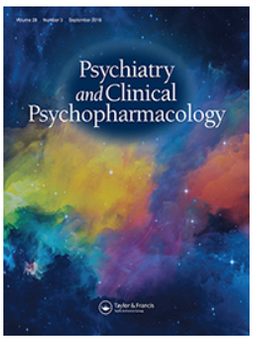

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A comparison of depot and oral atypical antipsychotics in terms of metabolic syndrome markers

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ABSTRACT

OBJECTIVES: The duration of life of patients with schizophrenia is shorter than that of the general population for various reasons. Especially cardiovascular diseases are one of the most important causes of death in patients with schizophrenia. Our aim in this study is comparison of second-generation depot antipsychotics and second-generation oral antipsychotics used in the treatment of patients with schizophrenia in terms of metabolic syndrome criteria.

METHODS: We included 39 patients treated with second-generation depot antipsychotics and 124 patients treated with second-generation oral antipsychotics, who were diagnosed with schizophrenia. Positive and Negative Syndrome Scale was applied to all the patients and blood pressure, weight, height, body mass index, waist circumference, fasting blood glucose, triglyceride level, and high-density lipoprotein (HDL) levels were recorded.

RESULTS: In terms of metabolic syndrome criteria, the waist circumference and triglyceride levels of the patients treated with the second-generation depot antipsychotics were lower than those of the patients treated with second-generation oral antipsychotics, and the HDL levels were statistically significantly higher.

CONCLUSION: In this study, second-generation depot antipsychotics used in the treatment of schizophrenia patients were found to be associated with more positive results in terms of metabolic syndrome criteria than oral antipsychotic drug forms.

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KEYWORDS
Schizophrenia; metabolic sydrome; second-generation antipsychotics; oral antipsychotics; depot antipsychotics; adverse effect

Introduction

The life span of patients with schizophrenia is lower than that of society in general for various reasons, such as the prevalence of accidents, cardiovascular disease (CVD), and contagious diseases among these patients [1,2]. CVDs are one of the principal causes of death of patients with schizophrenia. These patients have a 2- to 3-fold greater risk of CVD than healthy controls [2], and CVDs are responsible for 45% of the increased mortality seen in patients with schizophrenia [3].

Patients with schizophrenia are known to be at risk in terms of CVDs and cerebrovascular events due to various factors, including poor diet, tobacco use, weight gain, and low levels of physical exercise [4–6]. Higher fasting blood sugar and insulin resistance have been reported in patients with schizophrenia who have never been exposed to antipsychotic therapy [7]. In addition, various drugs, particularly antipsychotics, have been identified in recent years as having adverse effects in terms of CVD development [8]. Studies have reported that, in addition to increased risk factors in patients with schizophrenia, antipsychotic therapy itself increases the risk of metabolic irregularities, weight gain, and obesity [9]. Several wide-ranging reviews have revealed that atypical antipsychotics significantly increase the risk of CVDs, such as diabetes, compared to typical antipsychotics [10]. Some studies have reported a higher incidence of diabetes and hypertension in patients with schizophrenia compared to healthy controls [11]. The increased prevalence of CVD, diabetes, and hypertension and greater mortality may partly be attributed to metabolic syndrome [1]. The metabolic syndrome including visceral adiposity, insulin resistance, increased blood pressure, elevated triglyceride levels, and low high-density lipoprotein (HDL) cholesterol levels is an important risk factor for CVD [12]. The prevalence of metabolic syndrome is reported to be 2–4 times higher in patients with schizophrenia than in healthy individuals [13,14].

Due to high rate of adherence with long-acting antipsychotics has better protection than oral antipsychotics [15], but they have been associated with further adverse events, including metabolic disturbances and cardiovascular events [16,17]. The purpose of this study was to compare second-generation depot antipsychotics and oral antipsychotics used in the treatment of patients with schizophrenia in terms of metabolic syndrome criteria.

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Materials and methods

Sampling

Patients presenting to the psychiatry clinic of a regional Mental and Neurological Diseases Hospital between January and July, 2014, diagnosed with schizophrenia based on Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), under the observation with second-generation depot antipsychotics or second-generation oral antipsychotics for the previous 9 months based on information from psychiatrists and patient record checks, and identified as not being in the active disease period based on clinical decisions and a Positive and Negative Syndrome Scale (PANSS) score <70, were cross-sectionally included in the study. Thirty-nine of the patients enrolled were being treated with depot antipsychotics and 124 with oral antipsychotics. The patients enrolled were not using any psychotropic medication other than antipsychotics. Patients' treatments were initiated and maintained by other physicians, and patients were evaluated in a cross-sectional manner by the same author in terms of study data production. Overnight fasting blood tests were requested by monitoring physicians for routine control purposes. They were later evaluated by the authors for the purpose of this study.

