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METABOLIC SYNDROME IN SCHIZOPHRENIA - WHO IS MORE TO BLAME: FGA POLYPHARMACY OR CLOZAPINE MONOTHERAPY?

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SUMMARY

Background: *To establish the prevalence of metabolic syndrome and its parameters in group of patients with schizophrenia in polypharmacy – receiving first generation antipsychotics versus clozapine alone treated group.*

Subjects and methods: *48 outpatients with schizophrenia divided into two groups: the first group of 21 patients in polypharmacy with first generation antipsychotics, and the second group of 27 patients treated with clozapine alone were assessed for the presence of metabolic syndrome. We used logistic regression models to assess the relationship between metabolic syndrome and antipsychotic therapy, gender and age.*

Results: *Metabolic syndrome was found in 52.1% of all subjects. Compared to first generation antipsychotics polypharmacy, the monopharmacy with clozapine was associated with elevated rates of metabolic syndrome (28.6% vs. 70.4%, p=0.004). With regard to particular parameters of metabolic syndrome, the elevated plasma triglycerides were significantly more present in subjects within Clozapine group (p=0.03). Logistic regression analysis showed that female gender (p=0.004), and clozapine treatment (p=0.005) were significantly associated with metabolic syndrome.*

Conclusion: *Compared to polypharmacy with first generation antipsychotics, the higher prevalence of metabolic syndrome is found in patients treated with Clozapine alone. The most prevalent metabolic disorder is dyslipidemia.*

Key words: *schizophrenia - metabolic syndrome – polypharmacy - clozapine*

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INTRODUCTION

There are number of studies and emerging data which indicate frequent metabolic abnormalities in patients with schizophrenia (Dixon & Wohlheiter 2003, Bobes et al. 2007). Number of factors and their interactions are behind this phenomenon. Literature data points at habits and lifestyle, impact of disease itself, and influence of medication, and antipsychotics in particular (Bobes et al. 2003, Saari et al. 2005, Schorr et al. 2008, Rejas et al. 2008). In comparison with the general population, patients with schizophrenia have an increased tendency of weight gain (Thakore et al. 2007). It can be caused by a number of factors while their interaction, and morbogenous contribution of each still remains unclear (Ellingrod et al. 2008, Connolly & Kelly 2005, Thakore et al. 2007). A higher prevalence of abdominal obesity is observed in these patients, and it is unrelated to the effects of medication (Thakore et al. 2007). Compared with the general population, mortality in patients with schizophrenia related to diabetes mellitus is increased 2.7 times, and regarding cardiovascular diseases 2.3 times (Curkendall et al. 2004). There are suggestions that metabolic disregulation exists even prior to antipsychotics introduction into therapy and contribute to their metabolic side effects (Fernandez et al. 2009). Metabolic syndrome can contribute to significant morbidity and premature mortality and should be accounted for in the treatment of mental disorders (Jakovljević et al. 2007). Prevalence of metabolic syndrome in patients with schizophrenia is higher (up to 35%) in comparison with the general population (from 8 to 17%) (Heiskanen et al. 2003, McEvoy et al. 2005). Impact of antipsychotics on metabolic syndrome development is focus of intense research efforts. Antipsychotic indubitably improves the quality of life in patients with schizophrenia and represent foundation of adequate treatment. But, in some cases, some of them increase the risk of cardiovascular and metabolic diseases, especially diabetes (AACE Diabetes Mellitus Clinical Practice Gudelines Task Force 2007), and lipid metabolism disorders (Wirshing et al. 2002). It was suggested that choice of antipsychotic is the key factor in the prevention regarding lowering metabolic abnormalities in these patients (Newcomer 2007a). Second generation antipsychotics are especially incriminated (Miller & Craig 2002, Jones et al. 2006, Atmaca et al. 2003, Newcomer 2007b). Some of them, such as olanzapine and clozapine manifest more side effects compared with others, such as amisulpride and risperidone (Rummel-Kluge et al. 2010). Gain weight, the most prevalent disorder caused by these drugs, often considered to be „normal“ and „common“, and consequently ignored with regard to other, like neurological side

