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THE IMPACT OF ANTIPSYCHOTICS ON WEIGHT-GAIN OF PATIENTS WITH MENTAL DISORDERS

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In this article are examined some of the key issues surrounding weight-gain in individuals suffering from mental disorders. It is showed that Weight gain is a common adverse effect of using anti-psychotic medications, and can be rapid and difficult to control. Weight gain does not seem to be dose dependent within the normal therapeutic range. The effect is worse with clozapine and olanzapine; minimal with aripiprazole and ziprasidone; and intermediate with other antipsychotics, including low-potency First Generation Antipsychotics.

ВПЛИВ НЕЙРОЛЕПТИКІВ НА ЗБІЛЬШЕННЯ МАСИ ТІЛА ПАЦІЄНТІВ З ПСИХІЧНИМИ РОЗЛАДАМИ

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У статті розглянуто ключові питання, пов'язані з коефіцієнтом збільшення маси тіла у людей, які страждають від психічних розладів. Показано, що збільшення маси є поширеним побічним ефектом використання антипсихотичних препаратів, що досить швидко розвивається і складно контролюється. Збільшення маси, ймовірно, залежить від середнього терапевтичного дозування препарату. Ефект найбільш виражений при застосуванні клозапіну й оланзапіну; мінімальний при застосуванні арипіпразолу і зипразидону; і займає проміжне місце, порівняно з іншими антипсихотичними препаратами, в тому числі з антипсихотиками першого покоління.

Introduction. Over the last years, significant weight gain in psychiatric patients also became an issue of increasing concern for medical community and society in general. It is a well-known adverse effect of several psychotropic medications, especially atypical (second-generation) antipsychotics. Recent studies show that psychiatric patients, including patients with schizophrenia [1] and affective disorders [2, 3] are predisposed to weight gain as well as metabolic syndrome even without the exposure to psychotropic medications. The nature of this association is not completely understood. In addition to medications and genetic predisposition, many factors contribute to weigh gain and the development of metabolic syndrome in psychiatric patients, including low physical activity [4] and poor diet [5]. Therefore, health care providers have to be aware of weight gain and metabolic syndrome in these patents.

Main text. Patients on antipsychotic medications frequently report increased appetite and "food craving", and cardiometabolic side effects of antipsychotics can be partially explained by increased appetite and weight gain. Histaminergic H1 and serotonergic 5HT-2C receptors play crucial role in regulating appetite. Those antipsychotics which block both these receptors, namely clozapine, olanzapine and quetiapine, cause the most significant weight gain [6]. In addition, the blocade of H1 receptors is associated with sedation, which in turn can lead to weight gain due to inactivity. However, increased appetite and weight gain is not the only mechanism of the metabolic side effects of antipsychotics, and sometimes antipsychotics can cause diabetes even without obesity. Of note, second generation antipsychotics are associated with metabolic changes prior to changes in hunger, satiety, and food intake. This temporal separation suggests that there are differential mechanisms mediating antipsychotic-associated changes in metabolism and food intake [7]. One of the possible mechanisms is the blocade of the muscarinic M3 receptors of the pancreas, as antipsychotic agents with high binding affinity to these receptors are associated with an elevated risk for type 2 diabetes [8].

A total 36 patients with mental disorders were selected for the study. 18 men with average age 37 ± 7 years (range: 28-55 years) and 18 females with average age 37 ± 5 years (range: 31-51 years) were weighed and their height was measured. Additionally, we measured the waist circumference of the patients. The weighing and waist circumference measurement procedures were repeated three times monthly in October, November and December of 2015 - the period of the treatment with one of the following medications: risperidone, quetiapine, amilsulpride and olanzapine. Within the each sex group, patients were subjected to Risperidone, while Quetiapine, Amilsulpride and Zyprexa were prescribed to groups of three patients each. The control measurements were made before the beginning of the treatment.

Weight, height and Body mass index (BMI) were determined. BMI was computed as body weight (kg) divided by the square of height (m2). Nurses measured height and weight for each patient in the study group at the time of blood examination.

