CLINICAL SCIENCE

METABOLIC DISTURBANCES DURING TREATMENT WITH SECOND GENERATION ANTIPSYCHOTICS

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Abstract

Second generation antipsychotics (SGA) cause side effects through weight gain, dyslipidemias (cholesterolemia, hypertriglyceridemia) as well as affected glucose homeostasis in terms of hyperglycemia, insulin resistance and the incidence of type 2 diabetes mellitus. The aim of this study was to investigate metabolic changes in patients treated with SGA. Materials and methods: This was a prospective study of 50 patients treated with SGA (olanzapine, clozapine, risperidone, quetiapine, aripiprazole) at the PHI University Clinic of Psychiatry who met the relevant ICD-10 criteria. The following parameters were monitored: history and clinical examination, blood pressure and pulse, height, weight, body mass index (BMI), Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression Scale (CGI-S), dose of prescribed SGA,as well as: fasting glycemia, lipid status, HDL, LDL, glycosylated hemoglobin (HgA1C). The parameters were determined at the beginning and after three months of treatment. Results: The subjects in terms of the criteria of metabolic syndrome were: 64% with a larger waist circumference, 53.2% with an increase in systolic and/or diastolic blood pressure, 31.3% with a BMI>30, and 39% with an increase in glycaemia and reduced HDL values at 23.4%. Also,18% of the respondents met three or more criteria. Statistical analysis of the differences in the analyzed parameters showed statistically significant differences for the CGI-S score (p = 0.00007) and for the diastolic pressure (p = 0.038). Correlation of equivalent doses of SGA with BMI (r = -0.637) was obtained. Discussion: The study confirmed presence of metabolic disorders in patients treated with SGA. Although there was no significant difference of metabolic syndrome parameters in relation to the general population, a correlation with BMI has been established. Conclusion: This study showed that patients treated with second-generation antipsychotics should be monitored during their treatment for the parameters of the metabolic syndrome, particularly BMI.

КЛИНИЧКО ИСТРАЖУВАЊЕ

МЕТАБОЛНИ НАРУШУВАЊА ПРИ ПРИМЕНА НА ВТОРА ГЕНЕРАЦИЈА НА АНТИПСИХОТИЦИ

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Клучни зборови: метаболен синдром, втора генерација антипсихотици, психијатриски растројства

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Извадок

Втората генерација на антипсихотици (second generation antipsychotics–SGA) предизвикуваат несакани ефекти преку пораст на телесна тежина, дислипидемии (холестеролемија, хипертриглицеридемија) како и засегната хомеостаза на гликозата во смисол на хипергликемија, резистентност на инсулин и појава на диабетес мелитус тип 2. Цел на ова истражување е да се испитаат метаболните промени кај пациентите третирани со SGA. Материјали и методи: Ова беше проспективна студија на 50 пациенти третирани со SGA (olanzapine, clozapine, risperidone, quetiapine, aripiprazole) на ЈЗУ Универзитетска клиника за психијатрија кои ги исполнуваа соодветните МКБ-10 критериуми. Беа следени следните параметри: анамнеза и преглед, ТА и пулс, висина, тежина, индекс на телесна маса (bodymassindex-BMI), Кратка скала за психијатриска проценка(BPRS), скала за глобален клинички впечаток (CGI), дозата на ординираниот SGA, како и: гликемија на гладно, липиден статус, HDL, LDL, гликолизиран хемоглобин (HgA1C). Параметрите беа одредувани на почеток и после три месечен третман. Резултати: Испитаниците во однос на критериумите на метаболен синдром беа: 64% со поголем обем на струк, 53,2% со пораст на систолен и/или дијастолен крвен притисок, 31,3% со BMI>30, а 39% со пораст на гликемија и намалени вредности на HDLкај 23,4%. Со исполнети три и повеќе критериуми беа 18% од испитаниците. Статистичката анализа на разликите во анализираните параметри покажа статистички сигнификантни разлики за CGI-S скорот (p=0.00007) и за дијастолниот притисок (p=0.038). Добиена е корелација на еквивалентните дози на SGA со BMI (r= -0,637). Дискусија: Истражувањето ја потврди присутноста на метаболни нарушувања кај пациентите третирани со SGA. Иако на самиот почеток на третманот не постои битна разлика во однос на присуството на метаболниот синдром во однос на општата популација, сепак утврдена е корелација со BMI. Заклучок: Ова истражување покажа дека пациентите кои се третирани со втора генерација на антипсихотици треба да бидат мониторирани во текот на нивниот третман во однос на параметрите кои го сочинуваат метаболниот синдром, особено BMI.