effects. Besides being a threat to health and longlivity, obesity affects the self-esteem and body image causing significant psychological distress, especialy among children and adolescents who are more sensitive to the negative impacts of metabolic adverse effects (Merchán-Naranjo et al. 2012). This SGA's side-effect surpasses other side effects such as sedation and sexual dysfunctions (Green et al. 2000). On the other hand, there are few information about frequency of metabolic syndrome in patients with schizophrenia with regard to polypharmacy and lifestyle (Misawa et al. 2011), and a very few examine the relationship between polypharmacy with antipsychotics and metabolic syndrome (Correll et al. 2007, Tirupati & Chua 2007). Despite the fact that polypharmacy was frequent in 70-ies and 80-ies of 20th century, it is still present in wide range from 13 to 90% of all treated patients with schizophrenia (Zink et al. 2010, Schumacher et al. 2003, Tapp et al. 2003). In particular it is frequent in Japan with higher prevalence compared to other countries (Sim et al. 2004). It remains unclear whether polypharmacy with antipsychotics contribute to higher prevalence of metabolic syndrome in patients with schizophrenia. Due to increasingly rare use of the first generation antipsychotics (FGA), especially in developed countries, studies of its contribution to MetS are very rare. Usage of FGAs and polypharmacy are still being held in a lesser-developed and developing countries (Ramadas et al. 2010). In Bosnia and Herzegovina, the use of polypharmacy and FGAs is common in the treatment of patients with schizophrenia (Loga-Zec & Loga 2011).

The present study aims to assess the prevalence of metabolic syndrome and its parameters in group of patients with schizophrenia in polypharmacy, receiving treatment with more than one of the first generation antipsychotic agents versus clozapine alone treated group. Metabolic syndrome was defined according to NCEP ATP III (National Institutes of Health 2001) as „constellation of lipid and non-lipid risk factors of metabolic origin closely linked to insulin resistance."

SUBJECTS AND METHODS

Subjects

48 patients with schizophrenia treated in the Psychiatric Clinic of the University Clinical Centre Tuzla (Tuzla Canton region, Bosnia & Herzegovina) in the period from 1.1. 2002. to 31. 1. 2005. were recruited by a trained psychiatrist from the inpatient and outpatients facilities. 29 male and 19 female patients (mean age = 45.48, SD=12.19) were enrolled; 27 patients were treated with clozapine alone (150 mg/day up to a maximum 600 mg/day) and 21 patients were treated with combination of two or more antipsychotic agents of the first generation, with no other psychotropic medication. Doses range 300 to 1000 chlorpromazine equivalents. Patients were required to meet DSM-IV criteria for schizophrenia, and could have no history of diabetes mellitus, malignant illness, renal failure, and family history of hyperlipoproteinemia and obesity. Duration of medication minimum of six months was one of inclusion criteria. Only patients in clinical remission who were able to give written consent were enrolled. Except of antipsychotics, no other psychotropic medications were used. Demographic data of the sample are presented in Table 1.

Table 1. Demographics of the sample

Measure	Schizophrenia (n=48)
Age (years) (Mean, SD)	45.48 ± 12.186
Gender (n)	
Male (n, %)	29 (60.4%)
Female	19 (39.6%)
Marital status (n, %)	
Single	31 (64.6%)
Divorced	6 (12.5%)
Married	10 (20.8%)
Widow/er	1 (2.1%)
Education (n, %)	
Elementary school	13 (27.1%)
High school	12 (25%)
Without education	11 (22.9%)
Qualified workers	8 (16.7%)
High qualified workers	2 (4.2%)
University	2 (4.2%)
Work status (n, %)	
Employed	1 (2.1%)
Unemployed	26 (54.2%)
Retired	21 (43.8%)

Legend: M-male; F-female; n- number of patients; SD – standard deviation. Parameters are presented as central value with dispersion measure and in absolute number

Methods

Sociodemographic questionnaire constructed for this study is used for data collection about age, gender, occupation, educational level, marital status, duration of psychiatric treatment, and lifestyle characteristics: tobacco smoking, alcohol consumption, nutrition habits, and physical daily activity. History of previous treatment of diabetes mellitus, high blood pressure and hiperlipideamia is recorded. Data about current therapy are gathered from medical records (case records and patient charts), and its duration was defined as six months minimum.

