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THE RELATIVE RISK OF DEVELOPING TYPE 2 DIABETES MELLITUS IN YOUNG ADULTS WITH SCHIZOPHRENIA TREATED WITH DIFFERENT ATYPICAL ANTIPSYCHOTIC

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Abstract

Background and aim: While the link between antipsychotic treatment and metabolic adverse events, including type 2 diabetes mellitus (T2DM) are clear in adults with schizophrenia, in young this association is not so well studied although the use of second-generation antipsychotics (SGA) is more and more frequent. Material and methods: The local diabetes register was compared with the list of all registered young adults (18-35 years) with schizophrenia 2 years retrospective and 2 years prospective. Cumulative incidence, rate of incidence and relative risk was calculated knowing the number of persons in this age group within this region. Results: Cumulative incidence for exposed group was 0.7% with a rate of incidence of 6.27 (95%CI: 4.1-10.5) per 1,000 patient-years, when in normal population was 0.2%, respectively 2.01 (95%CI: 0.72-3.79). This means a relative risk of 3.4736 (95%CI: 1.79-6.72), p=0.0002 and NNH=202 (95%CI: 134-404). Multivariate analysis showed that gender male (OR=1.83; 95%CI: 0.9-2.7; p=0.002) and olanzapine prescription (OR=4.76; 95%CI: 1.7-7.7; p=0.0001) were independent risk factors for T2DM. Conclusions: The metabolic risk should be taken in account every time introducing or changing a SGA in young schizophrenic patient, balancing the benefits and negative metabolic effects (especially with olanzapine). Healthy nutrition and physical activities are necessary components of these patients lifestyle to avoid early onset of T2DM.

key words: *Schizophrenia, Young Adult, Second-generation Antipsychotic Agents, Metabolic Side Effects of Drugs and Substances, Diabetes Mellitus Type 2, Olanzapine.*

Background and aims

What is known

The prevalence of diabetes mellitus is 4 to 5 times higher in patients with schizophrenia than in general population [1]. Those who suffer from both diseases have a mortality rate of 3 to 4 times higher than general population and in case of death; at least one third is due diabetes and its complications [2]. Much more, diabetes contributes to development of cardiovascular diseases which can be lethal, shortening with over 20 years the life expectancy of patients with

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schizophrenia [3,4]. Young people with schizophrenia (up to 40 years old) are at risk of developing early type 2 diabetes (T2DM) [5]. This is a rapidly progressive disease through micro and macrovascular complications [6,7].

Studies from the period prior to the discovery of neuroleptics reported an increased prevalence of altered glucose tolerance, insulin resistance and diabetes mellitus [8,9]. Abnormal glucose tolerance is more common in patients with schizophrenia who have never received antipsychotics compared to healthy subjects, this association is independent of body mass index (BMI) or unhealthy lifestyle [10,11]. Moreover, there are studies that have shown an increased prevalence of diabetes mellitus in first-degree relatives of patients with schizophrenia, indicating a possible genetic link between schizophrenia and diabetes [12,13]. Two of the most commonly replicated genes susceptible to the development of type 2 diabetes (TCF7L2 and IGF2BP2) have been associated with schizophrenia [14-16]. In addition, there are also genetic association studies and pathogenic analyzes that support common risk factors for these two pathological entities [17-19].

Since the introduction of chlorpromazine in schizophrenia treatment in 1952 there have been numerous reports regarding the association with the occurrence of diabetes and the decrease in glucose tolerance [20]. Since the advent of second generation antipsychotics this association has been investigated more systematically [21-25]. A multicenter study that did not include aripiprazole, ziprasidone and amisulpride demonstrated that second-generation antipsychotics (SGA) are associated with a higher risk of developing diabetes than conventional antipsychotics [26]. Subsequently, a study with a longer follow-up period counteracted this result, saying that both generations of antipsychotics increase the risk of diabetes, but SGA, as a class, confer a significantly lower risk than first-generation antipsychotics [27]. Individually, the drugs from SGA may have variable risk of developing diabetes [28,29]. Clozapine appears to confer a higher risk compared to other second generation antipsychotic preparations [28,30]. A recent meta-analysis reported an incidence of T2DM among patients between 2-24 years old exposed to antipsychotics of 3.09 (95% confidence interval - CI = 2.35-3.82) per 1,000 people per year [31]. This study also demonstrates a significantly increased risk of developing early T2DM among patients treated with SGA.