Introduction

Second generation antipsychotics (SGA) reduce the risk of extrapyramidal symptoms, but cause side effects through weight gain, dyslipidemias (cholesterolemia, hypertriglyceridemia) as well as affected glucose homeostasis in terms of hyperglycemia, insulin resistance and the onset/occurrence of type 2 diabetes mellitus[1].

According to some authors, as many as 50% of SGA patients meet the criteria for metabolic syndrome, which increases the risk of cardiovascular disease. This metabolic syndrome is often not diagnosed in psychiatric patients, because according to some authors only 2.4% of patients were evaluated, and 34.5% of them met the criteria for this condition[2]. According to the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness), specific gender differences have been identified in terms of metabolic risk in women[3]. It is considered that in schizophrenia, especially in the female population, the obesity would have higher values, while in bipolar affective disorder (BD) it would have a 50% increase in incidence. Numerous epidemiological studies indicate that people with affective disorders and schizophrenia have an increased relative risk of mortality that is 1.5 to 3.3 times higher than the general population, which can be attributed to cardiovascular disease or cerebrovascular incidents. It is considered that this may be due to poor diet or reduced physical activity, smoking or various forms of alcoholism and other addictions, but also other high-risk behaviors for the health (various infections, etc.). The treatment itself carries a special risk, i.e. the medications that are used[4].

Bipolar affective disorder and schizophrenia are endogenous mental disorders with common clinical features such as psychotic or affective symptoms, sometimes cognitive symptoms, but also common genetic risk for obesity, DM and CVD, which are thought to have a 15-20year shorter lifespan compared to the generalized population. In addition, antipsychotics are used in therapy, which in addition to the expected therapeutic effect, carry certain risks in terms of side effects, especially the second generation of antipsychotics that affect general health in terms of the occurrence of metabolic changes[5].

In the treatment of various psychiatric disorders and conditions, especially psychotic disorders, different antipsychotics are used, which can significantly differ in their effectiveness and profiles of side effects. The differences in efficacy, but also the occurrence of side effects depend on the mechanism of action on different neurotransmitter systems and receptors[6]. A difference in the effect on metabolic function in patients treated with SGA is shown in a meta-analysis published in 2020[7].

The use of antipsychotics worldwide has grown exponentially in the last 15 years. In the United States for the period 1997-2007 the number of users increased from 2.2 to 3.9 million people, and in the pediatric population by 60% in the period 2002-2007[8]. This is considered to be due to an improved profile with reduced extrapyramidal symptoms, the use as adjunctive therapy in affective disorders, and the improved patient acceptance. The meta-analysis confirmed the prevalence of metabolic syndrome in both acute and chronic forms of schizophrenia, independent of antipsychotics, and that percentage was about 32%. On the other hand, cross-sectional studies have shown that the prevalence of meta-

bolic syndrome (MetS) in patients treated with AP was 45-50% with a correspondingly high risk of CVD8. SGA is increasingly used outside the indication area, in terms of treatment of psychotic depressions, at inadequate personality structures, as well as other conditions that are refractory to therapy (eating disorder, obsessive-compulsive syndrome, etc.)[9].

Metabolic syndrome can be diagnosed if three of five criteria focused on specific cardiovascular risk factors are met: abdominal obesity, low HDL values, elevated triglycerides, hypertension, and affected fasting plasma glucose. This definition is accepted by the International Diabetes Federation[10] and also by the American Society of Cardiology[11]. The prevalence of meeting three, four, or five components of metabolic syndrome is often examined and in relation to the most prevalent combinations: triglyceride elevations, blood pressure and glycaemia, which in the Korean study case are described as more often in men (30, 8%) in relation to women where they were present in 14.5% of the respondents[12].