Patients included in the study were informed about the research. Once written informed consent had been obtained, sociodemographic characteristics were recorded. All patients were consecutively administered the PANSS in order to determine the severity of symptoms. Blood pressure values, weight, height, body mass index (BMI) and waist circumference, and biochemical tests including triglyceride and HDL levels and fasting blood glucose requested by patients' physicians for routine control purposes were recorded.

Subjects with additional psychiatric diagnoses in addition to schizophrenia based on DSM-IV at the application of SCID-I, with a previous diagnosis of dementia, with a history of physical disease affecting the central nervous system, with a history of head trauma resulting in loss of consciousness, with mental retardation or from whom informed consent could not be obtained were excluded from the study. Patients using psychotropic drugs other than antipsychotics were not included in the study.

The study commenced following official permission from the Province of Trabzon Public Hospitals' Union General Secretariat Kanuni Training and Research Hospital Clinical Research Ethical Committee and the hospital management.

Evaluation tools

Sociodemographic data form

This form was designed by the authors of the study in order to evaluate patients' sociodemographic characteristics (such as age, sex, marital status, and employment status) and clinical characteristics (such as age at onset of disease, total duration of disease, and total number of hospitalizations).

Structured clinical interview for DSM-IV axis I disorders (SCID-I)

SCID-I was developed in 1987 for the diagnosis of DSM-III-R axis I disorders using a structured clinical evaluation tool [18]. It was subsequently updated for DSM-IV.

Positive and negative syndrome scale (PANSS)

The PANSS is a semi-structured interview scale was developed by Kay et al. [19] consisting of 30 items and involving a 7-point evaluation of symptom severity. Seven of the 30 psychiatric parameters belong to the positive symptoms subscale, 7 to the negative symptoms subscale, and the remaining 16 to the general psychopathology subscale. The reliability and validity of the Turkish-language version were established by Kostakoğlu et al. [20].

Statistical analysis

Normal distribution of variables was examined using the Kolmogorov–Smirnov test. Descriptive data were expressed as mean and standard deviation for normally distributed variables and median and minimum – maximum values for non-normally distributed variables. The chi-square test was used to compare qualitative data, Student's *t*-test for normally distributed parameters and the Mann–Whitney *U*-test for non-normally distributed parameters. *p*-Values less than 0.05 were regarded as statistically significant.

Results

Sixty-seven (41.1%) of the 163 patients included in the study were female and 96 (58.9%) were male. Thirteen (33.3%) of the patients treated with second-generation depot antipsychotics were women and 26 (66.7%) were men. Fifty-four (43.5%) of the patients treated with second-generation oral antipsychotics were women and 70 (56.5%) were men. The mean age of the patients using depot antipsychotics was 37.41 ± 9.11, and the mean age of those using oral antipsychotics was 37.57 ± 10.64. There was no statistically significant difference between the second-generation depot and oral antipsychotic groups in terms of sex or age. Eighty-six (52.8%) of the subjects were single, and 75 (46.0%) had income generating occupations. A statistically significant difference was determined between the two groups in terms of marital status ($p = 0.027$), but none in terms of other sociodemographic characteristics ($p > 0.05$). In terms of clinical characteristics, no difference was determined between the patients using

depot or oral antipsychotic drugs in terms of total duration of disease or total length of last treatment ($p > 0.05$) (Table 1).

The 39 patients receiving the second-generation depot antipsychotics were not using any additional antipsychotic therapy. The second-generation antipsychotics used and the dose ranges were risperidone consta 25, 37.5, and 50 mg once every 15 days, and paliperidone palmitate 75, 100, and 150 mg once monthly. One hundred and nine of the 124 patients treated with the second-generation oral antipsychotics were receiving a single medication and 15 were receiving two. The dosage ranges of the second-generation antipsychotics used were quetiapine 600–1100 mg/day, olanzapine 15–30 mg/day, paliperidone 6–9 mg/day, aripiprazole 15–30 mg/day, risperidone 4–8 mg/day, amisulpride 600–1200 mg/day, and clozapine 200–600 mg/day.