Regarding the causal mechanisms of the association between antipsychotics and diabetes multiple pathophysiological pathways [17] and a dose-response effect have been described [27]. Central and peripheral antagonism of M3, H1 and 5-HT_{2c} receptors and other serotoninergic and adrenergic receptors may have direct diabetic effects or may indirectly contribute to the development of diabetes by promoting weight gain and decreasing insulin sensitivity [17,28,32].

What is unknown

There are still many question marks in our knowledge about the endogenous diabetes risk in patients with schizophrenia and that related to antipsychotic treatment. There is no study in a larger group of schizophrenic patients without antipsychotic treatment to investigate the endogenous metabolic risk compared to the general population. But also, researches focusing on the early onset of T2DM in young patients with schizophrenia are reduced in number [31].

The metabolic and cardio-vascular adverse effects due to antipsychotics occur faster and are more severe in young people than in adults [33-35]. Antipsychotic treatment results in a significant increase in weight in most young

people [36,37]. It remains controversial whether this increased risk of short-term metabolic effects in young people versus adults is due to differences in the developmental stage of the organism or due to less previous exposure to antipsychotics [38]. It also remains to be discussed whether this weight gain is temporary or lifelong [39].

While in adults the clear link between antipsychotic treatment and decreased glucose tolerance, increased insulin resistance and the risk of developing type 2 diabetes seems to differ between the substances used [28], in young people the risk of developing T2DM due to SGA treatment is less studied, although their use in young people becomes more and more frequent [40,41].

What is the aim of the proposed study?

Given these uncertainties and the lack of multicenter studies on this topic, we have proposed to monitor young adults with schizophrenia in order to identify the risk of developing diabetes by following the local diabetes registry for medium/long term. The values will be compared with those recorded in the general population and between different second generation antipsychotic preparations.

The comparison of the results from the discussion chapter will have to take into account the characteristics of the geographical area regarding eating habits, smoking, sedentary lifestyle.

Material and method

Study design and patients

The study being an observational and mixed one will include a retroactive analysis over a period of 2 years of the consultation register of the Center for Adult Mental Health of the Municipal Clinical Hospital "Dr. Gavril Curteanu "Oradea. All cases of schizophrenia consulted in the age group 18-35 will be identified. The study sheet will be completed with:

- the patient's demographic data: age, gender, place of origin;
- metabolic and psychiatric history;
- the atypical antipsychotic preparation in the treatment plan and dose;
- other risk factors for type 2 diabetes: obesity, smoking, sedentary lifestyle, high blood pressure, hyperlipidemia.

Patients previously diagnosed with diabetes mellitus or decreased tolerance to oral glucose, pregnant or postpartum, oncological patients will be excluded from the study group.

At the same time we started to study the County Diabetes Register within the Ambulatory of Oradea County Clinical Hospital to detect all new cases of T2DM in Bihor County. This register will be followed for all new cases of T2DM in the age category 18-35 years for a period of 4 years (2 years retrospectively and 2 years prospective). Thus the minimum follow-up period will be 2 years and the maximum will be 4 years.

In order to determine the general population of Bihor County in the age category 18-35 we consulted the Statistical Yearbook of Bihor County, which indicates 144,057 persons out of the total population of 618,881 [42].

Comparing the two registries, we identified the patients enrolled in the study who develop type diabetes in the follow-up period. This allows us to calculate the annual and multiannual incidence compared to the general population. The relative risk calculation will be derived for patients with schizophrenia in this age group in general and for different antipsychotics separately.

For the multivariate analysis we also included the risk factors identified when enrolling the cases; the results of these studies

will indicate whether any of the variables constitute an independent risk factor or not.

Statistical analysis

The cumulative incidence of T2DM was calculated by dividing the number of patients with T2DM onset during follow-up with the total number of people in the cohort. The incidence rate per patient-year was defined by the product between the number of patients discovered with T2DM and the number of patients-years of follow-up. The relative risk and 95% confidence interval (95% CI) was obtained by comparing the incidence rate for T2DM in young adults with schizophrenia with the incidence rate for T2DM in the general population. The number needed to harm (NNH) was calculated by dividing 1 with the risk difference. The same test will also be applied to compare the incidence rates for T2DM in patients treated with different SGA.

A logistic regression model with a gradual inclusion of the variables was built for incidence with the purpose to study the influence of different clinical and demographic factors. The statistical significance was established at the p-value of 0.05. All statistical studies were performed using the MedCalc® statistical software version 12.5.0.0 (MedCalc® Software, Mariakerke, Belgium).