The ATP III criteria (National Institutes of Health 2001) were used to establish metabolic syndrome: waist circumference from 102 cm for male and 88 cm for female patients, elevated triglyceride level:1,69 mmol/L, and higher, or current hypoglycemic therapy, low level of high density lipoprotein (HDL) bellow 1.04 mmol/L in male, and 1.29 mmol/L in female, or current hypoglycemic therapy, fasting plasma glucose level 5.6 mmol/L or higher, arterial blood pressure 130/85 mm

Hg, and higher, or current antihypertensive treatment. Three or more criteria are required for diagnosis of metabolic syndrome. Waist circumference is measured in centimeters (cm). Arterial blood pressure is measured when sitted, with standard apparatus, after resting of 15 minutes minimum. Values are presented in mm Hg. After 12 hours of food abstinence, a blood sample was taken from cubital vein. Plasma glucose, triglyceride and HLD levels were determined. Values were presented in mmol/L. Laboratory tests were performed at the Department of Biochemistry of the University Clinical Centre Tuzla on the DIMENSION RXL® apparatus. For glucose level determination, the method presented by Kunst et al. (1984), which is adaptation of hexokinase-glukose-6-phosphate dehydrogenize test is used. Triglyceride determination method is founded on enzymatic procedure where combination of enzymes was used for triglyceride plasma level determination. AHDL Cholesterol assay was used to determine a high density lipoprotein. The method consists of direct measurement of HDL-c level without prior centrifugation. It is based on cholesterol oxidase acceleration with non HDL non esterified cholesterol and dissolved HDL with specific detergent.

Statistical Analysis

The application software Statistical Package for Social Sciences for Windows, version 20.0 SPSS Inc., Chicago, IL, USA is used for data analysis. Categorical variables are presented as frequencies or percentages. Continuous variables are presented as arithmetic means with standard deviations, or medians with an adequate dispersion measure, depending on data distribution. The t-test and Mann-Whitney test are used for hypothesis testing between two independent groups. Logistic regression Odds Ratio, Chi square test-2 by 2 or for multiple strata, 2 by k are used for hypothesis testing of differences of frequencies (distribution) of observed parameters and possible risk. The obtained p values is presented with chosen level of significance ($p<0.05$).

Univariate logistic regression analysis is used to evaluate the effects of predictors on the probability of occurrence of metabolic syndrome, and then the significant predictors were analyzed in the model. Original values of some predictors were subjected to recoding to ensure their suitability for this analysis. Due to a small number of cases in some categories data regrouping and redistribution into other categories is performed. Since the analysis is sensitive to high correlation between predictors, we have examined the preliminary analysis of assumptions regarding lack of multicollinearity. It has been shown that predictors are highly intercorrelated in the model (Collinearity statistics: 0.12-0.81 Tolerance, VIF 1.2-7.9). Given that the analysis is sensitive to outliers we have excluded two cases from the analysis, those who had resid-Z -2.82 and 2.87 (Cook's distance >1), and exceeded the critical Mahalanobis distance that the binary dependent variable is 13.82 (in our model the Mahalanobis distance of 21.25 was found, exceeding critical value of 13.82). The 6 significant predictors that we analyzed in the predictive model were selected by univariate nominal logistic regression, including gender, treatment duration, waist circumference, triglycerides, HDL-cholesterol, blood glucose level, treatment with antipsychotics (clozapine or polypharmacy as a binary variable).

RESULTS

No significant difference is found between groups of subjects regarding age, marital status, employment status, duration of psychiatric treatment and number of hospitalizations. Compared with other sociodemographic data, in group of subjects treated with clozapine alone were significantly more subjects with high education degree ($p=0.04$), and significantly more women ($p=0.002$). Out of total sample, only two subjects reported on the occasional use of alcohol. The majority of subjects were tobacco smokers (N=35), and reported on daily physical activity between two and eight hours (N=27). There was no significant difference between groups of subjects. (Table 2). Out of 21 subjects in the group in FGAs polypharmacy, a combination of haloperidol and levopromazine is used in seven subjects. Haloperidol and promazine in 5 subjects, flufenazine and levomepromazine in 4 subjects, flufenazine and promazine in two subjects, haloperidol and chlorpromazine in one subject, flufenazine and chlorpromazine in one subject, and haloperidol with levomepromazine and chlorpromazine in one subject.