According to the criteria that take into consideration the differences in populations according to the European criteria of IDF (Europid), i.e. the Mediterranean type to which we belong, the following values have been determined for the metabolic syndrome criteria: waist circumference for men ≥ 94 cm for men and ≥ 80 cm for women; triglycerides ≥ 1.7 mmol/L; HDL cholesterol for men <1.03 mmol/L and for women <1.29mmol/L; elevated systolic pressure ≥ 130mmHg and elevated diastolic pressure ≥85 mmHg, as well as elevated glycemic values ≥5.6 mmol/L.[13] In addition, it is necessary to describe the categories according to the body mass index, such as malnutrition with BMI ≤ 18.5; normal body weight with BMI of 18.5-24.9; overweight if BMI = 25-29.9 and obese with BMI ≥ 30.

The aim of this study is to examine metabolic changes in patients treated with SGA regardless of diagnosis.

Material and methods

This was a prospective study of 50 patients treated at the PHI University Clinic of Psychiatry and followed up after 3 months of treatment. Patients treated with inpatient or outpatient treatment with SGA (risperidone, olanzapine, clozapine, quetiapine, aripiprazole) were included. Patients met the ICD-10 criteria for: schizophrenia disorders, schizoaffective disorders, acute psychotic disorders, persistent delusional disorders (F20-F29), affective disorders (F30-F34) as well as other diagnoses such as inadequate personality structure (F60), compulsive disorder (F 42), inorganic insomnia (F51), and other disorders.

Inclusion criteria: Patients aged 18-65 who meet the criteria for the above disorders and who have given consent.

Exclusion criteria: no consent given, diagnosed with type 2 diabetes mellitus (DM) before SGA, pregnancy and lactation.

Using a clinical interview, demographic data were obtained (gender/sex, age, employed/unemployed, marital status, smoker, etc.), current and past illnesses, family history of diabetes mellitus, and then a psychiatric examination was performed and evaluation using clinical scales: Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impression - Severity (CGI-S). According to the recommendations of the European Psychiatric Association from

2009, the somatic condition was taken into consideration through vital signs: blood pressure (BP) and pulse, height, weight and measurement of waist and hip circumference from which BMI will be obtained. Laboratory tests that were monitored were: fasting glycaemia, lipid status, HDL (high density lipoprotein), LDL (low density lipoprotein), TG (triglycerides), glycosylated hemoglobin (HgA1C) which were determined before the beginning of the therapy and after three months. Each patient received information on the risk of developing metabolic syndrome and a recommendation for a hygienic-diet regimen according to the WHO.

The statistical analysis of the data obtained from the research was done in the statistical program SPSS 23.0. Shapiro Wilk's test was used to test the normality of the data distribution. The categorical (attributive) variables are represented by absolute and relative numbers. The numerical (quantitative) variables are represented by average, standard deviation, minimum and maximum values, median value and interquartile rank. Student t-test for dependent samples and Wilcoxon matcher pairs test were used to compare the analyzed variables before the start of therapy and 3 months later, while Chi-square test, Student t-test were used to compare the variables in relation to gender, independent samples and Mann-Whitney test. Equivalent dose correlation with certain variables was analyzed using Pearson's linear correlation coefficient and Spearman's rank correlation coefficient. Statistical significance was defined at the level of $p < 0.05$.

Results

The survey included 50 respondents who met the inclusion criteria. From the beginning, due to the current symptomatology and the need for correction of the treatment or due to the somatic condition, 5 respondents were excluded (one patient was transferred to another treatment facility, one patient had high glycemic values, one patient was placed in a depot preparation which is not included in the study, one patient was diagnosed with psychoorganic syndrome, and one patient developed a complication of a metabolic nature that has been described as a case study[14]. Out of the remaining 45 patients, at the first control after 3 months, only 15 patients were followed up who received appropriate parameters for analysis and comparison. An overview of this data is given in Figure 1.

