Psychiatr. Pol. 2014; 48(6):1155–1165
PL ISSN 0033-2674
www.psychiatriapolska.pl

Tardive dyskinesia in patients with schizophrenia treated with olanzapine – results from a 20-month, prospective, open study under naturalistic conditions

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Summary

Objectives. The objective of the study was to assess the prevalence and incidence of tardive dyskinesia in patients treated with olanzapine during the follow-up period of 20 months.

Methods. It was a prospective, observational, non-interventional study under naturalistic conditions, without a control group. The evaluation of the severity and presence of tardive dyskinesia was performed with the Abnormal Involuntary Movement Scale and research criteria by Schooler and Kane.

Results. The study included 573 patients (woman 43.3%) with the diagnosis of schizophrenia (ICD-10), the mean age of 41.8 (± 12) years. The mean dose of olanzapine was 15.9 (± 4.2) mg. The prevalence of tardive dyskinesia was 16.4%. The cumulative incidence assessed in the group of 479 patients was 6.47%. The annual incidence was 3.9%. An increased risk of tardive dyskinesia was observed in smokers – RR of 1.99 (CI 0.88-4.49), those taking higher doses of olanzapine 1.57 (CI 0.91-2.7) and in those who used polytherapy: 3.55 (CI 1.43-8.82). Only in the case of polytherapy a multidimensional analysis confirmed that this factor had a significant influence on the risk of tardive dyskinesia (p=0.006)

Conclusions. The study demonstrated high (16.4%) prevalence of tardive dyskinesia, and the annual incidence (3.9%) comparable to the results of a meta-analysis by Corell et al. In the case of olanzapine in monotherapy the annual incidence was lower (1.96%) but the use of antipsychotics in polytherapy more than tripled the risk of tardive dyskinesia

Key words: schizophrenia, olanzapine, tardive dyskinesia

Conflict of interest: The author has received honoraria for consulting or speaker fees from: Angelini, Apotex, Bristol-Myers-Squibb, Glaxo, Glenmark, Janssen-Cilag, Lekam, Lundbeck, Pro.med, Servier.

Introduction

Tardive dyskinesia (TD) is a group of extrapyramidal disorders consisting in abnormal involuntary movements (myoclonic, athetotic, dystonic and choreic) induced by agents blocking dopamine receptors (antidopaminergic). Symptoms develop in the muscles of the face, oral cavity, tongue, extremities, neck and the trunk. The course of this condition may be undulating, with relapses and remissions, but usually symptoms progress and become more intense. Tardive dyskinesia becomes more intense under stress and regresses during sleep. According to the diagnostic criteria for tardive dyskinesia, symptoms should last for at least 4 weeks, and the exposure to antipsychotics should last for at least 3 months. TD symptoms should begin while taking the medicinal product or within several weeks since the discontinuation of an antidopaminergic agent [1-3].

Tardive dyskinesia may result in disturbances of speech, swallowing, gait and posture. Significant problems associated with everyday activities are observed in approximately 20% of subjects with TD. It is usually associated with higher severity of psychopathological symptoms and a worse course of the illness. Some reports indicate a higher mortality rate among patients with schizophrenia and with TD. Risk factors for tardive dyskinesia include, first of all, a total dose of antidopaminergic agents consumed within a life, namely therapy with high doses of potent classic neuroleptic agents. Other factors include combined treatment with lithium salts, a history of extrapyramidal symptoms, alcohol consumption, psychostimulants, tobacco smoking and CNS damage [1-3]. In case of tardive dyskinesias a genetic predisposition for their development has been indicated. Candidate genes include, among others, DRD2, MDR1, DRD3, GSTT1, 5HT2A [4]. However, Tsai et al. (2009), who analysed 128 candidate genes in a group of 710 subjects of the CATIE study did not observe any significant associations with any of single markers or haplotypes [5]. Gałecki et al. indicated that the risk of TD was associated with manganese superoxide dismutase (MnSOD) polymorphism what indicates the role of oxidative stress in the TD pathophysiology [6]. Association of the vesicular monoamine transporter gene SLC18A2 with tardive dyskinesia was recently described [7].Hypotheses on the pathophysiology of TD indicate neurotoxic effects of medicinal products on the structures of the basal ganglia (cytotoxic properties?), hypersensitivity of D2 dopamine receptors ("up-regulation" developing during treatment with dopamine antagonists resulting in hypersensitivity to endogenous dopamine). The role of D3 dopamine receptors may also be significant. There are also theories indicating the role of other systems [8-10].

