Relationship between antipsychotic medication, obesity and cognitive functions

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Abstract

Introduction: The purpose of this study was to examine whether the combination of atypical and typical antipsychotic medications is related with metabolism and cognitive functions in the same manner and degree as taking medications of one kind only, i.e. atypical or typical.

Material and methods: The participants of the study comprised of 91 adults with diagnosed mental illness (F-20-F69). The participants were divided into groups on the basis of the kind of administered medications: T+A (typical and atypical medications), A (atypical medications), T (typical medications), P (antidepressants, sedatives, normothymic/antiepileptic drugs). In the study, Short Test of Mental Status (STMS), Verbal Fluency Test (VFT), Rey Auditory Verbal Learning Test (RAVLT) were used for the purpose of examining cognitive functions.

Results: The kind of antipsychotic medications taken by the patients did not differentiate the group in relation to BMI (p<0.13), nor in relation to the level of general cognitive function (p<0.72) or verbal fluency (p<0.34). Both atypical antipsychotic medications and the combination of atypical and typical medications were related to the occurrence of abdominal obesity (p<0.01). An increase in waist circumference decreased an ability of abstract reasoning (p<0.005). When it comes to the body mass index, waist circumference negatively correlated with the delayed memory (p< 0.03, p<0.004).

Discussion: Both the combination of atypical and typical antipsychotic medications and atypical medications are associated with the occurrence of abdominal obesity. The deposition of fat tissue in the abdomen negatively correlated with an ability to learn.

Conclusions: The future studies might explain the interactions between antipsychotic medications, obesity and cognitive function.

Keywords: metabolic disorders, memory, abstract reasoning

Streszczenie

Wstęp: Celem niniejszych badań było sprawdzenie czy kombinacja leków atypowych i typowych jest powiązana w takim samym stopniu z przemianą metaboliczną i funkcjami poznawczymi co leki z jednej grupy, to jest: atypowe, bądź typowe.

Materiał i metoda: Do badań włączono 91 dorosłych z diagnozą zaburzeń psychicznych (F-20-F69). Uczestnicy zostali podzieleni na grupy w zależności od rodzajów przyjmowanych leków: T+A (leki typowe i atypowe), A (leki atypowe), T (leki typowe), P (antydepresanty, środki uspokajające, leki normotymiczne / leki przeciwpadaczkowe). Do diagnozy funkcji poznawczych użyto testów: STMS, VFT, RAVLT.

Wyniki: Rodzaj przyjmowanych przez pacjentów leków nie różnicował grup pod względem BMI (p<0,13), ani też w odniesieniu do ogólnego poziomu funkcji poznawczych (p <0,72) i fluencji słownej (p <0,34). Zarówno leki przeciwpsychotyczne atypowe, jak i połączenie leków atypowych i typowych były związane z występowaniem otyłości brzusznej (p <0,01). Wzrost obwodu talii zmniejszał zdolność do myślenia abstrakcyjnego (p <0,005). Wskaźnik masy ciała, obwód talii korelował negatywnie z pamięcią odroczoną (p <0,03, p <0,004).

Dyskusja: Zarówno kombinacja leków przeciwpsychotycznych atypowych i typowych jak i leki atypowe są związane z występowaniem otyłości brzusznej. Odkładanie się tkanki tłuszczowej w okolicy brzusznej koreluje negatywnie ze zdolnością do uczenia się.

Konkluzje: Niewątpliwie niezbędne są przyszłe badania wyjaśniające interakcje między lekami przeciwpsychotycznymi, otyłością a funkcjami poznawczymi.

Słowa kluczowe: przemiana metaboliczna, pamięć, myślenie abstrakcyjne.

Introduction

Overweight and obesity are one of the most important health problems in today's world. Growing food industry contributes to propagation of diets rich in fats and carbohydrates, and eating large portions of food [1]. According to the World Obesity Federation in the world, approximately 475 million adults are obese and more than twice of this number are overweight, what indicates that more than 1.5 billion people worldwide has the wrong body mass [2].