Out of 48 subjects with schizophrenia, 25 have fulfilled ATP III criteria for metabolic syndrome. Complete metabolic syndrome was present in 19 subjects with clozapine treatment and in six subjects treated with FGAs polypharmacy. Statistically significant difference in the prevalence of metabolic syndrome is found between the groups ($\chi^2=8.27$, df=1, $p=0.004$). In regard to certain parameters of metabolic syndrome, a significantly higher levels of tryglyceride were found in subjects treated with clozapine alone (Mann-Whitney test, Z -2.09, $p=0.03$), although there was no statistical difference with regard to other parameters (Table 3).

In logistic regression analysis (Table 4), the selected model is statistically significant, which is confirmed by the Omnibus Tests of Model Coefficients ($\chi^2=35.86$, df-6, $p=0.001$).

Model with predictors makes a better distinction in the dependent variable (metabolic syndrome), explaining between 52.6% (r2 Cox Snel) and 70.2% (r2 Nagelkerkea) variance in metabolic syndrome status and accurately classified 89.6% of cases, which is better assessment compared to 52.1% in zero-model. The percentage of correct classification (PPV-positive predictive value) was 92%, and negative predictive value was 87%.

Table 2. Characteristics of lifestyle and duration of psychiatric treatment of participants

Measures	Patients with schizophrenia (n=48)		p*
	Treated with polypharmacy (n=21)	Treated with clozapine alone (n=27)	
Gender (n, %)			0.004
Male	18 (37.5%)	11 (22.9%)	
Female	3 (6.25%)	16 (33.3)	
Smoking (n, %)			0.65
Yes	16 (33.3%)	19 (39.6%)	
No	5 (10.4%)	8 (16.7%)	
Alcohol consumption			0.10
Yes	2 (4.16%)	0 (0%)	
No	19 (16.7%)	27 (56.2%)	
Physical activity			0.22
>8 h	2 (4.16 %)	0 (0%)	
2-8h	12 (25%)	15 (31.2%)	
Mostly inactive	7 (14.6%)	12(25%)	
No of hospitalizations			0.24
1-5	3 (6.25%)	9 (19.1%)	
6-10	10 (21.%)	8 (17.0%)	
>10	8 (17.0%)	9 (19.1%)	
Duration of treatment (in years)			0.09
1-5	0 (0%)	8 (16.7%)	
6 -10	3 (6.25%)	3 (6.25%)	
11 - 15	4 (8.33%)	4 (8.33%)	
16 - 20	3 (6.25%)	4 (8.33%)	
>20	11(22.9%)	8 (16.6%)	

Legend: Parameters are presented as numbers, %, or as mean ± SD: standard deviation, p-statistical significance p<0,05. *-Hi Square test: Pearson Chi-Square (Continuity Correction) 8.198, df-1, p=0.004; *-Hi Square test 2xk; Pearson Chi-Square 11.10, df-4, p=0.09 NS

Table 3. Parameters of metabolic syndrome in patients treated with polypharmacy and clozapine

Parameters of metabolic syndrome	Patients with schizophrenia (n=48)		p*
	Treated with polypharmacy (n=21)	Tretated with clozapine alone (n=27)	
Waist circumference (cm) (Mean, SD)	97.0±9.67	101.9±11.75	0.12
TGL (mmol/L) (median)	1.64 (0.49-4.54)	2.29 (0.80-7.42)	*0.03
HDL (mmol/L) (median)	1.11±0.33	1.07±0.28	0.63
BGL (mmol/L) (median)	4.90±0.63	5.09±0.57	0.28
Hypertensio arterialis (number)			
Yes	5 (10.4%)	10 (20.8%)	0.32
No	16 (33.3%)	17 (35.4%)	
Systolic (mmHg) (median)	120 (100-140)	120 (100-190)	0.52
Diastolic (mmHg) (median)	80 (60-100)	80 (70-120)	0.62
Full metabolic syndrome	6	19	0.004

Legend: Parameters are presented as central value ± SD: standard deviation, as numbers, %, or median; TGL: trigliceride; HDL-high density cholesterol; BGL: blood glucose level; p-statistical significance p<0.05. *Mann-Whitney test, Z -2.09, p=0.03;

Table 4. Predictors of metabolic syndrome in sample of patients with schizophrenia (n=48)

