in two samples of outpatients with psychosis treated for at least 2 months with long acting injectable olanzapine or risperidone. We assessed the socio-demographic data, the cardiovascular risk factors, and the echocardiographic parameters. Subjects receiving risperidone had significantly more frequent regional myocardial contractility abnormalities ( $\chi^2 = 6.896$ ,  $p = 0.009$ ) and diastolic dysfunction of the left ventricle than those on olanzapine ( $\chi^2 = 5.416$ ,  $p = 0.02$ ), and were more frequently hypertensive. Patients with associated mood stabilizers presented more abnormalities related to the contractile function of the left ventricle than those receiving only antipsychotic treatment ( $\chi^2 = 4.138$ ,  $p = 0.042$ ). There were no differences between the two samples concerning tobacco use or the presence of the metabolic syndrome.

### Rezumat

Pacienții tratați cu antipsihotice prezintă un risc crescut de complicații cardiovasculare consecutiv tratamentului sau bolii. Acest studiu a comparat factorii de risc cardiovascular și parametrii ecocardiografici a două loturi de pacienți cu psihoză, aflați de cel puțin 2 luni în tratament ambulatoriu cu preparate injectabile *depôt* cu olanzapină sau risperidonă. Au fost analizate datele socio-demografice, factorii de risc cardiovascular și parametrii ecocardiografici. Subiecții tratați cu risperidonă au prezentat mai frecvent tulburări de contractilitate miocardică regională ( $\chi^2 = 6,896$ ,  $p = 0,009$ ) și disfuncție diastolică a ventriculului stâng ( $\chi^2 = 5,416$ ,  $p = 0,02$ ), comparativ cu cei tratați cu olanzapină și au fost mai frecvent hipertensivi. Pacienții cu medicație timostabilizatoare asociată au avut mai frecvent tulburări de contractilitate miocardică a ventriculului stâng față de cei tratați doar cu antipsihotice ( $\chi^2 = 4,138$ ,  $p = 0,042$ ). Nu au fost evidențiate diferențe între cele două loturi privind fumatul sau prezența sindromului metabolic.

**Keywords:** olanzapine, risperidone, cardiovascular risk, echocardiography

### Introduction

Cardiovascular complications in patients with psychosis need special attention, largely because they may reduce life expectancy. Individuals suffering from schizophrenia have a higher prevalence of cardiovascular diseases compared with the general population and adjusted with age [5]. This finding is a consequence of several factors, some induced by the disorder itself, others by medication. The negative symptoms of schizophrenia may encourage a sedentary

lifestyle, while positive symptoms such as delusions and hallucinations may induce anxiety and depression, which increase the risk of developing cardiovascular complications. Retrospective [13] and prospective [23] studies identified metabolic dysfunctions in patients with psychosis, before, as well as after the introduction of antipsychotics in the treatment of these patients. This implies that both psychosis and psychotropic medication are equally involved in the development of the metabolic disturbances.

Cardiovascular risk factors are classified into three categories [9]: major independent factors (smoking, hypertension, elevated serum total and LDL cholesterol, low serum HDL cholesterol, diabetes mellitus, and advancing age), predisposing factors (obesity, abdominal obesity, physical inactivity, family history of premature coronary heart disease, psychosocial factors, ethnic characteristics) and conditional factors (elevated serum triglycerides, small LDL particles, elevated serum homocysteine, elevated serum lipoprotein a, pro-thrombotic factors inflammatory markers). By combining these parameters, algorithms were developed to predict coronary heart disease risk [28]. The concept of the metabolic syndrome (MS) was created using some of the major (hypertension, low HDL, hyperglycaemia), predisposing (abdominal obesity) and conditional (elevated serum triglycerides) cardiovascular risk factors [9].

Antipsychotic medication may influence in various degrees the carbohydrate and the lipid metabolism through central and/or peripheral mechanisms depending on the specific pharmacodynamic profile. At the level of hypothalamus, antipsychotics have an orexigenic effect by blocking histaminic 1 (H1) [14] and serotonergic 2C (5HT2C) receptors. Animal studies showed that the blockade of H1 receptors activates AMP-kinase in mice [11]. In addition, agonism at 5HT2C receptors of the anorexigenic pro-opiomelanocortin neurons in hypothalamus decrease food intake in animals [15]. At the peripheral level, antipsychotics which block muscarinic 3 (M3) receptors at the level of pancreatic  $\beta$  cells, inhibit insulin secretion [24]. A combined affinity of an antipsychotic for 5HT2C, H1, and muscarinic receptors will increase the risk of developing diabetes mellitus [17].