There are several definitions of overweight and obesity, which are largely based on the measurement of weight and height [3], and the most common is considered to be the one proposed by the World Health Organization (WHO). To determine obesity, it is necessary to calculate body mass index (BMI). This index is formed by dividing the body mass in kilograms by the square of the height specified in meters, (body mass (kg)/height (m²). According to this indicator, the overweight status is recognized for people with BMI ≥25.00 kg/m², obesity from

BMI≥30.0 kg/m², but underweight when the value of the index is less than 18.5 kg/m² [4].

Obesity brings with it a number of negative health consequences. Cardiovascular disease (mainly hypertension, heart disease and stroke), type 2 diabetes, diseases of the musculoskeletal system (e.g. osteoarthritis), and certain cancers (a.o. endometrial cancer, breast or colon cancer) are among the most potent risk factors of obesity [5].

It should be emphasized that the accumulation of fat in the abdomen is strongly associated with the risk of developing cardiovascular disease [6]. The easiest way to diagnose obesity is to measure waist circumference [7]. Because there are differences within the correct diagnosis of body mass depending on age, gender and ethnicity. Several methods of abdominal obesity identification were proposed, but the most often used are those proposed by the National Cholesterol Education Program - Adult Treatment Panel III NCEP-ATP III) and the International Diabetes Federation (IDF) [8], [9]. According to the NCEP-ATP III obesity is recognized when waist circumference in men is ≥102 cm and ≥88 cm in women. In contrast, according to the IDF's definition of abdominal obesity in white race, it is diagnosed when waist circumference is ≥94 cm in men and in women ≥80 cm [10].

Persons suffering from mental disorders, including psychotic disorders, have greater tendency to have increased body mass [11]. Propensity for psychosis is influenced by several factors, including: specific diet and lifestyle, smoking and the effects of some psychotropic medications that cause mass gain [12]. The influence of the various medications on the body mass gain is varied. The largest increase is observed after the use of atypical antipsychotics medications, so-called new-generation, particularly such as clozapine and olanzapine. In terms of atypical antipsychotics medications, only those from the groups of molindone, ziprasidone, and aripiprazole do not cause mass gain. However, in the case of conventional medications, so-called first-generation antipsychotics, only those from the group of chlorpromazine cause mass gain [13].

It should be noted that the tendency to increased body mass was observed in psychiatric patients before taking antipsychotic treatment [14]. It is emphasized that there is a genetic predisposition of the mentally ill patients to excessive accumulation of body fat [15]. Obesity is strongly associated with cognitive impairment, which with age may lead to the formation of dementia [16]. Obesity can affect mental functions by changing plasticity of the brain, what may contribute to the development of cognitive and mood disorders [17].

In the present study, we attempted to examine the relationship between the cognitive impairment and the increased body mass, taking into account the types of the antipsychotics medications taken by the respondents.

Material and methods

We recruited 91 persons with mental disorders, participants of the Communal Home of Mutual Aid, the Occupational Therapy Workshops and the staff of the District Vocational Rehabilitation Facility. Among the group, there were 48 people with schizophrenia (F-20), 3 with schizoaffective disorders (F25), 3 with persistent delusional disorder (F22), 7 with affective bipolar disorder (F31), 6 with depression (F32), 13 with neurotic disorders associated with stress and somatoform disorders (F40-F48), 11 with personality disorders and adult behavior disorder (F60-F69). Each person had to sign a voluntary consent to participate in research in accordance with resolution of the Medical University of Lublin Bioethics Committee (No KE-0254/101/ 2013).