Predictors	B	S.E.	Wald	df	p-value	Exp(B)	95% C.I. for Exp (B)	
							Lower	Upper
Gender	1.96	0.68	8.12	1	0.004	7.12	1.86	27.28
Duration of treatment	-2.78	1.36	3.92	1	0.04	0.06	0.005	0.97
Waist circumference	0.10	0.03	7.46	1	0.006	1.10	1.02	1.18
Trigliceride	0.56	0.27	4.17	1	0.04	1.76	1.02	3.04
HDL	-2.70	1.18	5.26	1	0.02	0.06	0.007	0.67
BGL	-5.97	2.82	4.47	1	0.03	0.003	1.11	10.13
Groups of patients	-1.78	0.64	7.72	1	0.005	0.16	0.04	0.59

Legend: B-beta coefficient, S.E.-standard error, Wald statistics; df-degrees of freedom, Exp(B)-exponent coeffcient B (OR); 95% C.I. – confidence interval

Table 5. Prediction of probability for metabolic syndrome

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1a	Gender	1.901	1.168	2.647	1	0.104	6.692	0.678	66.075
	Waist circumference	2.772	1.102	6.331	1	0.012	15.995	1.846	138.615
	TGL	0.487	0.386	1.585	1	0.208	1.627	0.763	3.470
	HDL	-4.095	2.400	2.910	1	0.088	0.017	0.000	1.840
	BGL	1.328	0.998	1.770	1	0.183	3.775	0.534	26.704
	Therapy	-0.154	1.106	0.019	1	0.889	0.857	0.098	7.490
	Constant	-5.636	5.713	0.973	1	0.324	0.004		

Legend: B-beta coefficient, S.E.-standard error, Wald statistics; df-degrees of freedom, Exp(B) - exponent coeffcient B (OR); 95% C.I. – confidence interval

Waist circumference is the only variable that significantly contributed to the model with likelihood ratio Exp (B) or OR 15.99, showing that subjects with increased waist circumference are 15 times more likely to develop the metabolic syndrome than those with normal waist circumference (Table 5).

DISCUSSION

Results of this study are consistent with other similar studies, indicating that the usage of clozapine is linked to metabolic syndrome. At the same time, the results showed that polypharmacy with FGAs is unrelated to metabolic syndrome. Our study indicates a higher prevalence of metabolic syndrome in patients treated with clozapine alone compared to patients in FGAs polypharmacy. In their study, Misawa et al. (2011) have shown that antipsychotic agents polypharmacy, as an independent risk factor, contribute to pre-metabolic syndrome in patients with schizophrenia. Patients in monopharmacy with clozapine were not enrolled in Misawa's study, and authors did not attach importance to polypharmacy with FGAs. Our study indicates significantly higher levels of plasma triglycerides in patients treated with clozapine, although there was no significant difference in waist circumference between groups of patients. Arterial hypertension was more frequent in patients treated with clozapine alone, hence without statistic significance. Other studies that tackled this issue found a lower frequency of arterial hypertension compared with other parameters of metabolic syndrome among subjects in polypharmacy. Hypotensive effect of antipsychotic agents has been offered as an explanation, and occurrence of hypotension was incriminated that „mask metabolic syndrome" (Misawa et al. 2011). Higher prevalence of hypertension in our patients treated with clozapine alone, even though statistically insignificant can be explained by already developed metabolic syndrome despite hypotensive and sedative effects of clozapine.

In the large study of Dixon et al. (2000) on American sample of patients with schizophrenia, the life prevalence of type 2 diabetes mellitus was 14.9% with actual prevalence of 10%. Mean age was 43 years. There were more women, African Americans, with ethnic background marked as „nonspecified". Majority of these patients were treated with FGAs. In many reports that considered diabetes mellitus and hyperglycemia during the treatment with SGAs, clozapine was mostly associated with hyperglycemia (Wilson et al. 2003). In contrast to their results, our study indicate that there was no significant difference in glucose plasma levels in patients treated with clozapine alone and FGAs polypharmacy.

