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ASSESSMENT OF LONG TERM METABOLIC EFFECTS OF ATYPICAL ANTIPSYCHOTICS IN SCHIZOPHRENIA PATIENTS

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Abstract

Background and aims. *Patients with schizophrenia have a shorter life expectancy than normal population partially due to the metabolic side effects of antipsychotic treatment. The aim of this study is to evaluate the long-term evolution of the metabolic syndrome in chronic schizophrenia patients on fixed second generation antipsychotics (SGA).* ***Material and method.*** *The components of metabolic syndrome were evaluated repeatedly in a minimum 6 months and maximum 2 years follow-up period. The presence of metabolic syndrome (MetS) and metabolic risk scores (cMetS) according to National Cholesterol Education Program Adult Treatment Panel III were calculated and compared in time. In the prevalence, incidence and normalization logistic regression studies included all the known risk factors together with the follow-up period. Finally, all these rates were compared depending on the type of SGA.* ***Results.*** *Only cMetS, waist circumference and diastolic blood pressure presented significant increase in the follow-up period which was in average 385.5 days. The prevalence of MetS at base-line was 39.4%, which increased to 48.5% after the follow-up period. The calculated incidence of 30% was associated with a 23.1% rate of normalization. Logistic regression studies revealed as independent risk factors the age and base-line cMetS/weight for incidence and for normalization. In the aripiprazole group the normalization rate exceeded the incidence rate (33.3% vs 20%).* ***Conclusions.*** *The results emphasize the highly dynamic character of the metabolic syndrome even in chronic schizophrenia patients with fixed SGA regimen. The normalization of MetS is a possibility that should not ignored. The age and weight continue to remain independent risk factors, thus close monitoring in elderly and strict weight control plan are necessary. Aripiprazole showed better safety profile, but more extensive studies are required for definitive conclusions.*

key words: *schizophrenia, SGA, metabolic syndrome, aripiprazole*

Background and aims

What is known

Patients with schizophrenia have with twenty years shorter life expectancy then normal population and this difference seems to increase [1]. One of the possible causes for this mortality rate difference is that schizophrenia patients have a higher risk for metabolic syndrome

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(diabetes mellitus, obesity, arterial hypertension and hypercholesterolemia [2].

The concept of metabolic syndrome (MetS) was introduced like an early detection tool and active management [3]. People with metabolic syndrome have double risk to develop cardiovascular diseases and triple risk to develop diabetes mellitus [4]. Monitoring of MetS allow identification of population with high risk and progression to morbidity and mortality [5]. Considering these things, MetS gain more and more attention in current clinical trials. American Heart Association (AHA) has identified 6 major components of metabolic syndrome: abdominal obesity, dyslipidemia, hypertension, impaired glucose tolerance, proinflammatory and procoagulation states [6].

The relation between the mechanism of action of antipsychotics and metabolic syndrome seems to be very complex, probable multifactorial, involving probable an interaction between dopamine, histamine, orexigenic neuropeptides, adrenergic and muscarinic receptors and glucose homeostasis deficiency with other risk factors [7].

Antipsychotic medication represents the first line treatment in schizophrenia, being efficient in relieving basic symptoms like auditory hallucinations and delirium [8,9]. These drugs can be divided in two categories: first generation antipsychotics (typical antipsychotics) like haloperidol and second generation antipsychotics (atypical antipsychotics) like risperidone, olanzapine and quetiapine. Typical antipsychotics are dopaminergic antagonists which act on the three main ways of neurotransmitters, while atypical antipsychotics have, generally, affinity for both dopaminergic and serotoninergic receptors, being more selective for limbic system [10]. Aripiprazole differs from other atypical antipsychotics, being partial agonist of dopaminergic receptors and is thus considered by some authors like a third generation antipsychotic [11].

What is unknown

There is an entire literature describing the prevalence of metabolic syndrome in the context of using atypical antipsychotics. In a meta-analysis, the overall rate of MetS was estimated at 32.5% [12]. However, articles that study its incidence are few in number [13,14]. These studies followed patients after initiating treatment with antipsychotics for variable periods [15-17]. These studies give us information about emerging adverse effects at the beginning of the treatment period, but they may not necessarily apply to assessing the long-term effects of atypical antipsychotics. Investigating the evolution of the MetS in the late maintenance phase is also necessary to make decisions regarding the change in the therapeutic regimen or even its discontinuation [18].