Apart from the dual dopamine D2 and serotonin 5HT2A receptor blockade which ensures an antipsychotic action associated with a low profile of extrapyramidal and endocrine side effects, olanzapine and risperidone differ in respect to the complexity of their mechanisms of action. Olanzapine, having affinity for more receptors than risperidone is considered a multifunctional drug, therefore is an alternative to drug combinations [12]. As a fact, epidemiologic data show that clinicians prefer antipsychotics acting on multiple receptors [21]. On the other hand, a more complex mechanism of action may result in more various side-effects. Through combined H1, 5HT2C and M3 blockade, olanzapine has the most important impact on carbo-hydrate metabolism. Patients treated with olanzapine show increases in blood glucose levels with 10 mg/dL after one year of treatment [19]. By contrast, risperidone, with a simpler pharmacologic profile [26], interacts with H1 and  $\alpha$ -adrenergic receptors and insignificantly with cholinergic receptors [18].

Concerning the lipid metabolism, the treatment with antipsychotics induces hypertriglyceridaemia, low HDL cholesterol and high LDL cholesterol serum levels. Treatment with olanzapine is associated with hyperlipidaemia, while risperidone has a lesser impact on plasma lipids. Animal studies show that chronic administration of risperidone results in fatty tissue hypertrophy [5].

The direct effects of antipsychotics on the cardiovascular system include QTc prolongation, tachycardia, orthostatic hypotension and sudden death. Hypertension was not shown to have a higher prevalence in patients with schizophrenia compared to the general population [3]. Among antipsychotics clozapine was linked with the risk of developing myocarditis [10]. To our knowledge, echocardiographic examinations are not routinely performed in patients treated with antipsychotics, except specific occasions focusing mainly on clozapine [20].

The risk of developing cardiovascular diseases seems to be more important in patients that are either adherent to oral antipsychotics, or are treated with long acting injectable (LAI) formulations. In comparison to oral antipsychotics, LAI formulations produce lower and less fluctuating serum concentrations [16]. They also ensure a good adherence to treatment, knowing the fact that only 41% of patients with schizophrenia comply with the antipsychotic treatment [8].

The aim of this study was to assess the cardiovascular risk factors and changes in cardiac function through transthoracic echocardiography in patients treated with either olanzapine or risperidone.

## Materials and Methods

### *Study design*

It was conducted a two centres (Timișoara and Cluj-Napoca, Romania) cross-sectional study on outpatients diagnosed with schizophrenia and schizoaffective disorder according to ICD-10 criteria. Patients treated with oral antipsychotics were excluded from the study in order to assure a convincing treatment adherence. Patients on LAI treatment are required to be previously stabilized with the same medication in an oral form. This implies that the measurements were performed upon study entry because of treatment adherence issues with oral formulations. In addition, subjects with already diagnosed hypertension, glucose and lipid metabolism abnormalities and electrocardiographic or echocardiographic changes were excluded from the study. The investigated molecules were selected according to their different receptor profiles resulting in a more (olanzapine) or less (risperidone) complex mechanism of action.

Some patients received adjunctive mood stabilizers (sodium valproate, carbamazepine, or lamotrigine). The subjects receiving LAI olanzapine or risperidone for less than 2 months were not included in the study.

The patients were evaluated by a cardiologist searching for clinical, electrocardiographic and echocardiographic (ejection fraction, regional contractile abnormalities) data. The following parameters were assessed: cardiovascular risk factors (age, gender, smoking habits and presence of the MS), transthoracic echocardiographic parameters, medication and BPRS-E scores (Brief Psychiatric Rating Scale – Expanded version 4.0). The expanded version of BPRS, was used to measure the severity of the psychiatric symptoms in patients with psychotic disorders [27]. The metabolic syndrome was diagnosed according to the consensus statement from the International Diabetes Federation published in 2006 [1]. Fasting glycaemia was measured using the PalmLab SC-101 glucometer. The lipid profile was determined using the LipidPro ILM-0001A lipid meter.