The literature reports different data on the incidence and prevalence of tardive dyskinesia depending on the studied population and differences with regard to research methodologies. Second generation antipsychotics (SGAs) are thought to be associated with a lower risk of TD than classic agents [1, 3, 9]. De Leon [11] evaluated the prevalence of tardive dyskinesia in a group of 516 patients treated with antipsychotics and it was in fact the highest among patients chronically treated for more than 5 years with classic medicinal products (42%). Among patients treated with classic medicinal products for less than 5 years the prevalence of TD was 19%, similarly as in a group

of patients with a history of treatment with classic agents, but currently taking SGAs. In patients treated only with SGAs the prevalence of TD was the lowest – only 5% [11]. The meta-analysis published in 2008 by Correll and Schenk [12] indicated that the annual incidence of tardive dyskinesia is 3.9% for those treated with SGAs, and 5.5% for those treated with classic medicinal products. The prevalence of TD in patients with the diagnosis of schizophrenia was 13.1% among those treated with SGAs, 15.6% in those who did not take any antipsychotics, and 32.4% in those treated with classic antipsychotics. The authors concluded that their meta-analysis confirmed a lower risk of TD in the case of SGAs in comparison with classic medicinal products; however, the presence of TD in patients was higher than expected [12]. In 2010 Woods et al. published a study indicating that the prevalence and incidence of TD were not significantly different between those receiving classic medicinal products and SGAs, and, what is more, even despite wide use of SGAs, the prevalence of tardive dyskinesia in the study population was similar to the one observed in the studies conducted in the 1980s [13].

Only few of studies performed so far were focused on the assessment of TD among patients treated with SGAs, and moreover, the mean follow-up duration did not usually exceed 12 months.

Olanzapine belongs to the second generation antipsychotics and is a medicinal product with a low potential for extrapyramidal symptoms and a suggested low risk of causing TD. The aim of this study was to assess the prevalence of tardive dyskinesia in a group of patients with the diagnosis of schizophrenia treated with olanzapine, to assess the frequency of new TD cases in a group of patients treated with olanzapine during the 20-month follow-up period and to assess clinical correlates of TD symptoms.

Material and methods

It was a prospective, observational, non-interventional study under naturalistic conditions, without a control group.

The study included patients treated in an outpatient setting who were diagnosed with schizophrenia based on the international WHO diagnostic criteria (ICD-10) and who had been receiving antipsychotic treatment with olanzapine and who gave their consent for participation in the study. The study was conducted by seven researchers in seven centres in Poland .The evaluation of the presence and severity of tardive dyskinesia was performed with the AIMS scale (Abnormal Involuntary Movement Scale). The AIMS scale was developed by Guy and it is the most commonly used tool to assess tardive dyskinesia [14]. A complete examination takes approximately 15-20 minutes and makes it possible to evaluate involuntary movements in 7 regions: face, lips and mouth, jaw, tongue, upper extremities, lower extremities, neck, shoulders and chin. The researchers received a detailed instructions on the study rules and rules of assessing symptoms severity. The severity is assessed on a scale from 0 (symptoms are not present) to 4 (severe symptoms); range 0-40. The evaluation was performed at the beginning of observation and then every 8 weeks on the average for the period of 20 months.