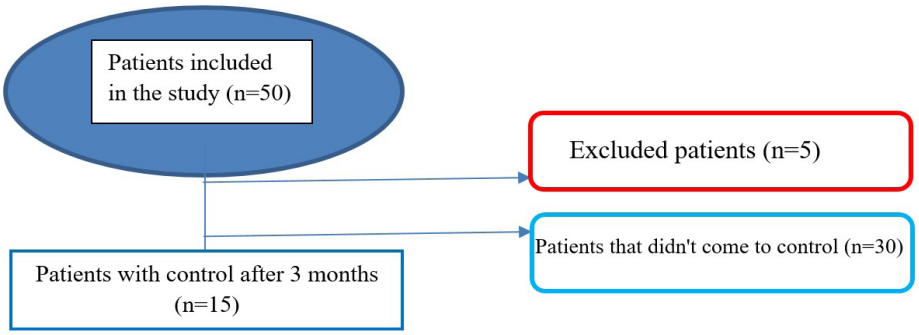

Figure 1. Diagram of patients involved

From the obtained parameters we present the demographic indicators in Table 1. The research included 50 respondents, aged 18 to 63 years, with average age 37.4 ± 12.5 years. The gender structure of the respondents consists of 48% (24) male patients and 52% (26) female patients.

Table 1. Overview of the respondents according to demographic characteristics

Parameter	N (percent %)
Gender/Sex	
Men	24 (48)
Women	26 (52)
Age	
mean ± SD	37.44 ± 12.5
min – max	18 – 63
Marital Status	
- married	16 (32)
- devorced	6 (12)
- single	27 (54)
- no data	1 (2)
Employment Status	
- unemployed	29 (58)
- employed	19 (38)
- pensioner	2 (4)
Smoker	
- yes	23 (46)
- no	27 (54)
Previously treated	
- yes	22 (44)
- no	28 (56)
Family anamnesis for DM	
- yes	8 (16)
- no	42 (84)

Table 2 shows patients according to diagnoses, and the presentation includes acute psychoses (F23), chronic psychoses (F20, F21, F22, F25), affective disorders (F30, F31, F32, F33, F34) and other disorders (F41), F42, F45, F51).

Table 2. Overview of patients according to diagnoses

Diagnosis	N (%)
Acute Psychosis (AP)	18 (36)
Chronic Psychosis (CP)	17 (34)
Affective disorders (AD)	11 (22)
Other Disorders (OD)	4 (8)

Table 3 shows distribution of respondents in relation to the type of the prescribed therapy.

Table 3. Overview of used second generation antipsychotics

Diagnosis	Start N (%)	mean ± SD	Second visit N (%)	mean ± SD
Aripiprazole	11 (22)	22,50±36,20	6 (12)	16,67±6,83
Clozapine	2 (4)		1 (2)	
Quetiapine	4 (8)	75,00±35,36	3 (6)	56,25±12,5
Risperidone	17 (34)	3,19±1,33	4 (8)	4,25±0,96
Olanzapine	16 (32)	9,71±5,15	2 (4)	

Table 4 shows the data on how many criteria of the metabolic syndrome were present at the beginning of the study. On this table it can be seen that out of the total number of respondents, 64% are those who have a larger waist circumference according to the criteria for the population of the Mediterranean or according to EUROID, of which 14 male and 18 female respondents.

Table 4. Present criteria of metabolic syndrome in the respondents

Criteria	N	%
Waist Circumference	50	100
Men ≥ 94cm	14	28
Women ≥ 90cm	18	36
Blood Pressure(BP)	47	100
Systolic>130mmHg	7	14,9
Diastolic>85mmHg	18	38,3
BMI	48	100
25-29,9	13	27,1
≥ 30	15	31,3
Glycaemia	46	100
Fasting ≥ 5,6 mmol/L	18	39,1
HDL	30	100
Men<1,03mmol/L	2	6,7
Women<1,29mmol/L	5	16,7
Fulfilled Criteria	50	100
≤ 1	30	60
2	11	22
3	8	16
4	1	2

In the criterion of increase in blood pressure, at 53.2% of the respondents it is with higher values, and the percentage is higher in diastolic pressure. Regarding the body mass index (BMI) of the total number of respondents with values higher than 30 (obese) were 29.2% of the respondents, but

also the percentage of persons with TT above average (overweight) were 27,1% of respondents. Fasting blood glucose was above the recommended average at 18 people or 39.1% had an increase. The parameter with lower HDL values was present in 23.4% of the respondents, a slightly higher percentage in women. In relation to the criteria present for metabolic syndrome, it can be seen in Table 4 that even on the first visit, 18% had 3 and more fulfilled metabolic syndrome diagnosis criteria, which should be prevented from further progression.