When the patient groups using depot and oral antipsychotic groups were compared in terms of PANSS scores, a significant difference was observed in terms of PANNS P scores ($p = 0.028$), but none in respect of PANNS N or PANNS G ($p = 0.068$, $p = 0.664$). No significant variation was determined between the two groups in terms of metabolic values such as systolic blood pressure, diastolic blood pressure, weight, BMI, or fasting blood glucose ($p > 0.05$), while waist circumference was significantly lower in the depot antipsychotic group than the oral antipsychotic group ($p = 0.020$). HDL levels were significantly higher in the patients using depot antipsychotics ($p < 0.001$), while triglyceride levels were significantly lower ($p = 0.004$) (Table 2). When patients using two antipsychotic agents ($n = 15$) were excluded and patients using a single antipsychotic ($n = 109$) were compared with those using depot antipsychotics ($n = 36$), variations in the subjects using depot antipsychotics compared to those using oral antipsychotics in terms of waist circumference, low triglyceride levels and high HDL levels were continue to be significant ($p = 0.025$, $p = 0.001$, and $p = 0.041$).

Discussion

The five principal components of metabolic syndrome are abdominal obesity, hypertension, increased fasting blood glucose level, hypertriglyceridemia, and a

Table 1. Socio-demographic and clinical characteristics of study groups.

	Depot AP ($n = 39$) N %	Oral AP ($n = 124$) N %	p
Age [Mean ± SD]	37.41 ± 9.11	37.57 ± 10.64	0.932**
Gender [*n* (%)]			
Women	13 (33.3)	54 (43.5)	0.345*
Men	26 (66.7)	70 (56.5)	
Marital status [*n* (%)]			
Single	24 (61.5) (63.6)	62 (50.0)	0.027*
Married	8 (20.6) (15.2)	52 (41.9)	
Widow	7 (17.9)	10 (8.1)	
Duration of education (years) [Mean ± SD]	9.36 ± 3.53	9.36 ± 3.58	0.995**
Employment status [*n* (%)]			
Positive	19 (48.7)	56 (45.2)	0.838*
Negative	20 (51.3)	68 (54.8)	
Smoking status [*n* (%)]			0.791*
Positive	18 (46.2)	54 (43.5)	
Negative	21 (53.8)	70 (56.5)	
Substance, alcohol status [*n* (%)]			1.000*
Positive	1 (2.6)	4 (3.2)	
Negative	38 (97.4)	120 (56.9)	
Total usage time of the last treatment (months) [Median (min – max)]	12 (6 – 96)	12 (6 – 96)	0.484***
Total duration of disease (years) [Mean ± SD]	13.13 ± 8.49	12.05 ± 8.63	0.495**

Notes: Mean ± SD: mean ± standard deviation. *Ki-kare testi, **Student *t* testi, ***Mann–Whitney *U* testi.

Table 2. Comparison of PANNS, blood pressure, weight, BMI, waist circumference, HDL, TG, fasting blood glucose values of study groups.

	Depot AP ($n = 39$) N %	Oral AP ($n = 124$) N %	p
PANSS P [Median (min – max)]	8 (7 – 20)	7.5 (7 – 20)	0.028*
PANSS N [Median (min – max)]	7 (7 – 23)	7 (7 – 27)	0.068*
PANSS G [Median (min – max)]	16 (16 – 32)	17 (15 – 38)	0.664*
Systolic blood pressure [Mean ± SD]	120 (100 – 140)	120 (90 – 170)	0.435*
Diastolic blood pressure [Mean ± SD]	80 (60 – 90)	80 (60 – 90)	0.220*
Weight [Mean ± SD]	82.87 ± 12.05	83.94 ± 17.57	0.668**
BMI [Mean ± SD]	28.53 ± 4.66	30.01 ± 6.34	0.179**
Waist circumference [Mean ± SD]	90.23 ± 11.99	96.65 ± 15.61	0.020**
HDL [Mean ± SD]	50.33 ± 12.08	43.09 ± 10.35	<0.001**
TG [Mean ± SD]	131.00 ± 57.81	168.32 ± 90.51	0.003**
Fasting blood glucose [Mean ± SD]	91.79 ± 19.16	90.00 ± 14.,168	0.531**

Notes: AP: antipsychotic; BMI: body mass index; HDL: high-density lipoprotein; mean ± SD: mean ± standard deviation; PANSS: Positive and Negative Syndrome Scale; TG: triglyceride. *Mann–Whitney *U* testi, **Student *t* testi.