In order to discriminate between the pharmacologic and the disorder induced effect, we assessed the following time intervals: duration of psychosis (DP defined as months from the onset of the psychotic disorder to the present assessment); time spent (months) on LAI treatment (LAI treatment period); time interval (months) from the onset of the psychotic disorder to the LAI treatment initiation (pre LAI period).

The protocol of the study and the informed consent were approved by the Scientific Research Ethic Committee of “Victor Babeş” University of Medicine and Pharmacy from Timișoara, Romania. This project was conducted in accord with the Helsinki Declaration. Each subject enrolled in the study, signed the informed consent. The authors have undertaken this study in the course of their employment, with no funding from any other source.

#### Statistical analysis

Data were analysed using IBM SPSS Statistics (version 20). The Shapiro-Wilk test revealed a non-Gaussian data distribution. Therefore, to analyse group differences, a non-parametrical test was used (Mann-Whitney U).  $\chi^2$  (chi-square) test was used for categorical (nominal) variables. Associations between scores were analysed using Spearman’s correlation coefficients. The level of significance was set at 0.05 and all results were two-tailed.

### Results and Discussion

We assessed 64 outpatients diagnosed with schizophrenia and schizoaffective disorder, currently in remission. All subjects were enrolled between 2015 and 2016. The socio-demographic and clinical characteristics of the sample are presented in Table I.

**Table I**  
Socio-demographic and clinical characteristics of the sample

Sample characteristics	Entire sample		Men		Women	
	n	%	n	%	n	%
	64	100	37	57.8	27	42.2
Mean age (years) at disorder onset	29.54 ± 10.45		28.45 ± 10.66		31.03 ± 10.15	
Mean age (years) at present assessment	41.25 ± 11.14		42.02 ± 12.05		40.18 ± 9.88	
Diagnosis						
Schizophrenia	51	79.7	28	54.9	23	45.1
Schizoaffective disorder	13	20.3	9	69.2	4	30.8
Mean BPRSE-E total score	38.76 ± 11.57		40.72 ± 12.34		36.07 ± 10.02	
Associated mood stabilizer						
yes	42	65.6	22	52.4	20	47.6
no	24	34.4	15	68.2	7	31.8

Patients were divided in two samples, one receiving olanzapine LAI and the other one, risperidone LAI. There were no differences between the two samples in respect to: age at study entry, age at disorder onset, gender and adjunctive associated mood stabilizers.

The dosage of each long acting injection and the choice of the adjunctive mood stabilizer were established for each patient by the prescribing psychiatrist. In Table II are presented the doses and duration of the LAI treatment.

**Table II**  
Sample characteristics according to LAI antipsychotic dosages

LAI Antipsychotic	Dosage (mg/months)	Duration of LAI treatment (months)	Number of patients (n)	Percentage (%)
Olanzapine	1 injection of 210 mg/month	21 ± 12.72	2	3.1
Olanzapine	1 injection of 300 mg/month	17.83 ± 14.23	6	9.4
Olanzapine	1 injection of 405 mg/month	13.9 ± 11.87	6	9.4
Olanzapine	2 injections of 300 mg/month	8.94 ± 6.67	18	28.1
Risperidone	2 injections of 37.5 mg/month	19.85 ± 16.58	14	21.9
Risperidone	2 injections of 50 mg/month	30.0 ± 21.5	18	28.1

Cardiovascular risk factors are: tobacco use, metabolic syndrome and hypertension.

#### *Tobacco use*

From the entire group of 64 subjects, 26 (40.6%) patients were smokers among which 22 (84.6%) men and 4 (15.4%) women. Males were significantly more frequent smokers than females ( $\chi^2 = 12.89$ ,  $p < 0.0001$ ) and smoked more cigarettes *per day* ( $U = 272$ ,  $Z = -3.487$ ,  $p < 0.0001$ ). No differences were found between patients on olanzapine and risperidone regarding the number of cigarettes smoked *per day*. The link between smoking, schizophrenia and antipsychotic treatment is difficult to explain. Nicotine might enhance cognition [6] and thus be used as a “treatment” for the disorder induced cognitive dysfunctions or by drug induced sedation. On the other hand, smoking is an enzymatic inducer lowering the serum concentrations of olanzapine [2, 7].