In order to determine the differences in the analyzed parameters of the metabolic syndrome that were available for comparison after 3 months of treatment, only the results of population of 15 respondents who had complete data were taken for mutual comparison. The results of the statistical analysis for the tested differences in the analyzed parameters between the two time points, before the start of therapy and after 3 months of therapy are shown in Table 5. No statistically significant difference was found in the values of BMI (p = 0.13), glycaemia (p = 0.75), total cholesterol (p = 0.64), triglycerides (p = 0.67), HDL (p = 0.15), LDL (p = 0.75), HgA1C (p = 0, 18), BPRS score (p = 0.63), and systolic pressure (p = 0.27), whereas after 3 months of therapy a significant difference was found in the values of CGI-S score (p = 0.00007) and diastolic pressure (p = 0.038). After 3 months of therapy, a significant reduction in CGI-S score (4.67 ± 0.65 vs. 3.75 ± 0.62) and diastolic pressure (91.9 ± 14.9 vs. 79.7 ± 6,4) was registered.

Table 5. Overview of the tested differences before and after 3 months of treatment

Parameters	First visit mean ± SD	Second visit mean ± SD	p-value
BMI	30.5 ± 8.8	31.8 ± 8.5	t=1.6 p=0.13
Glycaemia	5.48 ± 0.9	5.57 ± 0.4	t=0.3 p=0.75
Total cholesterol	5.0 ± 0.9	4.9 ± 0.8	t=0.5 p=0.64
Triglycerides (TG)	1.32 ± 0.4	1.38 ± 0.6	t=0.4 p=0.67
HDL	2.07 ± 0.6	1.68 ± 0.3	t=1.7 p=0.15
LDL	2.57 ± 0.9	2.38 ± 0.9	t=0.3 p=0.75
HgA1C	5.8 ± 0.5	4.9 ± 2.4	t=0.9 p=0.37
BP- systolic	121.3 ± 19.2	116.7 ± 10.0	t=1.2 p=0.27
BP - diastolic	91.9 ± 14.9	79.7 ± 6.4	t=2.5 *p=0.038
BPRS	34.4 ± 12.2	38.9 ± 32.5	Z=1 p=0.3
CGI-S	4.7 ± 0.6	3.7 ± 0.6	t=6.2 ***p=0.00007

t (Student t-test for dependent samples) *p<0.05;***p<0.0001

Z (Wilcoxon matched pairs test)

The study also analyzed the correlation between the equivalent dose of SGA with BMI, glycaemia, total cholesterol, TG, HDL, LDL, blood pressure and HgA1C. The correlation between the equivalent dose of SGA and BMI (p = 0.014) was confirmed as significant, which according to the value of Pearson's correlation coefficient is negative, i.e. indirect and of moderate intensity (r = -0.637). It shows that with increasing the equivalent dose of the SGA, the

body mass index decreases, and vice versa. The obtained correlation of BMI with the applied equivalent dose of SGA is graphically shown in Figure 2.