The study consisted of two stages:

(1) Physical examination: Height, weight, waist circumference, hip circumference, calculation of BMI and abdominal obesity diagnosis according to the clinical IDF guidelines, clinical interview with the tested person concerning his/her career (co-existing diseases, medications, number of hospitalizations);

(2) Psychological tests: in order to diagnose cognitive functions. They were assessed using:

• a Short Test of Mental Status (STMS), used to measure cognitive functions, consisting of test of orientation trials (allo and autopsychic orientation), attention, learning, calculation, abstract reasoning, messages, drawings (constructional praxis), recall,

• Verbal Fluency Test (VFT), to examine the verbal semantic and categorical fluency,

• Rey Auditory Verbal Learning Test (RAVLT) – to assess short term memory, direct and delayed memory.

Description of the group

The study involved 91 participants (including 51 women and 40 men, mean age of patients was 46 years, the standard deviation +/-13,3 years). The group consisted of persons who were currently under constant psychiatric care. The exclusion criteria were: (1) substance abuse or dependence (2) a history of neurologic disorders (3) serious or unstable medical condition (i.e. poorly controlled hypertension, diabetes or coronary artery disease).

Because of the variety of taken medications, participants were divided into several groups according to defining features shown in Table 1. The largest group of participants (34%) were receiving atypical antipsychotics medication (known as second generation antipsychotics), usually olanzapine, clozapine, amisulpride, risperidone, quetiapine, and sertindole, when it comes to 14% of participants, they were receiving typical antipsychotic medications (known as first generation antipsychotics), usually perazinum, haloperidol, while the other group (30%) was taking both typical and atypical antipsychotic medications. The remaining 21% of participants were taking other medicines: antidepressants, sedatives, sleeping pills normothymic/antiepileptic.

Statistical analysis

The obtained results were statistically analyzed using STATISTICA software, version 10.

Because of the lack of normality distribution of several variables, the study correlation between variables was carried out using a correlation coefficient of Spearman's rank. Due to the lack of normality distribution, testing hypotheses were performed using Mann-Whitney U test (comparing 2 groups). An analysis of the differences in the individual parameters was carried out using a Kruskal-Wallis test for independent trials, taking into account post hoc analysis (Dunn's Test). The results are shown in the charts using the median. The results were found to be significant at the level of $p < 0.05$.

Results
Overweight and obesity

Among all the investigated, overweight was found in 32 people (35%), while in 27 (30%) persons the correct

Figure 1. The BMI index and abdominal obesity according to the IDF guidelines in the group of women and men as measured in percentages.
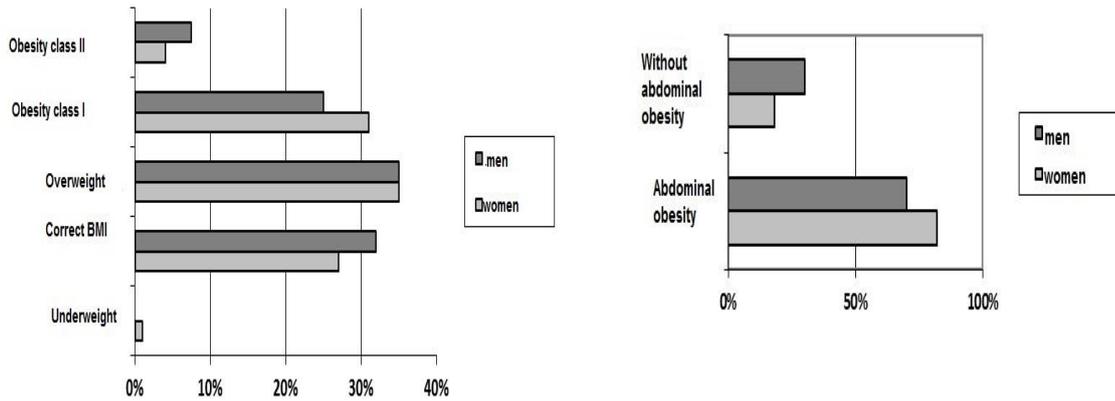