#### *Hypertension*

Patients receiving risperidone LAI had significantly higher values for either systolic ( $U = 364.5$ ,  $Z = -1.993$ ,  $p = 0.046$ ) and diastolic blood pressure ( $U = 357.5$ ,  $Z = -2.108$ ,  $p = 0.035$ ). The patients presenting hypertension had a longer duration of pre LAI treatment than those without hypertension ( $U = 170$ ,  $Z = -2.924$ ,  $p = 0.003$ ), with no differences in respect to the total duration of psychosis (DP) and duration of LAI treatment. This may suggest that a period of uncertain adherence to treatment may result in clinical stress which is reflected in higher blood pressure values. Given the fact that these patients were not diagnosed before the introduction of LAI treatment with hypertension, this result is relative. When looking to the BPRS-E results, the total score positively correlates with the duration of pre LAI treatment period ( $r = 0.304$ ,  $p = 0.015$ ).

#### *The metabolic syndrome (MS)*

The criteria for the MS diagnostic were fulfilled by 38 (59.4%) patients, among them, 17 (44.7%) on olanzapine and 21 (55.3%) on risperidone. There were no differences between patients treated with olanzapine and risperidone regarding the presence of the MS. In addition, the occurrence of the MS in the whole group of patients was not influenced by gender, age at study entry, tobacco use, associated mood stabilizers, BPRS-E scores, or dosage. Literature data also suggests that there is no clear relationship between medication induced weight gain and the dose of antipsychotics [22, 25]. However, patients presenting the MS had the disorder onset at a significantly earlier age ( $U = 394$ ,  $Z = -1.986$ ,  $p = 0.047$ ).

We found that patients presenting the criteria of MS had a longer duration of psychosis ( $U = 329.5$ ,  $Z = -2.252$ ,  $p = 0.024$ ), and a longer duration of LAI treatment ( $U = 197$ ,  $Z = -4.075$ ,  $p < 0.0001$ ), with

no significant differences regarding the pre-LAI treatment period. This means that the MS may be a consequence of either the disorder itself, or the antipsychotic treatment. In this respect, olanzapine and risperidone share the same risk of inducing MS.

#### *Echocardiographic findings*

The following echocardiographic modifications were identified in our sample: regional contractility abnormalities, valve abnormalities, and diastolic dysfunction as illustrated in Table III. We found that the echocardiographic findings were not influenced by age at disorder onset, gender, tobacco use, metabolic syndrome or hypertension.

The subjects presenting echocardiographic modifications were significantly older than those without echocardiographic findings (regional contractility abnormalities  $U = 254$ ,  $Z = -2.552$ ,  $p = 0.011$ ; valve abnormalities  $U = 271.5$ ,  $Z = -2.801$ ,  $p = 0.005$ ; diastolic dysfunction  $U = 203$ ,  $Z = -3.463$ ,  $p = 0.001$ ). In patients presenting diastolic dysfunction, both the total duration of the psychosis ( $U = 223.5$ ,  $Z = -3.141$ ,  $p = 0.002$ ) and the pre-LAI period ( $U = 241$ ,  $Z = -2.883$ ,  $p = 0.004$ ) were longer. Conversely, the LAI treatment period was significantly longer in patients with regional contractility abnormalities ( $U = 273$ ,  $Z = -2.279$ ,  $p = 0.023$ ). In this respect, it is possible that the regional contractility abnormalities may be influenced by medication (antipsychotics, mood stabilizers).