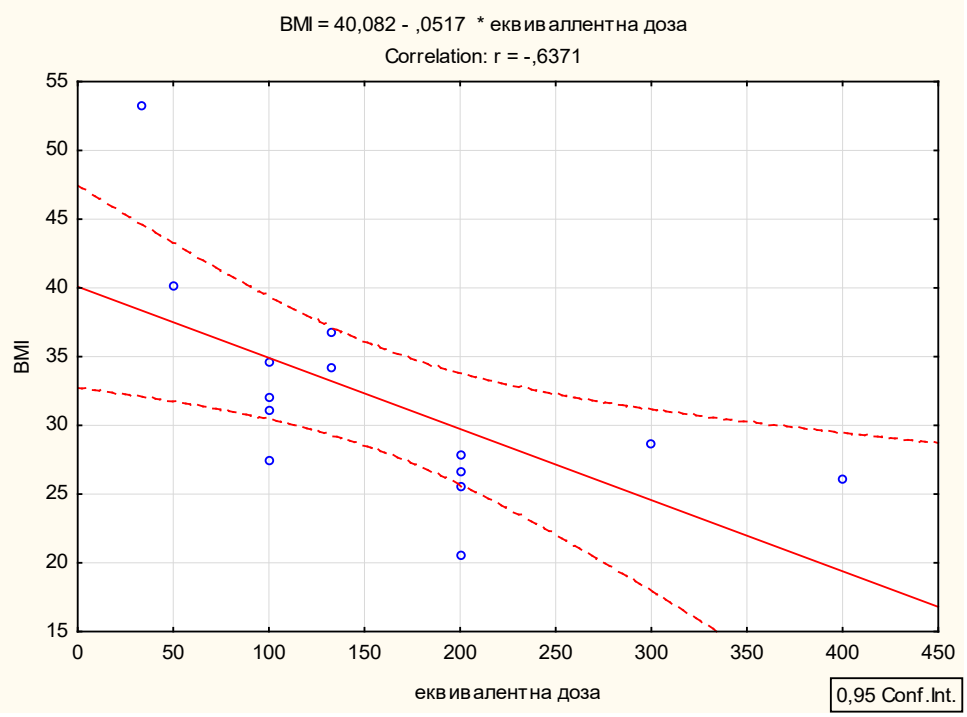

Figure 2. Correlation of BMI with the equivalent dose of administered SGA

Discussion

This is a first study in our country that monitors and controls the parameters that are key to diagnosing metabolic syndrome in patients treated with SGA. The results confirmed the presence of metabolic disorders in patients that can lead to increased cardiovascular risk and the occurrence of type 2 diabetes mellitus. The results of the study showed that at the beginning 64% of respondents had an increased waist circumference, and 53.2% were with elevated blood pressure values. In terms of BMI, 31.3% of respondents were with a score higher than 30, but also 27.1% of respondents were overweight. Examination of the laboratory parameters of glycaemia showed elevated values in 39.1% of the subjects, and decreased values of HDL in 23.4%. Thereby, 18% of the respondents met 3 or more criteria for MetS.

These data are in line with data from the IDF, which estimates that metabolic syndrome occurs due to a sedentary lifestyle in the modern world, and it is estimated that about 25% of the world's population has metabolic syndrome[15]. Therefore, predictors of metabolic syndrome through anthropometric measurements and bioelectrical measurements (Bio-Electrical Impedance Analysis i.e. BIA-test values) belonging to the latest technologies are introduced. Numerous other studies have confirmed a prevalence of MetS of 23–29% depending on gender16 or 20–30% in the general population, and which increases with age with respect to gender[17-19].

Regarding the examined differences in the parameters of MetS[20-24] after three months of treatment, a highly significant difference was found in the values of the CGI-S score (registered significant decrease thereof), as

well as a statistically significant difference in diastolic pressure which showed a significant reduction in initial values. Both parameters indicate a significantly improved state, one (CGI-S score) by directly measuring the condition, and the other indirectly by calming the mental state leading to a reduction in anxiety and a consequent reduction in diastolic blood pressure[7,25]. Unlike other studies which, after 6 months[26,27] of monitoring MetS parameters, found weight gain and increase in total cholesterol and triglyceride levels, whereas our study found no changes, perhaps because the monitoring was only three month long.

Because SGAs vary widely in their effect on MetS parameters[6,7,28-31] and to avoid dose influence, conversion to chlorpromazine equivalent doses was performed[32-34]. The obtained correlation between the equivalent doses of SGA and MetS which is negative, i.e. indirect and of moderate intensity, shows that with increasing the equivalent dose of SGA, the body mass index decreases and vice versa. This is significant because there is no direct positive correlation between the doses used and the increase in TT and the occurrence of MetS.