In order to confirm the presence of TD research criteria suggested by Schooler and Kane [15] were used and they are as follows:

- At least 3 months of total exposure to antidopaminergic medicinal products
- Exclusion of other reasons for involuntary movements (such as vascular changes in the CNS)
- Any involuntary movements in two different regions the severity of which is assessed as at least mild (2 in the AIMS scale) or involuntary movements in one region if their severity is assessed as moderate (3 in the AIMS scale)

Data regarding the conducted treatment were collected via a questionnaire, the attending physician assessed the general severity of positive and negative symptoms using a modified CGI scale (range from 1 – no symptoms to 7 – very high severity). Moreover, the severity of rigidity and tremors was assessed (the range from 1 – no symptoms to 5 – high severity). The evaluation of the presence and severity of tardive dyskinesia was performed with the AIMS scale (Abnormal Involuntary Movement Scale). Questionnaires filled in by physicians based on information obtained from patients were fully anonymous and collected data made it impossible to identify patients participating in this study.

The analysis of results was performed using statistical software PQStat ver. 1.4.2.324. The results of quantitative scales (such as age, BMI, illness duration, number of cigarettes smoked, mean dose of olanzapine, positive and negative symptoms, assessment of rigidity and tremor and AIMS score), comparing groups of patients were analysed using the Mann-Whitney U test (testing hypotheses on the difference between distributions) and the Student's t-test (testing hypotheses on the difference between means). The results of qualitative scales (such as age groups, sex, BMI groups, groups divided based on disease duration, cigarette smoking, therapy, groups with regard to olanzapine doses, dental status), comparing groups of patients were analysed using the chi^2 test and the chi^2 test with the Yates correction for tables with the cell number below 10 cases, and if any number in a table was zero the Fisher's exact test was used. In case of different tardive dyskinesia ocurrance depending on age groups, sex, BMI groups, groups divided on the basis of illness duration, cigarette smoking, therapy, groups with regard to olanzapine doses, the relative risk was assessed, and for a multidimensional model a logistic regression analysis was conducted. The analysis of changes in the AIMS scores during subsequent visits was performed with the Friedman test. The test probability at the level $p < 0.05$ was considered to be significant, and the test probability at the level $p < 0.01$ was considered to be highly significant.

Results

The study included 573 patients with the diagnosis of schizophrenia, the mean age was 41.8 (± 12) years, women constituted 43.3%. The mean illness duration was 15.7 (± 9.9) years. Smokers constituted 33.2%, and the mean daily amount of smoked cigarettes was 15.7 (± 9.9). On the basis of the BMI in the studied group of patients at the beginning of the study obesity (BMI > 30) was observed in 13.6%, 48.6%

of patients in the studied group were overweight, BMI values were within the norm in 37.1% of patients, and only in 3 people (0.54%) BMI was below 18.5.

All patients included in the study were treated with olanzapine, the mean dose during the study was 15.9 mg (± 4.2). Monotherapy with this antipsychotic drug was applied in 44.9% of subjects. Other subjects received combined treatment with classic antipsychotic agents or SGAs.

The severity of psychopathological symptoms in the studied group was mild/moderate. Positive symptoms at the beginning of treatment assessed in the CGI scale were 2.97 (± 1.3), and at the end of the study the severity reduced to 2.07 (± 1.2). Negative symptoms at the beginning of the study had the mean score of 2.99 (± 1.32), and at the end of the study 2.76 (± 1.22). Rigidity in the elbow joint had the mean score of 1.65 (± 0.74) during the first visit, and 1.43 (± 0.65) at the last visit. Tremor during the follow-up period reduced from 1.65 (± 0.84) to 1.49 (± 0.68).

Severity of symptoms assessed using AIMS scale.

The mean severity of involuntary movements assessed on the AIMS scale was 5.33 (± 6.1) in the whole studied group. During a 20-month follow-up it was observed that the severity of involuntary movements significantly reduced and the mean score at the last visit was 3.88 (± 5.1). With regard to individual regions, the assessed severity of symptoms was the highest in case of the face (0.75 ± 0.73), followed by the lips (0.6 ± 0.72), upper extremities (0.52 ± 0.82), tongue (0.46 ± 0.7), jaw (0.44 ± 0.67). The lowest severity of TD was observed for the lower extremities (0.35 ± 0.63) and the neck (0.32 ± 0.6). The general score for TD severity was 0.59 ± 0.78, disability score was 0.58 ± 0.77, and the subjective assessment of discomfort due to TD was 0.73 ± 0.86.