In order to investigate an effect of different medication, namely risperidone, quetiapine, amisulpride and zyprexa, used for the treatment of poly-etiological mental disorders on the BMI, we studied 36 patients (18 females and 18 men), that were subjected to the treatment by one of the medications. Considering a described in the scientific literature effect of patient's sex on the relationship between the studied parameters, females and men were analyzed separately. Thus, during three consecutive months of the treatment we examined a nine patients of the each sex subjected to risperidone, three patients of the each sex subjected to quetiapine, three patients of the each sex subjected to amilsupride, and three patients of the each sex subjected to zyprexa, monthly measuring their weight to BMI calculation. We also interviewed them in respect to their anthropometric parameters such as height and age. As the result we determined an average age of the selected group equal to 37 ages for both sexes (tab. 1).

Table 1. Average age ± StDev of the studied patients.

	Females	Men
Risperidone	37.2 ± 7.3	37 ± 8.8
Quetiapine	37 ± 5.6	37 ± 2.6
Amisulpride	37.3 ±4.7	37 ± 6.1
Olanzapine	37.3 ± 2.1	37 ± 1.2

To investigate an effect of different second-generation antipsychotics (SGA) on the main parameters associated with the weight gain we first compared the control values of the patients later subjected to different SGA. The results displayed that all parameters in the control groups were very similar and these low alterations can be neglected for the analysis of the SGA medication effect.

The results demonstrated a consistent increase of the waist circumference in both groups of the males and females patients subjected to the treatment by risperidone, quetiapine, amisulpride and olanzapine compared to the control measurements (fig. 1, 2). Thus, after one month of the treatment with risperidone waist circumference reached ≈ 104% of the control for both males and females and continued to increase during the next two months of the treatment, reaching ≈ 108% of the control. Intriguingly, the similar trend of the effects of the risperidone, quetiapine and olanzapine on males and females was not observed for amisulpride. Thus, in females the waist circumference under amisulpride treatment grew to 105% of the control already in October and remained almost stable in November and December, while in males the effect of amisulpride was weak after one months of the treatment and sharply increased in November and December reaching ≈ 109% of the control. Additionally should be noted that effect of quetiapine was slightly weaker compared to other tested SGA.

Body mass index (BMI) is one of parameter of the metabolic syndrome caused by SGA. We calculated BMI of the studied patients and the results revealed a time-dependent step-wise increase of BMI under the treatment by the all used medications during three months period. Similarly to the waist circumference, increase of BMI under quetiapine treatment was the lowest (≈ 103-107% of the control for both males and females) (fig. 3, 4). Moreover, the effect of quetiapine specifically on males BMI was notable weaker compared to the other medications, reaching 104% of the control at the last month of the study. The strongest effect on BMI for both groups was observed for amisulpride treatment that caused increase up to 110% of the control. Our findings add more information to inconsistent evidences about amisulpride effect on BMI existed in the literature. Thus, majority of the studies reported about significant effect of

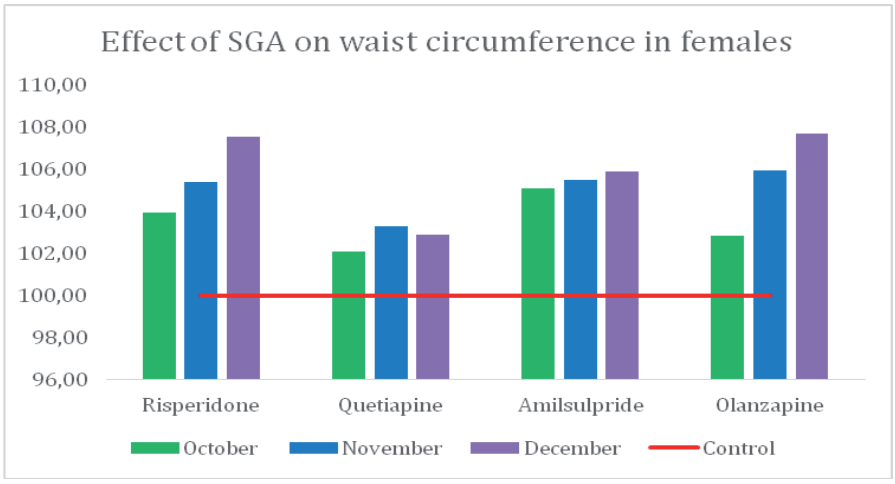

Figure 1. Effect of the tested SGA (see legend on the plot) on waist circumference in females.