Treatment with risperidone LAI was associated with significantly more frequent regional contractility abnormalities ( $\chi^2 = 6.896$ ,  $p = 0.009$ ) and diastolic dysfunction ( $\chi^2 = 5.416$ ,  $p = 0.02$ ) than the treatment with olanzapine LAI. No differences were found between the two samples regarding valve abnormalities. Patients receiving mood stabilizers presented more frequently regional contractility abnormalities than those without adjunctive treatment ( $\chi^2 = 4.138$ ,  $p = 0.042$ ). Knowing the fact that the total duration of the psychosis ( $U = 360$ ,  $Z = -2.038$ ,  $p = 0.042$ ) and the duration on LAI treatment ( $U = 277.5$ ,  $Z = -3.155$ ,  $p = 0.002$ ) were shorter in patients receiving olanzapine than in those on risperidone with no differences regarding the pre-LAI treatment period, the echocardiographic findings in patients treated with risperidone may be the consequence of a longer exposure to psychotropic treatment. To our best knowledge, at present, there are no other studies regarding echocardiographic changes in patients taking long acting antipsychotics. There are few studies conducted on patients taking clozapine in its oral form.

Because the clinical cardiologic examination and electrocardiographic recordings didn't reveal any significant abnormalities, these data were not included in Table III.

Table III

Sample characteristics according to cardiovascular risk factors and echocardiographic modifications

LAI antipsychotic	Patients group		Treated with olanzapine		Treated with risperidone	
	n	%	n	%	n	%
	64		33	51.6	31	48.4
Gender						
Men	37	57.8	18	48.6	19	51.4
Women	27	42.2	15	55.6	12	44.4
Mean age (years) at disorder onset	29.54 ± 10.45		29.36 ± 9.49		29.74 ± 11.53	
Mean age (years) at assessment	41.25 ± 11.14		38.87 ± 10.83		43.77 ± 11.08	
Smokers	26	40.6	12	46.2	14	53.8
Mean number of cigarettes/day	8.98 ± 13.12		7.57 ± 11.53		10.48 ± 14.68	
Metabolic syndrome	38	59.4	17	44.7	21	55.3
Echocardiographic findings						
Regional contractility abnormalities	19	29.7	5	26.3	14	73.7
Valve abnormalities*	23	35.9	9	39.1	14	60.9
Diastolic dysfunctions	20	31.3	6	30	14	70

\*Valve abnormalities: mitral, tricuspid, and/or aortic regurgitation, aortic calcifications, degenerative lesions

## Conclusions

In the assessed group of patients, treatment with risperidone LAI was associated with more echocardiographic findings and hypertension than the treatment with olanzapine LAI. The metabolic syndrome appears to be induced by both the disorder and the antipsychotic treatment, regardless of the molecule involved. Hypertension may be a consequence of disorder induced stress in the absence of a continuous antipsychotic treatment. The strengths of the present study are based on precise constant antipsychotic doses and confident adherence to treatment ensured by the LAI formulation. As study limitations, we did not assess risk factors such as physical inactivity, passive smoking, unhealthy diet and the family history of cardiovascular diseases.