In many cases changing the antipsychotic drug or discontinuing it is not possible and clinicians need to continue with the current medication despite the recognition of MetS. The effect of atypical antipsychotics in the treatment maintenance phase may be different from the acute phase. For example, clozapine did not show any more serious long-term metabolic adverse effects than other antipsychotics [19]. Thus, information about the metabolic effect of different antipsychotics from chronic patients with the same treatment regime would be invaluable. Those researches that have studied new cases of metabolic syndrome and their disappearance during chronic treatment phase have shown that the natural evolution of MetS is very dynamic, with the possibility of normalization [20,21].

To predict a specific result, knowing the risk factors is indispensable. Previous studies have shown that MetS is associated with the number

of recurrence episodes, age and duration of treatment [22,23]. The type of atypical antipsychotic is also important [24]. In some studies, it was assumed that early changes in metabolic indicators may be predictive for long-term metabolic changes [25,26]. However, these researches have focused on incidence, finding factors that favor or prevent the metabolism syndrome normalization can also be very useful. For example, an increased abdominal circumference predicts a lower chance of normalizing MetS [27].

What is the aim of the proposed study

Through this clinical study, we aimed to track metabolic syndrome components over a period of 0.5-2 years in patients with schizophrenia treated with various atypical antipsychotics. This tracking allows us to calculate metabolic risk score (cMetS), an effective tool in identifying risk populations for cardiovascular disease and diabetes mellitus [28]. Differences will be followed in evolution and comparatively between different antipsychotics for both the separate components and the severity score.

Talking about a broader age group (18-65 years), we must include in the statistical study other risk factors for the appearance of metabolic status, such as: duration of antipsychotic treatment, dose of atypical antipsychotic and family history of metabolic diseases.

Material and method

Study design and patients

Being a retrospective study, cases will be selected from patients admitted to the Psychiatry Clinic of the "Dr. Gavril Curteanu" Municipal Hospital Oradea with the diagnosis of schizophrenia in 2017. These patients will be followed up for a period of one year (by the end of 2018) for hospital readmissions.

Inclusion criteria:

- metabolic status assessed at least 2 times during the follow-up period with at least 6 month time difference;
- use of an atypical antipsychotic for at least 1 year before inclusion in the study and without a change in the treatment regimen 3 months before inclusion;
- without changing the antipsychotic treatment strategy, besides dose adjustment, between the two metabolic status evaluations;
- absence of antidiabetic, antihypertensive or hypolipidemic treatment between the two metabolic status evaluations.

Exclusion criteria:

- age under 18 or over 65;
- pregnancy or breastfeeding;
- oncological patients;
- previously diagnosed with diabetes mellitus.

The metabolic status for this study will be evaluated using the following parameters:

- fasting blood glucose level;
- serum level of triglycerides (TG);
- serum level of high density lipoproteins (HDL-C);
- systolic and diastolic blood pressure;
- abdominal circumference;
- body weight and body mass index.

The metabolic syndrome will be defined according to the National Cholesterol Education Program Adult Treatment Panel III (AHA NCEP ATP-IIIA) [29]. It defines the presence of metabolic syndrome by the occurrence of 3 or more of the following criteria:

- fasting blood glucose equal or greater than 110 mg/dl;
- serum level of triglycerides equal or greater than 150 mg/dl;
- HDL-C below 40 mg/dl in men and less than 50 mg/dl in women;

- systolic blood pressure equal or above 130 mmHg;
- diastolic blood pressure equal or above 85 mmHg;
- abdominal circumference equal or greater than 102 cm for men or 88 cm for women [28].

The prevalence of metabolic syndrome will be estimated according to the number of patients who met the MetS criteria at base-line. Incidence will be defined by new metabolic syndrome cases in patients with no metabolic syndrome at inclusion. The normalization of the metabolic syndrome will be defined as its disappearance at the follow-up in patients with initial metabolic syndrome [28].

The continuous values from the components of the metabolic syndrome define the metabolic risk score. cMetS is calculated using a predefined formula of the standard residual values (Z score) for blood glucose, TG, HDL-C, blood pressure (main arterial pressure – MAP) and abdominal circumference [30].

Multifactorial analysis of risk factors for the occurrence of metabolic syndrome will also include the following data extracted from the patient's observation sheet:

- age;
- family history of metabolic diseases;
- duration of antipsychotic treatment;
- dose of SGA.

These data will be analyzed and compared for the various atypical antipsychotics used during the follow-up period.