Prevalence and incidence

The prevalence of tardive dyskinesia in the studied population was evaluated on the basis of Schooler-Kane criteria. It was observed that in the studied group at the beginning of the study tardive dyskinesia was present in 16.4% of patients (n = 94). The mean severity of symptoms on the AIMS scale in a group with dyskinesia was 16.1 (± 5), and 3.21 (± 3.46) in a group without dyskinesia.

The group of patients without tardive dyskinesia at the beginning of the study included 479 subjects and it was the population where the presence of new cases of TD was assessed. In general, in this group tardive dyskinesia meeting the Schooler-Kane criteria was observed, at any time during a 20-month follow-up, in 31 patients, namely in 6.5% of monitored subjects.

At the end of the study the mean severity of symptoms in a group with "new dyskinesia" was 11.26 (± 6.99), and 2.27 (± 2.93) in a group of patients without TD symptoms.

The annual incidence of tardive dyskinesia is the number of new cases of tardive dyskinesia divided by the factor of patient-years of exposure. In our study we followed up 479 patients for 20 months, and it gives the factor of 789.3 patient-years of expo-

sure. The number of new TD cases is 31 subjects, therefore the annual incidence is 31/789.3= 0.039 (3.9%).

Risk factor for tardive dyskinesia

In the study group of 479 subjects the relative risk (RR – rate-ratio) for the incidence of tardive dyskinesia was calculated with regard to such variables as age, sex, illness duration, BMI, smoking, olanzapine dose and the use of other medicinal products.

A relationship between the age and tardive dyskinesia was analysed in three age categories: less than 35 years of age, 35-50 years and over 50 years of age. The youngest age group was assumed to be the reference level RR=1. It was concluded that for subjects aged 35 to 50 years the relative risk was 0.82 compared to those aged < 35 years (confidence interval – CI = 0.37 to 1.08) and it was not significant (p =0.6). Moreover, the risk of TD developing in the studied group of subjects aged over 50 years was 0.87 (CI 0.35 to 2.17) compared to those aged < 35 years and it was not statistically significant (p = 0.8).

The risk of TD among women was 0.9 (CI 0.44 to 1.82) compared to men and it was not statistically significant (p = 0.8).

In addition, a relationship between TD and BMI of patients was analysed. Patients were divided into four groups depending on the BMI value: the underweight group (BMI < 18.5), overweight group (BMI 25-29.9) and the obese group (BMI > 30). The reference group (RR=1) included patients with normal BMI values (18.5-24.9). It was concluded that the relative risk for TD in the case of overweight subjects was lower and equal to 0.35 (CI 0.16 to 0.8) compared to those with normal BMI and it was statistically significant (p = 0.012). The relative risk in the case of obese subjects was 0.86 (CI 0.33 to 2.23) compared to those with normal BMI and it was not statistically significant (p = 0.8). Due to a low number of subjects it was not possible to assess RR in the group of patients with BMI < 18.5.

With regard to illness duration patients were divided into four groups: subjects in whom the illness has been observed for less than 5 years, 6-10 years, 11-15 years and over 15 years. The category with the shortest illness duration was the reference category. In the case of subjects in whom the illness has been observed for 6 to 10 years the relative risk was 1.1 (CI 0.41 to 3.00, p = 0.8) compared to those with disease duration less than 5 years; in subjects suffering from the disease for 11 to 15 years the relative risk was 0.34 (CI 0.07 to 1.64, p = 0.2), and in the case of subjects suffering longer than for 15 years the relative risk was 0.9 (CI 0.35 to 2.32, p = 0.8).