## References

- Alberti KGMM, Zimmet P, Shaw J, Metabolic syndrome – a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med.*, 2006; 23: 469-480.
- 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(2): 119-127.
- Davidson S, Judd F, Jolley D, Hocking B, Thompson S, Hyland B, Cardiovascular risk factors for people with mental illness. *Aust NZ J Psych.*, 2001; 35(2): 196-202.
- Davidson M, Risk of cardiovascular disease and sudden death in schizophrenia. *J Clin Psych.*, 2002; 63: 5-11.
- Echim G, Vari CE, Kolcsar M, Cotoi OS, Osz BE, Groşan A, Gall Z, Dogaru M, Time and dose-related side effects of risperidone in rats. *Farmacia*, 2015; 63(6): 845-850.
- Ernst M, Heishman SJ, Spurgeon L, London ED, Smoking history and nicotine effects on cognitive performance. *Neuropsychopharmac.*, 2001; 25(3): 313-319.
- Gex-Fabry M, Balant-Gorgia AE, Balant LP, Therapeutic drug monitoring of olanzapine: the combined effect of age, gender, smoking, and comedication. *Ther Drug Monit.*, 2003; 25(1): 46-53.
- Gilmer TP, Dolder CR, Lacro JP, Folsom DP, Garcia P, Jeste DV, Adherence to treatment with antipsychotic medication and health care costs among Medicaid beneficiaries with schizophrenia. *Am J Psych.*, 2004; 161(4): 692-699.
- Grundy SM, Pasternak R, Greenland P, Smith S, Fuster V, Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations. A statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *Circulation*, 1999; 100: 1481-1492.
- Kilian JG, Kerr K, Lawrence C, Celermajer DS, Myocarditis and cardiomyopathy associated with clozapine. *Lancet*, 1999; 354: 1841-1845.
- Kim SF, Huang AS, Snowman AM, Teuscher C, Snyder SH, Antipsychotic drug-induced weight gain mediated by histamine H1 receptor-linked activation of hypothalamic AMP-kinase. *Proc Natl Acad Sci USA*, 2007; 104: 3456-3459.
- Kim DH, Maneen MJ, Stahl SM, Building a better antipsychotic: receptor targets for the treatment of multiple symptom dimensions of schizophrenia. *Neurotherap.*, 2009; 6(1): 78-85.
- Kohen D, Diabetes mellitus and schizophrenia: historical perspective. *Br J Psych.*, 2004; 184(47): 164-166.
- Kroeze WK, Hufeisen SJ, Popadak BA, Renock SM, Steinberg S, Ernsberger P, Jayathilake K, Roth BL, H1-histamine receptor affinity predicts short term weight gain for typical and atypical antipsychotic drugs. *Neuropsychopharmac.*, 2003; 28: 519-526.
- Lencz T, Robinson DG, Napolitano B, Sevy S, Kane JM, Goldman D, Malhotra AK, DRD2 promoter region variation predicts antipsychotic-induced weight gain in first episode schizophrenia. *Pharmacogenet Genom.*, 2010; 20(9): 569-572.
- Mannaert E, Vermeulen A, Remmerie B, Bouhours P, Levron, JC, Pharmacokinetic profile of long-acting injectable risperidone at steady-state: comparison

- with oral administration. *L'Encéphale*, 2005; 31(5): 609-615.
17. Matsui-Sakata A, Ohtani H, Sawada Y, Receptor occupancy-based analysis of the contributions of various receptors to antipsychotics-induced weight gain and diabetes mellitus. *Drug Metab Pharmacokin.*, 2005; 20: 368-378.
  18. Megens AAHP, Awouters FHL, Schotte A, Meert TF, Dugovic C, Niemegeers CJE, Leysen JE, Survey on the pharmacodynamics of the new antipsychotic risperidone. *Psychopharmac.*, 1994; 114(1): 9-23.
  19. Meyer JM, A retrospective comparison of lipid, glucose and weight changes at one year between olanzapine and risperidone treated inpatients. *J Clin Psych.*, 2002; 63: 425-433.
  20. Murch S, Tran N, Liew D, Petrakis M, Prior D, Castle D, Echocardiographic monitoring for clozapine cardiac toxicity: lessons from real-world experience. *Australas Psych.*, 2013; 21(3): 258-261.
  21. Nasrallah HA, Atypical antipsychotic-induced metabolic side effects: insights from receptor-binding profiles. *Nature*, 2008; 13: 27-35.
  22. Nussbaum L, Hoge LM, Călina D, Andreescu N, Grădinaru R, Ștefănescu R, Puiu M, Modern treatment approaches in psychoses. Pharmacogenetic, neuroimaging and clinical implications. *Farmacia*, 2017; 65(1): 75-81.
  23. Remington G, Schizophrenia, antipsychotics, and the metabolic syndrome: is there a silver lining?. *Am J Psych.*, 2006; 163: 1132-1134.
  24. Robinson DS, Insulin secretion and psychotropic drugs. *Prim Psych.*, 2006; 13: 26-27.
  25. Simon V, van Winkel R, De Hert M, Atypical antipsychotics dose dependent? A literature review. *J Clin Psych.*, 2009; 70(7): 1041-1050.
  26. Stahl SM, Essential psychopharmacology, neuroscientific basis and practical applications, Second Edition, Cambridge University Press, 2000; 433.
  27. Velligan D, Prihoda T, Dennehy E, Biggs M, Shores-Wilson K, Crismon ML, Rush AJ, Miller A, Suppes T, Trivedi M, Kashner TM, Brief psychiatric rating scale expanded version: How do new items affect factor structure?. *Psych Res.*, 2005; 135(3): 217-228.
  28. Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB, Prediction of coronary heart disease using risk factor categories. *Circulation*, 1998; 97: 1837-1847.