Statistical analysis

Demographic and clinical characteristics will be described by mean ± standard deviation and median with interquartile range in case of skewed distribution and number of observations and percent for categorical variables. Their comparison for the two genders was done using the Student t-test, Mann-Whitney and Chi-square tests with Yates' correction. The evolution in time of the continuous variables involved the use of paired samples t-test, respectively Wilcoxon test, depending on the type of distribution. The dichotomous variable presence or absence of MetS at inclusion and re-evaluation was used to calculate the prevalence, incidence and normalization rate.

To study the correlation between the risk factors and the evolution of the metabolic indicators, the Pearson respectively Spearman correlation coefficient (for normal respectively skewed distribution) was determined.

A logistic regression model with gradual inclusion of variables was constructed for prevalence, incidence and for the normalization of metabolic syndrome in order to study the influence of various clinical and demographic risk factors. The statistical significance was set at 0.05. All statistical studies were performed using MedCalc® version 12.5.0.0 (MedCalc® Software, Mariakerke, Belgium).

Study limitations

Analyzing the design of this study we identified several possible limitations that can alter the results:

- reduced sample size due to the multiple inclusion and exclusion criteria (especially the lack of laboratory determinations in some admissions, as well as changes in the antipsychotic regime between admissions);
- unequal periods between measurements can generate errors that can be countered by introducing the period as co-variate in multifactorial analysis;
- data analysis only at 2 points of evolution does not allow accurate analysis of fluctuation in the state of metabolism;

- unequal subgroups determined by the type of antipsychotic can limit the statistical power of comparisons between subgroups.

Results

Applying the inclusion and exclusion criteria, 84 patients were identified during the study period, of which in 66 were all data necessary for the identification of the metabolic syndrome at both inclusion and re-hospitalization.

The initial demographic and clinical characteristics divided by gender are shown in Table 1.

Table 1. Initial demographic and clinical characteristics.

	Male	Female	Total	Statistical significance (p)
Number of patients (%)	22 (33.3)	44 (66.7)	66 (100)	**0.0097**
Age (years) – mean±SD	42.3±12	47.1±8.8	45,5 (10.2)	0.0706
Provenience (urban/rural)	18/4	20/24	38/28	**0.0107**
Family history of metabolic disorders (%)	1 (4.6)	5 (11.4)	6 (9.1)	0.6497
Duration of treatment (years) – mean (interquartile range)	9 (4-18)	11 (6-17)	10 (4-16)	0.8457
Follow-up period (days) – mean±SD	387.3±107	384.5±101	385.5±102.7	0.9160
Equivalent dose of chlorpromazine (mg) – mean value ±SD	464.5±162	432.2±149	443± 153.5	0.4242
Type of SGA (%): - Aripiprazole - Clozapine - Olanzapine - Quetiapine - Risperidone - Amisulpride	 8 (36.4) 2 (9.1)2 (9.1) 6 (27.2) 2 (9.1) 2 (9.1)	 14 (31.8) 10 (22.7) 10 (22.7) 4 (9.1) 6 (13.7) 0 (0)	 22 (33.4) 12 (18.2) 12 (18.2) 10 (15.1) 8 (12.1) 2 (3)	0.0613
SD – standard deviation; % - percent; p – statistical significance under 0.05				

Gender differences occurred only in the number of patients and the provenience. The need for an atypical antipsychotic dose was higher for male gender and the duration of treatment was longer for female gender, but none reached the threshold of statistical significance.

The average follow-up period exceeded the 1-year threshold and the duration of antipsychotic treatment was around 10 years,

with no gender differences. Studying the type of atypical antipsychotic used we noticed the increased frequency of Aripiprazole in both women and men.

The results on the evolution of metabolic indicators demonstrated that only cMetS, abdominal circumference and diastolic blood pressure showed significant increases in the follow-up period (Table 2).

Table 2. Evolution of metabolic indicators in the follow-up period.