In order to get a more complete picture of the impact of SGA on the occurrence of MetS, it is necessary to process data from patients who have not been previously treated with such drugs (drug-naive). In addition, another limitation of this research is the insufficient number of respondents for the reliability of the obtained data. It should be emphasized that the research was conducted during the period of the declared pandemic with Covid-19, which prevented the monitoring of patients and complete processing of respondents, because laboratory tests were reduced to a minimum and of what is necessary. Apart from these changes in the overall organization of the health system, the current situation had an impact on the mental health of both the general population and the respondents. On the other hand, the fact from numerous studies that persons with psychiatric disorders do not adhere to research protocols and do not report to scheduled appointments should be emphasized[24].

Conclusions

It is very important that patients respond well (60-80%) to antipsychotic treatment in the first episode of psychosis, but the side effects should be considered from the very beginning. Although second-generation antipsychotics are better tolerated, they also carry the risk of side effects in terms of occurrence of metabolic syndrome features, and should be monitored regularly for these parameters.

Psychiatrists, as well as family physicians who are in frequent contact with their patients, in addition to the therapeutic response to the applied SGA, need to monitor these parameters of the metabolic syndrome regularly, especially BMI, in order to early recognize and diagnose the initial changes. Since there is an individualized response to a particular SGA that the patient is receiving, it is necessary, when the early detection of an increase in one of the parameters of the metabolic syndrome, to change the antipsychotic with another that carries a lower risk of developing metabolic disorders. In the meta-analysis that includes 18 antipsychotics, a recommendation is given which drug has the least effect and an individualized approach to treatment is recommended.

In such conditions, there is a need for an interdisciplinary approach and close cooperation, i.e. teamwork with a specialist in the field of endocrinology who would have a role in managing the risk of type 2 diabetes mellitus and the risk of cardiovascular disease.

Although not scientifically proven, there is hope that understanding the diagnosis of metabolic syndrome will motivate people and their GPs to take appropriate steps to reduce the risk of CVD and DM2, especially in the practice of lifestyle modification. The risk of metabolic disorders can be reduced by appropriate psychoeducation of patients in terms ofa hygienic-diet regime and proper nutrition, as well as advice on increased psycho-physical activity. However, if necessary, appropriate pharmacological interventions should be applied depending on the parameters involved.

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References

1. Uçok A, Gaebel W. Side effects of atypical antipsychotics: a brief overview. World Psychiatry 2008;7(1):58-62.
2. Lui K, Randhawa G, Totten V, Smith AE, Raese J. Is Metabolic Syndrome On the Radar? Improving Real-Time Detection of Metabolic Syndrome and Physician Response by Computerized Scan of the Electronic Medical Record. Prim Care Companion CNS Disord 2016;18(1).
3. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005; 22;353(12):1209-23.
4. Sharif Z. Side effects as influencers of treatment outcome. J Clin Psychiatry 2008;69(Suppl 30):38-43.
5. Jahr Vedal TS, Steen NE, Birkeland KI, Dieset I, Reponen EJ, Laskemoen JF, et al. Adipokine levels are associated with insulin resistance in antipsychotics users independently of BMI. Psychoneuroendocrinology 2019;103:87-95.
6. Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. Lancet 2019; 394: 939–951.

7. Pillinger T, McCutcheon RA, Vano L, Mizuno Y, Arumuham A, Hindley G, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. Lancet Psychiatry 2020;7: 64–77.

8. Shulman M, Miller A, Misher J, Tentler A. Managing cardiovascular disease risk in patients treated with antipsychotics: a multidisciplinaryapproach.JMultidiscip Healthc2014;7:489-501. Published 2014 Oct 31.

9. Rojo LE, Gaspar PA, Silva H, Risco L, Arena P, Cubillos-Robles K, et al. Metabolic syndrome and obesity among users of second generation antipsychotics: A global challenge for modern psychopharmacology. Pharmacol Res 2015; 101:74-85.

10. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome-a new world-wide definition. A consensus statement from the International Diabetes Federation. Diabet Med 2006 May;23(5):469-80.

11. Grundy SM, Brewer HB, Cleeman JI, Smith SC, Lenfant C. Definition of Metabolic Syndrome. Circulation 2004;109:433–438.

12. Lee S, Ko Y, Kwak C, et al. Gender differences in metabolic syndrome components among the Korean 66-year-old population with metabolic syndrome. BMC Geriatr 2016;16:27.