Corell et al. (2007) suggest relationship between high incidences of metabolic syndrome in patients treated with polypharmacy compared with those in monopharmacy, while a higher frequency in their study is not related only to polypharmacy. The authors include demographic and clinical factors, and a significant association of metabolic syndrome with male gender, older age, diagnosis of bipolar affective disorder or schizophrenia, and co- therapy with FGAs is found. Another possibility is that cultural and environmental factors also contribute to metabolic syndrome (Gohlke et al. 2009, Azimi-Nezhad et al. 2012, Misra & Khurana 2008).

With regard to analyzed variables, our study suggests clozapine treatment, female gender and older age as a risk factors for development of metabolic syndrome. With regard to gender, our study differs in comparison with some other studies which showed higher prevalence of metabolic syndrome, or its components, in males, or no gender related differences (Misawa et al. 2011, Hägg et al. 2006, Correll et al. 2007). Conducted study was cross-sectional, and choosen sample was convenience sample. Future studies should include a larger, randomised sample of men and women with schizophrenia in order to avoid under-representation or over-representation of particular groups within the sample, and particulary to clarify the role of gender in metabolic abnormalities.

Misawa et al. (2011) emphasize that metabolic syndrome group was associated with male, longer duration of psychiatric treatment, and heavier smoking habit. Pre-metabolic syndrome group was associated with male and antipsychotic agents polypharmacy. The visceral fat obesity group was associated with male and a

higher total daily dose of antipsychotic agent. Analyzing the lifestyle of our subjects, a high percentage of those who reported on spending most of the day physically inactive is found. Although this percentage is higher in clozapine treated group, there was no statistical significance. Out of total 48 patients, 35 reported on cigarette smoking with a greater number in those treated with clozapine alone. Despite the fact that the use of FGAs in most of developed countries are reserved for small proportion of patients who are clinicaly stabile, and who tolerate those medications well, the indications for its use progressively vanish (McGorry 2005). But specifics of post-conflict society, transition, poverty, and social neglect are related to a poor access to SGAs for majority of patients with schizophrenia and other psychotic diseases (Loga-Zec & Loga 2011). With a number of FGAs, the clozapine was the only SGA included on the positive list of drugs of the Institute of Health Insurance of Tuzla Canton, and thus available to a broader users' population. This fact determined the sample of subjects in this study. Our study showed that clozapine was more often prescribed to women with high educational level compared with patients in FGAs polypharmacy which were more often prescribed to men with lower educational level, and longer psychiatric treatment. With respect to clinical potency of clozapine which has been designated as most effective antipsychotic, (McEvoy et al. 2006, Jones et al. 2006, Lewis et al. 2006), the results of this and other studies (Grover et al. 2011, Malhi et al. 2010) indicate its high potency for causing metabolic side effects.

Our study showed that FGAs polypharmacy was not significantly associated with metabolic syndrome, neither to particular components of this syndrome. However, with regard to the results of other studies which indicate association between polypharmacy and metabolic syndrome, the question on "which combination of antipsychotic is associated with metabolic syndrome?" remains open. Further research using a larger sample and focusing on the potential role of antipsychotic dose is required.