Figure 2.The body mass and the type of taken medications.
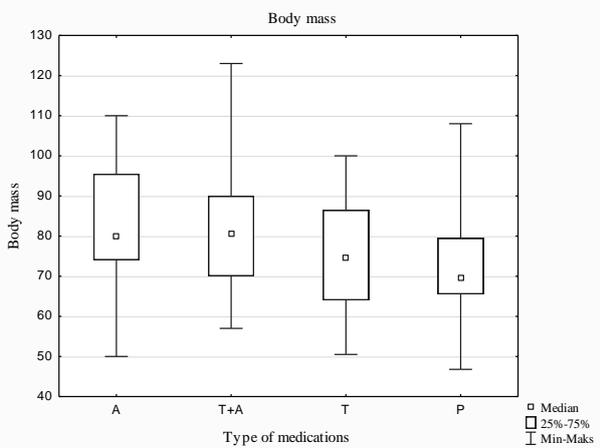

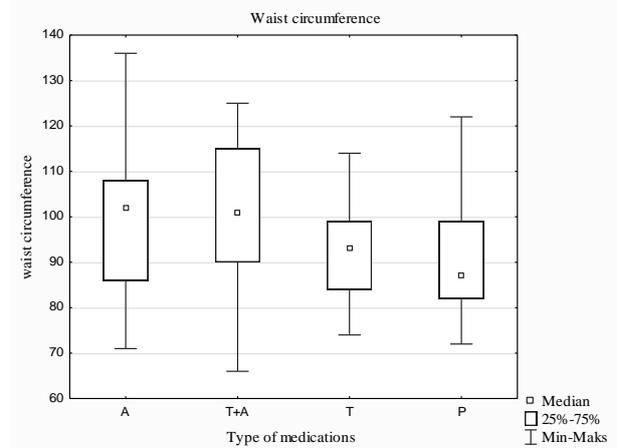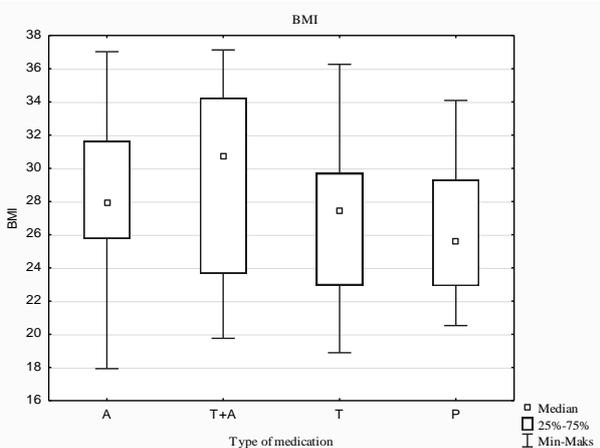Figure 3. The waist circumference and the type of taken medications

Figure 4. The BMI and the type of taken medications

body mass was found (Figure 1.). Obesity class I was diagnosed in 26 patients (28%), and obesity class II in 5 (5%). One person was underweight (2%). Abdominal obesity, according to IDF guidelines, was diagnosed in 70% of patients.

Psychotropic medications vs. overweight and obesity

The statistical analysis showed that the type of medications was associated with body mass, p<0.03, (Figure 2.). However, post hoc analysis indicated only the existence of certain tendency, particularly that people who did not take typical and atypical antipsychotics medicines (P) had lower body mass than persons taking both typical and atypical medications (T+A). Although, this tendency did not reach a level of statistical significance (p<0.08).

It has been noticed that the type of taken medications was also associated with the waist circumference, p<0.01, (Figure 3.). Post hoc analysis showed that persons who were not taking typical and atypical antipsychotics medications (P) had lower waist circumference than persons taking atypical antipsychotics medications (A), (p<0.04) and typical and atypical antipsychotics medications (T+A), (p<0.02). Medians were, respectively: 87 (P), 93 (T), 101 (T+A), 102 (A). It was also found that BMI did not differ significantly in the various working groups, p<0.13, (Figure 4.).