Study limitations

We identified several sources of errors that could limit the statistical and clinical power of the study:

- limited follow-up period: the metabolic side effects of atypical antipsychotics accumulate over time, so that the incidence in the first years after the introduction of the treatment does not indicate the real risk to which such a patient is exposed for longer periods;
- the partially retroactive nature of the study will probably cause the impossibility of obtaining some initial information, especially those related to the risk factors for T2DM, which will create errors in the multivariate analysis of the risk factors;
- considering the follow-up period and the extended territory covered by the study we must also consider the effect of the migration (not having a certainty that the patient was not registered in the Diabetes Register of another county or another country);
- failure to identify the entire cohort from Bihor county in case a patient did not attend any consultation during the 2 years of follow-up;
- combination of atypical antipsychotics is a common practice in establishing the treatment plan of schizophrenia patients, the subsequent introduction of a new antipsychotics produces interference in the comparative metabolic effects of the different atypical antipsychotics.

Results

In the register of the Center for Mental Health Adults we have found at least 1,440 young adults (18-35 years old) with schizophrenia treated with antipsychotics. In all cases, we identified at least one SGA. Due to the existence of at least one exclusion criterion, 144 patients were eliminated. We have found 765 males (59.0%) from the 1296 cases.

Demographic and clinical characteristics of the study group from the consultation sheet are summarized in Table 1.

Significant statistical differences between the two genders were observed only in terms of provenance. The most commonly used SGA was aripiprazole followed by olanzapine, clozapine and risperidone. The other drugs together did not reach the threshold of 10% of cases.

Table 1. Demographic and clinical characteristics of young adults with schizophrenia in Bihor County.

	Young adults with schizophrenia			p
	Male (n=765)	Female (531)	Total (n=1296)	
Mean age (years) ± SD	27.2 (6.1)	26.9 (6.8)	27.1 (6.4)	0.4065
Are of provenance Urban (%) Rural (%)	 498 (65.1%) 267 (34.9%)	 160 (30.2%) 371 (69.8%)	 658 (50.8%) 638 (49.2%)	 <0.0001
Type of SGA Aripiprazole (%) Clozapine (%) Olanzapine (%) Risperidone (%) Others (%)	 217 (45.2%) 138 (50.8%) 130 (55.6%) 96 (49.5%) 51 (44%)	 263 (54.8%) 134 (49.2%) 104 (44.4%) 98 (50.5%) 65 (56%)	 480 (37%) 272 (21%) 234 (18.1%) 194 (15%) 116 (8.9%)	0.0818

SD – standard deviation; SGA – second generation antipsychotics; % - percent; p – statistical significance between the 2 genders.

Table 2. Cumulative incidence and incidence rate for T2DM in young adults with schizophrenia treated with different SGA.

SGA drugs	Cumulative incidence	Incidence rate per 1000 patient-year	p
Aripiprazole	0.41%	4.07 (1.7-7.5)	0.7628
Clozapine	0.73%	6.50 (4.3-11.2)	
Olanzapine	1.3%	8.9 (6.2-14.9)	
Risperidone	0.51%	4.61 (2.1-8.8)	
Others	0.86%	6.93 (4.9-12.1)	

T2DM – type 2 diabetes mellitus; SGA – second generation antipsychotics; % - percent; p – statistical significance between the different drugs