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References

1. *AACE Diabetes Mellitus Clinical Practice Gudelines Task Force: American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. Endocr Pract 2007; 13(Suppl 1):1-68.*
2. *Atmaca M, Kuloglu M, Tezcan E, Ustundag B: Serum leptin and triglyceride levels in patients on treatment with atypical antipsychotics. J Clin Psychiatry 2003; 64:598-604.*
3. *Azimi-Nezhad M, Herbeth B, Siest G, Dadé S, Ndiaye NC, Esmaily H, et al: Metabolic Syndrome and Related Disorders 2012; 10:181-188.*
4. *Bobes J, Arango C, Aranda P, Carmena R, Garcia G G, Rejas J: Cardiovascular and metabolic risk in outpatients with schizophrenia treated with antipsychotics: results of the CLAMORS Study. Schizophr Res 2007; 90:162-173.*
5. *Bobes J, Rejas J, M. Garcia-Garcia, Villademoros FR, Garcia- Portilla MP, Fernandez I, et al: Weight gain in patients with schizophrenia treated with risperidone, olanzapine, quetiapine or haloperidol: results of the EIRE study. Schizophr Res 2003; 62:77–88.*
6. *Connolly M, Kelly C: Life style and physical health in schizophrenia. Advances in Psychiatric treatment 2005; 11:125-132.*
7. *Correll C, Frederickson A, Kane J, Manu P: Does antipsychotic polypharmacy increase the risk for metabolic syndrome? Schizophr Res 2007; 89:91-100.*
8. *Curkendall SM, Mo J, Glasser DB, Rose Stang M, Jones JK: Cardiovascular disease in patients with schizophrenia in Saskatchewan, Canada. J Clin Psychiatry 2004; 65:715-20.*
9. *Dixon LB, Wohlheiter K: Diabetes and mental illness: factors to keep in mind. Drug Benefit Trends 2003;15:33–44.*
10. *Dixon L, Weiden P, Delahanty J, Goldberg R, Postrado L, Lucksted A, et al: Prevalence and correlates of diabetes in national schizophrenia samples. Schizophr Bull 2000; 26:903–912.*
11. *Ellingrod VL, Miller DD, Taylor S: Metabolic syndrome and insulin resistance in schizophrenia patients receiving antipsychotics genotyped for the methylenetetrahydrofolate reductase (MTHFR) 677C/T and 1298A/C variants. Schizophr Res 2008; 98:47–54.*
12. *Fernandez E E, Bernardo M, Donner T, Conget I, Parellada E, Justicia A, et al: Metabolic profile of antipsychotic-naive individuals with non-affective psychosis. Br J Psychiatry 2009; 194:434-438.*
13. *Gohlke J, Thomas R, Zhang Y, Rosenstein M, Davis A, Murphy C, et al: Genetic and environmental pathways to complex diseases. BMC Systems Biology 2009; 3:46.*
14. *Green AI, Patel JK, Goisman RM, Allison DB, Blackburn G: Weight gain from novel antipsychotic drugs: need for action. Gen Hosp Psychiatry 2000; 22:224-235.*
15. *Grover S, Nebhinani N, Chakrabarti S, Avasthi A, Kulhara P: Metabolic syndrome among patients receiving clozapine: A preliminary estimate. Indian J Pharmacol 2011; 43:591-5.*
16. *Heiskanen T, Niskanen L, Lyytikäinen R, Saarinen PI, Hintikka J: Metabolic syndrome in patients with schizophrenia. J Clin Psychiatry 2003; 64:575–579.*
17. *Hägg S, Lindblom Y, Mjörndal T, Adolfsson R: High prevalence of the metabolic syndrome among a Swedish cohort of patients with schizophrenia. Int Clin Psychopharmacol 2006; 21:93-98.*
18. *Jakovljevic M, Crncevic Z, Ljubicic D, Babic D, Topic R, Saric M: Mental disorders and metabolic syndrome: a fatamorgana or warning reality? Psychiatr Danub 2007; 19:76-86.*
19. *Jones PB, Barnes TR, Davies L, Dunn G, Lloyd H, Hayhurst KP, et al: Randomized controlled trial of effect on quality of life of second-vs first- generation antipsychotic drugs in schizophrenia. Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). Arch Gen Psychiatry 2006; 63:1079-1087.*