Another analysed parameter included a relationship between cigarette smoking and tardive dyskinesia. In the studied group RR for smokers was increased compared to non-smokers, and it was 1.69 (CI 0.84 to 3.39), but it was not statistically significant (p = 0.14)

Depending on the mean dose of olanzapine used during a 20-month follow-up patients were divided into 4 groups. The group with the mean dose of olanzapine of 10 mg or lower was the reference group (RR=1), subsequent groups corresponded to the mean olanzapine dose of: 10-15 mg, 15.1-20 mg and over 20 mg/daily. In the case

of subjects with the mean olanzapine dose between 10 mg and 15 mg the RR for tardive dyskinesia was higher and was 2.89 compared to the group treated with the lowest doses, but it was not statistically significant (CI 0.61 to 13.59; p =0.18). Subjects treated with olanzapine at a dose of 15-20 mg had a higher risk of TD – RR was 4.31 and it was statistically significant (CI 1.03 to 18.05; p = 0.045). And in the group with the highest olanzapine dose (> 20 mg/d) RR was 2.6 in comparison with the reference group, but in this case it was not statistically significant (CI 0.25 to 27.3; p = 0.4).

The last assessed risk factor was the use of monotherapy (the reference group RR=1) compared to polytherapy. In the study group (n = 479) polytherapy was used by 49.7% of patients. In the case of subjects receiving polytherapy the relative risk (RR) of TD was 2.91 compared to those treated with olanzapine in monotherapy and it was highly statistically significant (CI 1.33 to 6.38; p = 0.008).

In order to assess the effect of individual analysed variables on the relative risk (RR) of TD a multidimensional logistic regression analysis was applied (see table 1). The increased risk of TD symptoms was observed in smokers – the hazard ratio of 1.99 (CI 0.88-4.49), subjects taking higher doses of olanzapine (1.57; CI 0.91-2.7) and those who used polytherapy (3.55; CI 1.43-8.82). Only in the case of polytherapy a multidimensional analysis confirmed that this factor had a significant influence on the risk of tardive dyskinesia (p = 0.006)

Table 1. **A multidimensional logistic regression analysis for tardive dyskinesia**

	b coefficient	b error	-95% CI	+95% CI	Wald stat.	p value	hazard ratio	-95% CI	+95% CI
Offset	-3.28	1.10	-5.45	-1.12	8.84	0.0029	0.04	0.004	0.33
Age	0.07	0.37	-0.67	0.80	0.05	0.8526	1.07	0.51	2.24
Sex (male)	-0.08	0.42	-0.91	0.74	0.04	0.8470	0.92	0.41	2.10
BMI	-0.378	0.32	-1.00	0.25	1.3788	0.2403	0.69	0.37	1.29
Illness duration	-0.22	0.24	-0.69	0.26	0.81	0.3693	0.80	0.50	1.29
Cigarette smoking	0.69	0.42	-0.12	1.50	2.76	0.0967	1.99	0.88	4.49
Polytherapy	1.27	0.46	0.36	2.18	7.48	0.0062	3.56	1.43	8.82
Olanzapine dose	0.45	0.28	-0.09	0.99	2.65	0.1039	1.57	0.91	2.70

Offset is -3.28, which means that if all other variables in the model adopt reference values (i.e., the patient is a woman less than 35 years, with normal BMI, illness duration less than 5 years, non-smoker and treated with monotherapy at a dose of olanzapine 10 mg or less), then the probability that tardive dyskinesia occur is very small. The hazard ratio in this case is 0.04.

Discussion

In our 20-month follow-up observational study under naturalistic conditions we concluded that the prevalence of tardive dyskinesia among patients with the diagnosis

of schizophrenia treated with olanzapine was 16.4%, and the annual incidence rate was 0.039 (3.9%).

The prevalence of TD is within the range of values cited in the literature for patients treated with SGAs [1, 3, 11-13]. However, it is higher than in several other studies comparing olanzapine and other SGAs with classic agents where the initial TD prevalence was 8.7% on the average [13]. In Poland the only study we identified to evaluate the point prevalence of tardive dyskinesia is the study by Krzystanek et al. [16]. It presents the results of an observational study with 6174 patients with the diagnosis of schizophrenia treated with olanzapine at the mean daily dose of 13.4 mg (in our study the mean dose was 15.9 mg). Krzystanek et al. observed tardive dyskinesia in 8% of patients; however, they do not present the criteria for tardive dyskinesia they used in their study. Blumberger et al. indicate that depending on the accepted criteria the results regarding the prevalence and incidence of TD may differ even ten-fold [17].