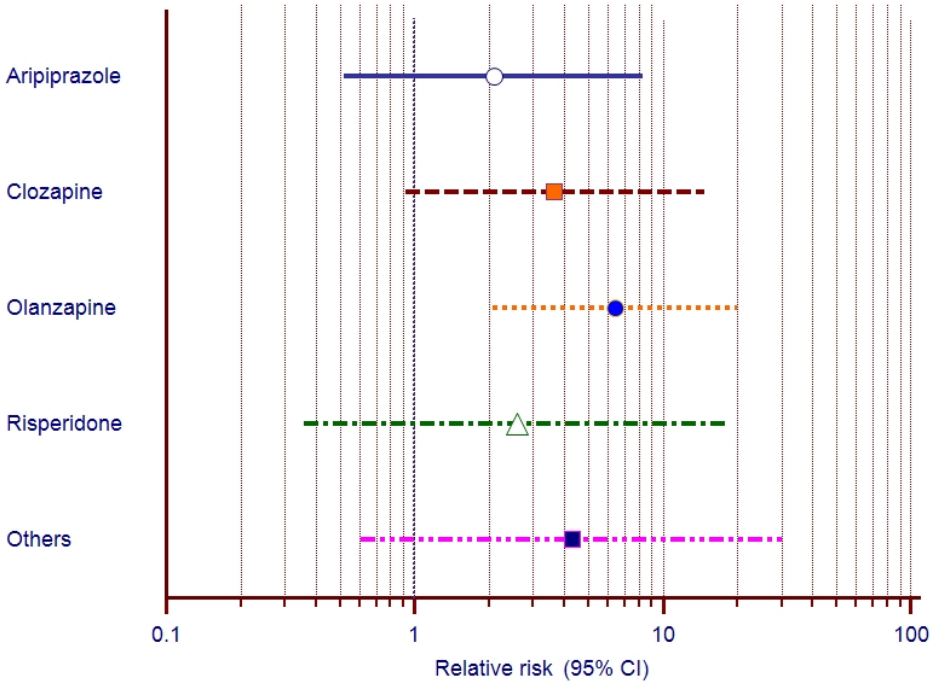

Figure 1. *The relative risks of developing T2DM for different SGA compared to the general population - age category 18-35 years (T2DM - type 2 diabetes mellitus; SGA - 2nd generation antipsychotics; 95% CI - confidence interval 95%).*

The median follow-up period was 3 years (interquartile range 2-4). After studying the registries of the County Diabetes Center we identified 9 common cases with the list of patients with schizophrenia. This means a cumulative incidence of 0.7% and an incidence rate of 6.27 (95% CI: 4.1-10.5) per 1,000 patient-years.

Considering the total number of persons in the age category 18-35 years old from Bihor county and the new cases of T2DM in this age category during the follow-up period (288 cases out of 144,057 persons) we calculated a cumulative incidence of 0.2% and an incidence rate 2.01 (95% CI: 0.72-3.79).

Comparing the two results we obtained a relative risk of 3.4736 (95% CI: 1.79-6.72), p=0.0002 and NNH=202 (95% CI: 134-404).

Dividing these data by different SGA we obtain the following results (Table 2).

The difference in the exposure to develop T2DM between SGA drugs does not reach the statistically significance threshold. However, comparing with the general population, the relatively more favorable risk for aripiprazole and risperidone is observed (Figure 1).

From the multivariate analysis for the incidence of T2DM in which the demographic, clinical characteristics and all identified risk factors were introduced, the following independent risk factors were found: male (OR = 1.83; 95% CI: 0.9-2.7; p = 0.002) and the prescription of olanzapine (OR = 4.76; 95% CI: 1.7-7.7; p = 0.0001).

Discussion

Our study shows a risk of developing T2DM about 3.5 times higher in young adults with schizophrenia compared to the general population of the same age category, which is consistent with the specialized studies in recent literature [43].

This increased risk should be weighed against the benefits of antipsychotics [44,45] in young adults with schizophrenia and indicates the need to exhaust all low-risk therapeutic alternatives prior to initiating antipsychotic treatment and careful monitoring of metabolic disorders and weight gain in these patients.

The clinical significance of these results is underlined by studies showing increased morbidity and mortality through the early onset of T2DM [46,47]. Also, we must take into account the fact that T2DM is the result of an interaction between genetic factors, lifestyle and exposure to antipsychotics.

Multivariable analysis of risk factors indicated a significantly increased risk of developing T2DM in male patients compared to women and those treated with olanzapine. The unfavorable evolution from this point of view in men is a consistent result in most published studies [25,47]. Our results confirm that the risk of T2DM is not homogeneous among different preparations of SGA and olanzapine is a major influence factor [43].

Regarding to the relative risks for different SGA preparations, one study showed that aripiprazole was associated with an increased risk of T2DM over risperidone [48]. Most likely, these metabolic adverse effects are due to other concomitant antipsychotics or from switching to second generation antipsychotics with low metabolic risk. Most prospective investigations, however, associate aripiprazole with a lower risk of T2DM compared to other reference SGA [49,50].

Conclusions

The results of this study reveal an association between antipsychotic treatment and an increased risk of type 2 diabetes in young adults with schizophrenia. This risk should be considered in the clinical risk-benefit assessment

when initiating or continuing antipsychotic treatment in this age category. Antipsychotics should only be used if other low-risk therapies have failed and the choice of antipsychotic should take into account differentiated tolerability, avoiding olanzapine.

Also, once started, treatment with antipsychotics involves active, routine monitoring to detect cardio-vascular risk factors. Patients and caregivers should be informed about the adverse metabolic effects of the treatment and encouraged for healthy nutrition and physical activities to prevent cardio-metabolic risk.

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