Overweight and obesity, and cognitive functions

Table 2. shows the correlations of Spearman's ranks between body mass indexes and waist circumference, and cognitive functions having regard to all the patients. The negative correlations were observed between several variables: age of patients and abstract thinking (rs -0.22, p<0.03), age and direct memory (rs -0.23, p<0.02), age of patients and delayed memory (rs -0.29, p<0.005).

Body mass also showed a negative relationship with the memory, but only with the delayed one (rs -0.27, p<0.005). The body mass index, waist circumference correlated with the memory. In the case of the first variable, a relationship with the delayed memory was observed (rs -0.23, p<0.03), in the case of the other two, both with the direct and delayed ones (rs -0.22, p<0.03), (rs -0.36, p<0.004).

It has been shown that an increase in waist circumference measured in centimeters was connected with a decreased ability to abstract reasoning (rs -0.29, p<0.005).

It should be noted, that overall cognitive functions, which are the sum of all the subtests of STMS and the results in the VFT and RAVLT tests showed no statistically significant relationship.

In addition, it was shown that people with abdominal obesity did worse in the test measuring the delayed memory (p<0.04).

In order to investigate the impact of BMI on cognitive function, statistical analyses were made in three groups: overweight (n = 32), obesity class I (n = 26), correct BMI (n = 27). Because of the small number of persons with obesity class II (n = 5) and underweight (n = 1), they were were excluded. Analysis by means of Kruskal-Wallis test did not reveal any statistically significant differences

between the BMI and cognitive functions in different groups (p>0.05).

Discussion

Persons suffering from mental disorders have greater tendency to overweight and obesity, what is caused by a number of factors, in particular, specific lifestyle and the negative effects of the antipsychotic treatment. As shown by studies of not yet treated patients, some diseases such as schizophrenia are closely associated with genetic predispositions to excessive depositing the adipose tissue [18], [19], [20], [21].

It shall be considered that 1 of 2 patients with schizophrenia is overweight [22]. As many as 68% of people treated for affective bipolar disease is overweight or obese and approximately 58% of people with heavier depression has obesity class I (BMI≥30) [23]. In the own study, 68% of the total tested were overweight and obese,, and obesity was found in 32% of them.

There are several extensive studies checking the effects of antipsychotic, typical and atypical medications on body mass indexes. It is assumed that atypical medicines have a greater impact on body mass gain than typical medication [24].

In the group of 42,437 patients suffering from a variety of mental illnesses, it was shown that both typical and atypical medications can affect body mass gain. Interestingly, no statistically significant difference between them was observed [25]. In our study, it was shown that prescribed antipsychotics medications were related to body mass gain, but no significant differences between the various types of medications were observed.

Body mass gain in persons suffering from mental illness is associated with the use of psychotropic medications, with impaired sense of satiety, metabolic disorder and specific less active lifestyle. These factors affect the growth of fatty tissues in the abdomen, that is why patients taking atypical drugs are more exposed to abdominal obesity than persons taking typical medications [13].

The existing scientific reports indicate that persons with mental disorders, particularly suffering from schizophrenia, schizoaffective disorders, mood disorders, single and bipolar disorders, have greater tendency to deposit fat tissue in the abdominal area, and this tendency is further enhanced with antipsychotic medications [14], [26].

Statistical analysis showed that the atypical medication and combination of typical and atypical medication were related to the increase in waist circumference. It should be noted that, in relation to BMI, there were no differences between the particular groups. It follows from this that antipsychotic medicines may lead to a deposit of the particularly harmful fat abdomen, what contributes to the creation of cardiovascular diseases. Probably, more accurate taking into account lifestyle and health habits of patients, would give a fuller picture of this phenomenon.

The previous studies show, that atypical medications contribute to a significant improvement of cognitive function, in contrast to typical medications, which usually lead to deterioration of cognitive abilities [27], [28], [29].

Table 1. Groups divided by the types of taken medications.