Metabolic indicator	At inclusion (n=66)	At readmission (n=66)	Statistical significance (p)
Fasting blood glucose level (mg/dl) – mean value±SD	111.6±26.4	119.5 (25.8)	0.0845
Triglycerides (mg/dl) – mean value±SD	218.7±87	228.1±81	0.5217
HDL-C (mg/dl) – mean value±SD	39.8±5.8	38.1±4.9	0.0712
SBP (mmHg) – mean (interquartile range)	130 (110-145)	135 (115-140)	0.1367
DBP (mmHg) – mean (interquartile range)	80 (70-90)	90 (70-110)	**0.0243**
Abdominal circumference (cm) – mean±SD	108.6±22	118.5±26	**0.0197**
BMI – mean value±SD	30.2±8.8	32.8±8.1	0.0797
cMetS – mean value±SD	0.962±0.7	1.254±0.7	**0.0180**
SD – standard deviation; HDL-C- serum level of high-density lipoproteins; SBP – systolic blood pressure; DBP – diastolic blood pressure; BMI – body mass index; cMetS – metabolic risk score; % - percent; p – statistical significance under 0.05			

There is a general worsening of each indicator at readmission. After performing correlations with the studied risk factors, we have been identified 3 which influence their evolution during the follow-up period: gender, age and dose of atypical antipsychotic. Thus, in men, a worsening of the results was observed in most metabolic indicators (increase in triglycerides, abdominal circumference, body weight, systolic and diastolic blood pressure, and decrease in HDL-C). Age was directly correlated with blood glucose and triglycerides levels and inversely proportional to cMetS and body weight. The equivalent dose of chlorpromazine to atypical antipsychotic showed direct correlation with the evolution of blood glucose, abdominal circumcision, and cMetS score (Figure 1).

According to the criteria established by the National Cholesterol Education Program Adult Treatment Panel III (AHA NCEP ATP-IIIA), 26 patients (39.4%) were identified with metabolic syndrome present at base-line. Building a logistic regression study on prevalence, male gender and antipsychotic dose were shown to be independent risk factors: odds ratio (OR) for

men = 3.24, 95% confidence interval (IC): 1.51-7.29, p=0.003 respectively for high doses of atypical antipsychotic = 1.18, IC95%: 1.04-1.26, p=0.040.

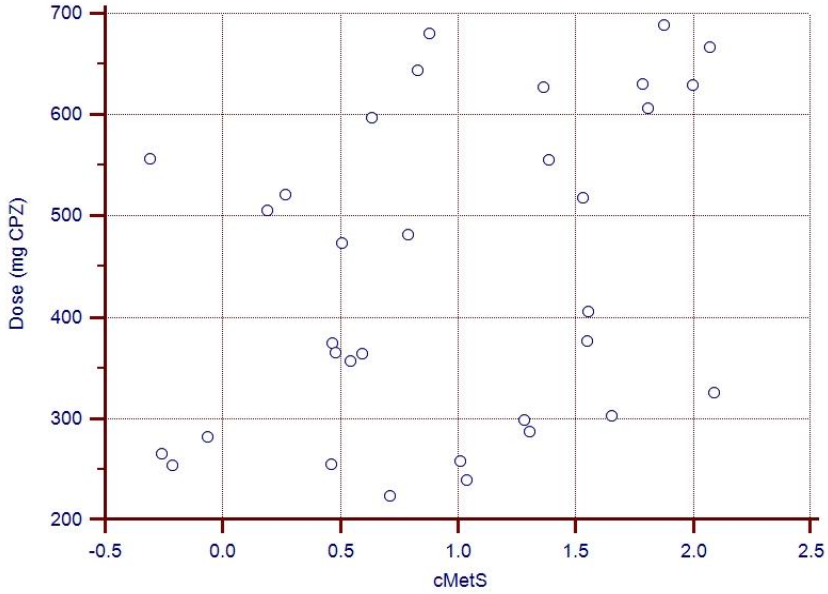

Figure 1. *Correlation between SGA dose and cMetS after follow-up period (mg CPZ = equivalent dose of chlorpromazine in milligrams, cMetS = metabolic risk score) - p = 0.0036.*

Table 3. The prevalence, incidence and normalization of MetS in the two subgroups of patients.

MetS	Aripiprazol (n=22)	Other SGA (n=44)	Statistical significance (p)
Prevalence (%)	12/22 (54.5)	14/44 (31.8)	0.1300
Incidence (%)	2/10 (20)	10/30 (33.3)	0.6903
Normalization (%)	4/12 (33.3)	2/14 (14.3)	0.4950
MetS – metabolic syndrome; % - percent; p – statistical significance under 0.05			

After assessing the metabolic syndrome at hospital readmission, the number of cases meeting the MetS criteria increased to 32 (48.5%). The incidence calculated according to the rule described in the chapter "Material and Method" was 30% (12 new cases of metabolic syndrome) and the rate of normalization was 23.1% (6 cases where the metabolic syndrome disappeared during the follow-up period).