13. Wang HH, Lee DK, Liu M, Portincasa P, Wang DQ. Novel insights into the pathogenesis and management of the metabolic syndrome. Pediatr Gastroenterol Hepatol Nutr 2020;23(3):189-230.

14. Manusheva N, Chabukovska E, Babinkostova Z, Markovikj S. Hyponatremia in olanzapine treated patient. Macedonian Journal of Anaesthesia 2021;5(2):78-83.

15. Pouragha H, Amiri M, Saraei M, Pouryaghoub G, Mehrdad R. Body impedance analyzer and anthropometric indicators; predictors of metabolic syndrome. J Diabetes Metab Disord 2021;1-10.

16. Beigh SH, Jain S. Prevalence of metabolic syndrome and gender differences. Bioinformation 2012;8(13):613-616.

17. Pucci G, Alcidi R, Tap L, Battista F, Mattace-Raso F, Schillaci G. Sex- and gender-related prevalence, cardiovascular risk and therapeutic approach in metabolic syndrome: A review of the literature. Pharmacol Res 2017;120:34-42.

18. Jiang B, Zheng Y, Chen Y, Chen Yi, Li Q, Zhu C, al. Age and gender-specific distribution of metabolic syndrome components in East China: role of hypertriglyceridemia in the SPECT-China study. Lipids Health Dis 2018;17:92.

19. Mauvais-Jarvis F. Epidemiology of gender differences in diabetes and obesity. Adv Exp Med Biol 2017;1043:3-8.

20. Huang PL. A comprehensive definition for metabolic syndrome. Dis Model Mech 2009;2(5-6):231-237.

21. De Hert M, Dekker JM, Wood D,

Kahl KG, Holt RI, Möller HJ. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). Eur Psychiatry 2009;24(6):412-24.

22. American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity. Consensus Statement: Consensus development conference on antipsychotic drugs and obesity and diabetes. J Clin Psychiatry 2004; 65(2):267-272.
23. Gebhardt S, Haberhausen M, Heinzel-Gutenbrunner M, Gebhardt N, Remschmidt H, Krieg JC, t al. Antipsychotic-induced body weight gain: predictors and a systematic categorization of the long-term weight course. J Psychiatr Res 2009;43(6):620-6.
24. Eckel RH, Alberti KG, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2010; 375(9710):181-3.
25. Robinson DG, Schooler NR, Correll CU, John M, Kurian BT, Marcy P, et al. Psychopharmacological treatment in the RAISE-ETP study: Outcomes of a manual and computer decision support system based intervention. Am J Psychiatry 2018;175(2):169-179.
26. Attux C, Quintana MI, Chaves AC. Weight gain, dyslipidemia and altered parameters for metabolic syndrome on first episode psychotic patients after six-month follow-up. Braz J Psychiatry 2007; 29(4):346-9.
27. Attux C, Martini LC, Elkis H, et al. A 6-month randomized controlled trial to test the efficacy of a lifestyle intervention for weight gain management in schizophrenia. BMC Psychiatry 2013;13:60.
28. Zhang J, Gallego JA, Robinson DG, Malhotra AK, Kane JM, Correll CU. Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: A systematic review and meta-analysis. Int J Neuropsychopharmacol 2013;16(6):1205-1218.
29. Kraal AZ, Ward KM, Ellingrod VL. Sex differences in antipsychotic related metabolic functioning in Schizophrenia Spectrum Disorders. Psychopharmacol Bull 2017;47(2):8-21.
30. 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(2-3):225-33.
31. Raben AT, Marshe VS, Chintoh A, Gorbovskaya I, Müller DJ, Hahn MK. The complex relationship between antipsychotic-induced weight gain and therapeutic benefits: A Systematic Review and Implications for Treatment. Front Neurosci 2018; 11:741.
32. Leucht S, Samara M, Heres

S, Davis JM. Dose Equivalents for Antipsychotic Drugs: The DDD Method. Schizophr Bull 2016;42(Suppl 1):S90-S94.

33. https://psychopharmacopeia.com/antipsychotic_conversion.php [пристапено на 3.9.2021]

34. https://cpnp.org/guideline/essentials/antipsychotic-dose-equivalents [пристапено на 3.9.2021]