Division	Type of taken medications	Sample percentage
T+A	Typical and atypical antipsychotic medications	27 (30%)
T	Typical antipsychotic medications	14 (15%)
A	Atypical antipsychotic medications	31 (34%)
P	Other medicines: antidepressants, sedatives, sleeping pills normothymic/antiepileptic	19 (21%)

Table 2. Correlation of Spearman's ranks between the BMI index, body mass, waist circumference and cognitive functions for all responders* - marked coordinates of correlation are significant at p <0.05.

	N - Important	R - Spearman	p
* Age & Abstract reasoning STMS	91	-0.2216	0.0347
* Age & Direct Recall	91	-0.2339	0.0256
*Age & Delayed Recall	91	-0.2872	0.0057
*Body mass & Delayed Recall	91	-0.2719	0.0091
*BMI & Delayed Recall	91	-0.2261	0.0311
*Waist Circumference & Abstract reasoning STMS	91	-0.2883	0.0055
*Waist Circumference & Direct Recall	91	-0.2248	0.0320
*Waist Circumference & Delayed Recall	91	-0.3591	0.0004

It is important to note that not only medicines affect the cognitive functions, but also the type of disorder is in this respect important. Psychotic mental disorders most seriously affect the deterioration in cognitive functions and these dependencies are becoming worse, especially with age, what refers to such diseases as schizophrenia or schizoaffective disorders [30], [31].

Many scientific reports indicate that obesity is a factor that leads to neurocognitive disorders [32], [33] and the latest results of the survey show that obesity leads to neurodegenerative diseases based on interferences in the white matter of the brain [34], [35], [36], [37], [38]. Research carried out on mice suggest that obesity leads to hippocampus function disorders, the structure responsible, inter alia, for learning and ability to learn [39].

Examining the relationship between cognitive functions and obesity in individuals with mental illness, the majority of correlations were detected in relation to memory processes. It was observed that both the increase in BMI, body mass and waist circumference negatively correlated with the delayed auditory memory and these dependencies increased along with the age of patients.

This is in line with other test results. Gunstad and co., in the group of 1703 people without mental disorders, demonstrated that abdominal obesity leads to cognitive impairment, including the disturbance of memory. The team noted that the increased mass leads to abnormalities in the verbal fluency and attentions, however such dependencies were not observed in the own study [32].

Spitznagel et al., in the group of 84 persons underwent bariatric surgery treatments and the assessment of cognitive functions before and after the surgery demonstrated that short-term memory is improving along with reduction in weight [40], what confirms

the claim that obesity is closely linked with the deterioration of cognitive functions, but this process is to certain extent reversible.

By analyzing the study group, the relationship between abdominal obesity and the ability to abstract reasoning was observed, and these dependencies increased along with age and thus, with the duration of the disease. It should be noted that in most mental diseases, particularly those of psychotic ground, it comes to the deterioration of overall cognitive functions [41]. Abstract reasoning plays in this particular role, as according to some researchers, it is distorted in people with the first, untreated episode of the disease, next to learning capacity and attention [42].

By analyzing the study group, it should be noted that cognitive functions such as auditory memory, especially the delayed one and abstract reasoning, which showed the first relations with obesity, are first symptoms of dementia changes. According to recent scientific reports, obesity and changes caused by it lead to dementia vascular disorders and Alzheimer's disease [43].

The presented own research is not free from limitations. The group tested by us is diverse in terms of the type of disturbance and taken types of medications as well as their doses. Most of the research in this area does not take into account knowledge of patients on the subject and, consequently, the lifestyle of the patients. There is a need for research on a wider range taking into account these variables.

Conclusions

The implementation of atypical and combination of typical and atypical medications are associated with the occurrence of abdominal obesity, which carries with it a

number of negative consequences such as cardiovascular disease, and diabetes type 2. Obesity correlates with worsening of cognitive functioning, particularly, in the area of memory and abstract reasoning. It was observed that both the increase in BMI, body mass and waist circumference are negatively related to auditory delayed memory and these dependencies intensify along with age of patients. Future studies are needed in this area.

Conflict of interest

The authors have declared no conflict of interest.

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