The incidence logistic regression model including all evaluated risk factors demonstrated independent influence of age (OR=1.09, IC95%: 1.03-1.17, p=0.009) and cMetS at inclusion (OR=1.77, IC95%: 1.29-2.55, p =0.0009).

In the model built for the normalization of metabolic syndrome, only the age and weight at inclusion remained as independent risk factors. The OR for the age was 0.74, IC95%: 0.57-0.89, p=0.006, respectively OR for body weight at inclusion was 0.85, IC95%: 0.72-0.95, p=0.016).

We can see that patients with a more advanced age and a higher weight at inclusion

have a higher risk of developing metabolic syndrome and, at the same time, lower chances of improvement.

In order to have a comparative view of the metabolic effects of different SGA and taking into account their known characteristics, we divided the sample of patients into 2 subgroups: those treated with aripiprazole (n=22) and those treated with other atypical antipsychotics (n=44).

Table 3 contains prevalence, incidence and normalization data for the aripiprazole group, respectively that treated with other atypical antipsychotics.

A rate of normalization exceeding the incidence in aripiprazole-treated patients is observed, although differences in different categories are statistically insignificant towards patients treated with other atypical antipsychotics.

Discussion

In this study, we have been assessed the long term metabolic effects of fixed-dose SGA in a group of patients with chronic schizophrenia. In a follow-up period of 0.5 to 2 years, the prevalence of metabolic syndrome increased from 39.4% to 48.5%. The metabolic risk score, along with abdominal circumference and diastolic blood pressure, increased significantly.

The logistic regression analysis confirmed the presence of several demographic and clinical features that influenced the evolution of time independent metabolic indicators. Our results confirm the data observed in other studies about the progressive worsening of metabolic status in patients treated with atypical antipsychotics [31-33]. It also coincides the observation that the advanced age and the atypical antipsychotic dose are associated with an increased prevalence of metabolic syndrome [20,34]. This evidence indicates a progressive worsening of the metabolic status of patients on SGA. However, observing individual data suggests a potential recovery that is still significant. The incidence rate (30%) is still higher than the normalization rate (23.1%), but at least they are of the same order of magnitude.

The chance of improvement may represent the hope for the treatment of metabolic syndrome, especially in patients where the change in treatment regimen is not possible [35]. In these cases, changing the lifestyle or drug treatment may be the only solutions [18]. However, many researchers have demonstrated the inefficiency of these measures [36,37].

The logistic regression models have shown that age and weight at inclusion are independent risk factors for both the incidence and the likelihood of normalization of metabolic syndrome in these patients. Anyway, age is a risk factor for the development of metabolic syndrome in the general population too but draws attention to the need for rigorous monitoring of the elderly population with schizophrenia. In contrast to the inevitable advancement in age, control of body weight through proper education and care is possible. Body weight fluctuations appear to precede the appearance of other manifestations of metabolic syndrome [38].

The most of metabolic parameters were correlated with initial weight gain in the study of Bai and colab. in long-term follow-up of patients on clozapine treatment [39]. The importance of our results lies in the fact that obesity not only aggravates the evolution of metabolic syndrome but also reduces the chances of recovery. Thus, all treatment plans for these patients should also include an aggressive weight control plan [40,41]. An appropriate education with encouragement of exercises is essential along with pharmacological interventions including antihypertensive, antidiabetic and hypolipidemic medication. A patient's metabolic status on long-

term antipsychotic treatment is very dynamic, showing changes both over time and through appropriate interventions [19].

The rate of incidence and normalization in the aripiprazole group was 20% respectively 33.3%, indicating a trend towards improvement. Multicentre studies are required on larger patient samples with multiple, serial determinations to observe this differential effect on different SGA.

Conclusions

In conclusion, the metabolic status of schizophrenic patients is gradually worsening even if the treatment regimen remains stable. However, individual data showed the very dynamic nature of these changes. Nearly one-third of patients developed MetS during follow-up, and nearly one-quarter of the cases showed a conversion to normal in about one year. The results emphasize the importance of considering the possibility of metabolic syndrome normalization in the analysis of its dynamic evolution.

In addition, age and body weight have an individual predictor role in the risk of incidence and normalization, suggesting that clinical management plans should also address to these variables too. Aripiprazole has shown a better safety profile than other atypical antipsychotics, but further studies are needed to draw definitive conclusions.

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