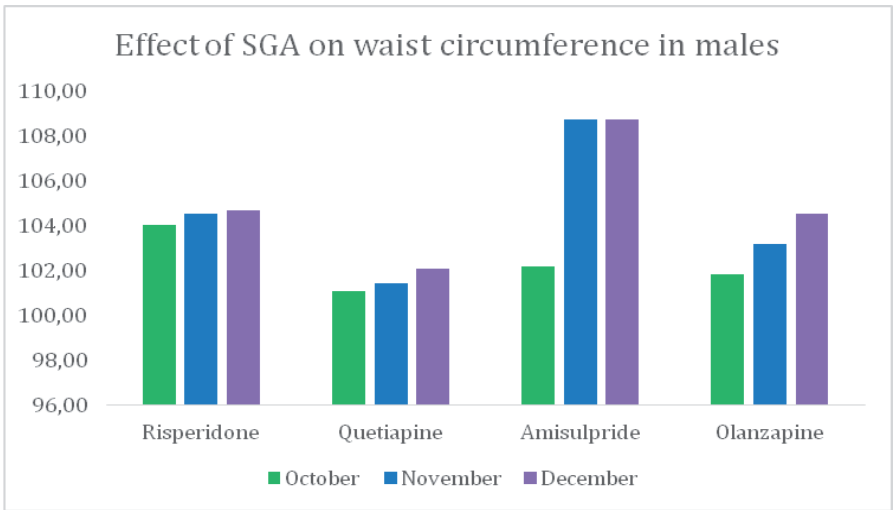

Figure 2. Effect of the tested SGA (see legend on the plot) on waist circumference in males.

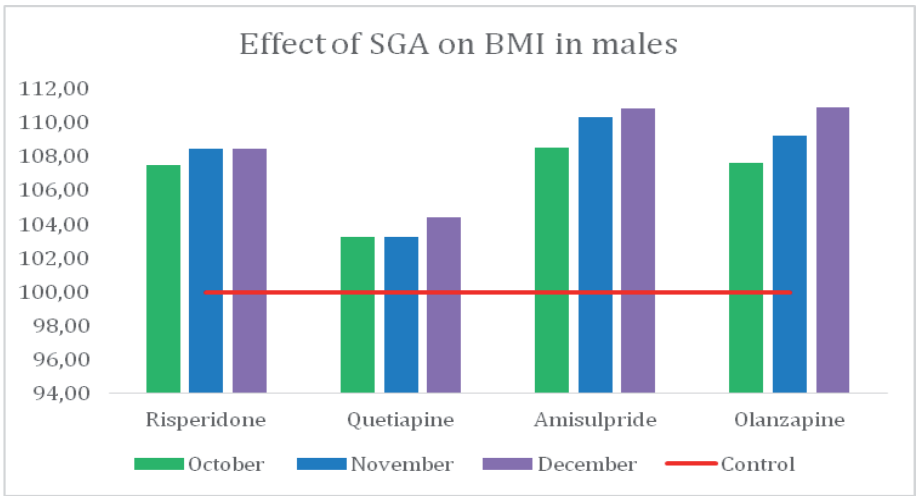

Figure 3. Effect of the tested SGA on BMI in males.

amisulpride on BMI increase [9, 10] that was also shown in this work. However, the authors also reported about more common use of amisulpride for the treatments of patients with high BMI. In our case the initial level of BMI