20. Kunst A, Draeger B, Ziegenhorn J. D-Glucose. In Bergmeyer HU (ed): Methods of Enzymatic Analysis, 3rd ed. Vol. 6. Weinheim, Deerfield Beach, FL: Verlag Chemie; 1984: p. 163–172.
21. Loga-Zec S, Loga S: Polypharmacy in the treatment of schizophrenic patients in three University Centers in the Federation of Bosnia and Herzegovina (F/BH). Psychiatria Danubina 2011; 23:60–63.
22. Lewis SW, Barnes TRE, Davies L, Murray RM, Dunn G, Hayhurst KP, et al: Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. Schizophr Bull 2006; 32:715–723.
23. Malhi G, Adams D, Plain J, Coulston C, Herman M, Walter G: Clozapine and cardiometabolic health in chronic schizophrenia: correlations and consequences in a clinical context. Australas Psychiatry 2010; 18:32-41.
24. McEvoy JP, Meyer JM, Goff DC, Nasrallah HA, Davis SM, Sullivan L, et al: Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates form NHANES III. Schizophr Res 2005; 80(Suppl 1):19–32.
25. McEvoy JP, Lieberman JA, Stroup TS, Davis SM, Meltzer HY, Rosenheck RA, et al. for the CATIE Investigators: Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. Am J Psychiatry 2006; 163:600–610.
26. McGorry P: Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of schizophrenia and related disorders. Aust N Zeal J Psychiatry 2005; 39:1-30.
27. Merchán-Naranjo J, Tapia C, Bailón C, Moreno C, Baeza I, Calvo-Escalona R, Morer A, Martínez-Cantarero C, Nestares PA, Alda JÁ, Muñoz D, Arango C: Secondary effects of antipsychotic treatment in naive or quasi-naive children and adolescents: design of a follow-up protocol and baseline results. Rev Psiquiatr Salud Ment 2012; 5:217-28.
28. Miller AL, Craig CS: Combination antipsychotics: pros, cons, and questions. Schizophr Bull 2002; 28(Suppl 1):105-109.
29. Misawa F, Shimizu K, Fujii Y, Miyata R, Koshiishi F, Kobayashi M: Is antipsychotic polypharmacy associated with metabolic syndrome even after adjustment for lifestyle effects?: a cross-sectional study. BMC Psychiatry 2011; 11:118.
30. Misra A, Khurana L: Obesity and the metabolic syndrome in developing countries. J Clin Endocrinol Metab 2008; 93(Suppl. 1):9-30.
31. National Institutes of Health: Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel 3) 2001; II-27.
32. Newcomer JW: Metabolic Syndrome and Mental Illness. The American Journal of Managed Care 2007; 13:170-177.
33. Newcomer JW: Metabolic considerations in the use of antipsychotic medications: a review of recent evidence. J Clin Psychiatry 2007; 68(Suppl 1):20-27.
34. Ramadas S, Kuttichira P, Sumesh TP, Ummer SA: A Study of an antipsychotic prescription pattern of patients with schizophrenia in a developing country. Indian J Psychol Med 2010; 32:13-6.
35. Rejas J, Bobes J, Arango C: Concordance of standard and modified NCEP ATP III criteria for identification of metabolic syndrome in outpatients with schizophrenia treated with antipsychotics: a corollary from the CLAMORS study. Schizophr Res 2008; 99:23–28.
36. Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Lobos CA, et al: Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. Schizophr Res 2010; 123:225-233.
37. Saari KM, Lindeman SM, Viilo KM: A 4-fold risk of metabolic syndrome in patients with schizophrenia: the northern Finland 1966 birth cohort study. J Clin Psychiatry 2005; 66:559–563.
38. Schorr SG, Lucas MJG, Slooff CJ: The prevalence of metabolic syndrome in schizophrenic patients in the Netherlands. Schizophr Res 2008; 102(Suppl.):241–241.
39. Schumacher JE, Makela EH, Griffin HR: Multiple antipsychotic medication prescribing patterns. Ann Pharmacother 2003; 37:951-955.
40. Sim K, Su A, Fujii S, Yang SY, Chong MY, Ungvari GS, et al: Antipsychotic polypharmacy in patients with schizophrenia: a multicentre comparative study in East Asia. Br J Clin Pharmacol 2004; 58(Suppl 2):178-183.
41. Tapp A, Wood AE, Secrest L, Erdmann J, Cubberley L, Kilzieh N: Combination antipsychotic therapy in clinical practice. Psychiatr Serv 2003; 54(Suppl 1): 55-59.
42. Thakore JH, Mann JN, Vlahos I, Martin A, Reznek R: Increased visceral fat distribution in drug-naive and drug-free patients with schizophrenia. Int J Obes Relat Metab Disord 2002; 26:137–141.
43. Tirupati S, Chua LE: Obesity and metabolic syndrome in a psychiatric rehabilitation service. Aust N Z J Psychiatry 2007; 41(Suppl 7):606–610.
44. Wilson DR, D'souza L, Sarkar N, Newton M, Hammond C: New-onset diabetes and ketoacidosis with atypical antipsychotics. Schizoph Res 2003; 59:1-6.
45. Wirshing DA, Boyd JA, Meng LR, Ballon JS, Marder SR, Wirshing WC: The effects of novel antipsychotics on glucose and lipid levels. J Clin Psychiatry 2002; 63:856-865.
46. Zink M, Englisch S, Meyer-Lindenberg A: Polypharmacy in schizophrenia. Curr Opin Psychiatry 2010; 23:103-111.

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