decreased HDL level [1]. Weight gain can lead to metabolic syndrome in patients using atypical antipsychotics by causing dyslipidemia, glucose intolerance, and hypertension [13,21,22]. This study compared patients the using second-generation depot and oral antipsychotics in terms of metabolic syndrome criteria. One of the study findings was that the waist circumference of patients using the second-generation depot antipsychotics was statistically significantly lower compared to those using oral antipsychotics. Abdominal obesity is regarded as one of the components of metabolic syndrome contributing significantly to the risk of diabetes [23] and cardiovascular problems [24]. BMI and waist circumference indicating abdominal obesity have been reported as predictors of the development of diabetes mellitus. Waist circumference has also been reported to be a more powerful predictor of development of diabetes than BMI [25,26]. In this study, patients treated with the oral forms of atypical antipsychotics were associated with poorer waist circumference outcomes than those treated with depot forms.

Excessive body fat resulting from weight gain is an important factor leading to insulin resistance and is also responsible for metabolic syndrome [27]. Insulin resistance is related to the atherogenic plasma lipid profile [28]. Some antipsychotic drug can lead to progressive lipid deposition by compromising the effect of insulin on adipocytes [29]. This impaired effect of insulin of adipocytes may partly account for weight gain-associated dyslipidemia [30]. In addition, studies have reported that impairment of lipoprotein lipase enzyme activity can contribute to the decrease in HDL cholesterol seen in conditions of insulin resistance [26,31]. According to our study findings, in terms of the lipid profile, triglyceride levels of patients with the second-generation depot antipsychotics were statistically significantly lower than those of patients treated with oral antipsychotics, while HDL levels were significantly higher. Several cross-section and prospective studies have reported an increase in fasting cholesterol and triglyceride levels after treatment in patients receiving atypical antipsychotic therapy [32]. Previous studies have shown that patients treated with clozapine or olanzapine have higher triglyceride [33] and cholesterol levels [34] than patients receiving risperidone therapy [22]. The second-generation depot antipsychotics in this study consisted of the depot forms of risperidone and its active metabolite paliperidone, while the oral antipsychotics included olanzapine and clozapine in addition to the oral forms of risperidone and paliperidone. Previous studies have compared risperidone with olanzapine in terms of the metabolic syndrome criteria of blood sugar, HDL, and triglyceride levels. Both drugs were observed to affect these parameters, but the change in the values was reported to be numerically greater with olanzapine compared to risperidone [26]. In another study, however, an insignificant decrease was reported in HDL levels after 8 weeks in patients treated with olanzapine, while a very small increase was determined in patients treated with risperidone. Low-density lipoprotein and triglyceride levels were reported to increase in both groups [35]. In contrast to these findings, another study involving a different patient group observed a small increase in HDL levels in patients receiving olanzapine after 8 weeks' treatment, while a decrease was observed in HDL levels in patients treated with risperidone [36].

An increased potential for diabetes has been reported as a side-effect of all atypical antipsychotics, and particularly clozapine and olanzapine [37]. In the CATIE study, metabolic syndrome criteria were met by 42.7% of patients, and fasting blood glucose levels were above the threshold value of 100 mg/dl [13,22]. In the present study, no significant variation was observed in terms of blood sugar between the two patient groups treated with the second-generation depot or oral antipsychotics. A recent study showed that there was no significant difference in baseline metabolic syndrome criteria between patients using one of the second-generation depot antipsychotics for 12 months, despite an increase in BMI and waist circumference of the patients [17] were detected. In this study, depot second-generation drugs were found to be associated with more favourable outcomes than oral forms in terms of waist circumference, HDL, and triglyceride levels from metabolic syndrome criteria.

The fact that the patients in both groups had been monitored with the same treatment for 9 months may be considered as a positive aspect of this study. The continuation of the remission states of the patients during these 9 months indicates that the drugs were used in effective doses. The sample size in both groups might be another limitation in this study. In addition, the pharmacological molecules of depot and oral antipsychotics are not exactly equivalent. Another limitation of this study may be the difficulty in establishing dose equivalence when different drugs were compared. The patients were evaluated in a cross-sectional manner by the same author, and this cross-sectional analysis may be regarded as another limitation.

The second-generation depot antipsychotics in this study were associated with better outcomes in terms of the metabolic syndrome criteria of waist circumference and triglyceride and HDL levels compared with the oral forms. This is an important factor in terms of determining which drug should be selected for which patient on an individual basis, and further large-scale methodological studies in this field are now needed.

Disclosure statement

No potential conflict of interest was reported by the authors.

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