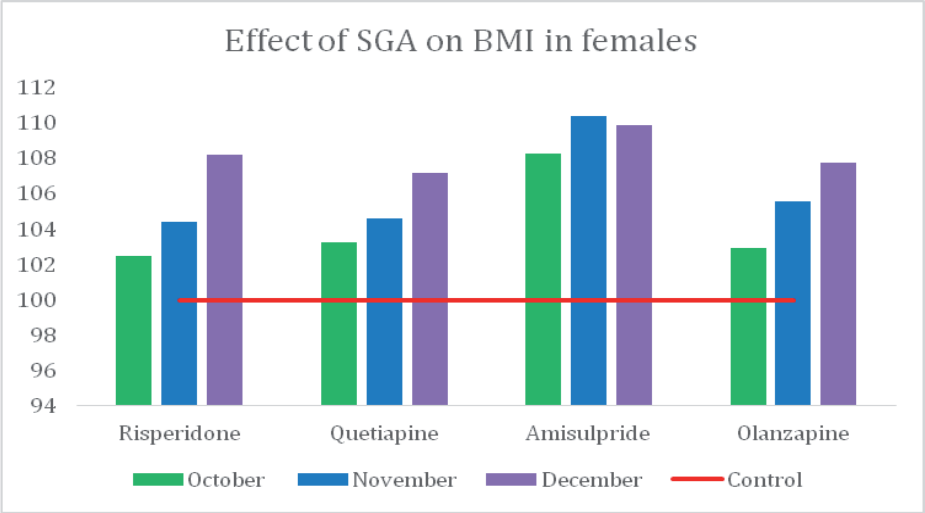

Figure 4. Effect of the tested SGA on BMI in females.

almost did not differ, but was the largest (insignificantly) for the group that was later subjected to quetiapine. Taken together, our results being in a row with the literature evidences that report high BMI of the patients subjected to amisulpride, do not show support observation of more preferably use of amilsulpride. On the other hand, our work argues with the evidences of the weaker effect of amisulpride on the weight gain [11]. Weight increases occurred in 7% of patients treated with amilsulpride for acute exacerbation of schizophrenia [12].

Recommended Monitoring Protocol

Prior to the initiation of SGA therapy, patients should be screened for diabetes, hypertension, dyslipidemia, and family history of cardiovascular disease. Weight, waist circumference should be encompassed in the screening.

Ongoing monitoring should follow baseline-screening measures. Reassessment of all measures, except personal and family history and waist circumference, is recommended after 12 weeks of treatment for all patients treated with atypical antipsychotic medications. Thereafter, fasting plasma glucose, blood pressure, and waist circumference assessments should be completed annually and fasting lipid profile measured every 5 years. Weight should be followed monthly for the first three months and quarterly thereafter. Ideally, obtain measurements monthly for the first 3 months of therapy, or after any medication adjustments, then at 6 months, and annually thereafter. Encourage patients to track their own weight. Obtain another set of measurements at 3 months, then annually thereafter, unless the patient develops type 2 diabetes mellitus [13].

Conclusion. Atypical antipsychotics are used extensively for Food and Drugs Administration-approved indications including schizophrenia and, more recently, bipolar mania. These agents are considered first-line treatments and have significant advantages over the typical antipsychotics due to their lower risk of extrapyramidal side effects and their beneficial effects on negative symptoms, cognition, and mood. Recent reports on weight gain, new-onset type 2 diabetes, and dyslipidemia require patients to receive ongoing monitoring for these conditions.

Although certain atypical antipsychotics, such as olanzapine and clozapine, have been associated with the greatest weight gain and the highest risk of diabetes and dyslipidemia, not all patients taking these agents gain a significant amount of weight.

Although there are differences in potential weight gain and, consequently, dyslipidemia among the atypical antipsychotics, differences in risk for diabetes are not as easily quantifiable. This may be due in part to the uncertain etiology of these metabolic abnormalities, but overall their prevalence seems to correlate with weight gain.

Risperidone and quetiapine have been shown to have intermediate effects, while ziprasidone and aripiprazole are reported with little or no significant weight gain.

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