The most important objective of our study was to determine the risk of incidence, namely new cases of tardive dyskinesia during treatment with olanzapine based on a relatively long, 20-month follow-up. Past studies that evaluated the incidence of TD in patients treated with olanzapine reported different values of the annual incidence. The values were lower than the ones in our study (Beasley [18] observed the annual incidence at the level of 0.6%, and Dossenbach [19] – 1.5%), but also higher (Woerner et al. [20] – 6.7%, Dossenbach et al. [21] – 9.1%, Liberman et al. in the CATIE study [22, 23] – 15.1%.). The meta-analysis by Correll and Schenk, cited at the beginning, indicated that the annual incidence of tardive dyskinesia was 3.9% among patients treated with SGAs [12]. It is exactly the same value we achieved in our study. We think that this fact makes our results more plausible. It has to certainly be taken into account that we evaluated a group of patients whose mean age was more than 40 years and the mean illness duration was 15 years.

A positive relationship between tardive dyskinesia and polytherapy is an extremely important conclusion of our study. Among risk factors analysed, such as age, sex, illness duration, tobacco smoking (a more marked oxidative stress), BMI, olanzapine dose, only polytherapy was the factor that statistically significantly increased the risk of TD almost three-fold. This relationship was confirmed by a multidimensional analysis and the adjusted hazard ratio (HR) remained at the same high level.

The total dose of antipsychotic medicinal products is one of the best documented risk factors for TD [1, 3, 9]. Polytherapy is the most frequently associated with taking high total doses of antipsychotics. When we estimated the annual incidence of TD separately in the group treated with olanzapine in monotherapy and in patients who used polytherapy we concluded that the annual incidence of monotherapy with olanzapine was 1.96%, and in case of polytherapy it was as high as 5.8%. On one hand, this observation confirms that the risk of tardive dyskinesia in case of treatment with olanzapine is relatively low. On the other hand, in case of polytherapy this beneficial aspect of treatment with olanzapine is lost and the risk of TD is significantly higher and close to the values observed for classic agents [3, 12].

Our study was a long observational study that evaluated the presence and severity of tardive dyskinesia in a large group of patients with schizophrenia using a standard tool – AIMS scale, and formal Schooler-Kane criteria.

Limitations of our study are associated with its open, observational character and lack of the control group. The assessment of involuntary movement severity was performed by specialists in psychiatry who had received instructions how to use the AIMS scale; however, they had not received any special training in this regard, moreover, a formal assessment of the accuracy and reliability of investigators had not been conducted [24]. Nonetheless, it is the first such prospective study in the population of Polish patients, and one of few and the longest observational studies on the effects of SGAs – olanzapine on the risk of tardive dyskinesia in patients with schizophrenia that has so far been published.

Tardive dyskinesia is a serious complication of treatment with antipsychotic agents.

Mild symptoms of TD may remain unnoticed; however, when managing treatment it is recommended to periodically document the presence or lack of dyskinesia, especially in patients treated chronically [1]. Some authors recommend to use a standard tool such as the AIMS scale at least once a year [1, 3]. TD treatment is difficult, and sometimes symptom regression cannot be obtained. In some patients symptoms may be irreversible and it may affect not only the patient's quality of life or prognosis, but also may result in claims on behalf of patients and their families. The latest recommendations of the American Academy of Neurology [25] demonstrate that among many different therapeutic options for tardive dyskinesia only some of them have confirmed efficacy and therefore can be cautiously recommended (clonazepam, Ginko biloba, amantadine, tetrabenazine). It is interesting to note that management standards and textbooks recommend to replace classical antipsychotics with SGAs in patients with TD symptoms [1]. Experts from the American Academy of Neurology estimated that data we have do not allow us to recommend or reject this strategy [25]. From a clinical point of view there are no doubts that in the case of patients with a TD risk and with a simultaneous need to use an antipsychotic agent it is necessary to choose a medicinal product (antipsychotic) with the lowest risk of TD. Our study confirms that olanzapine used in monotherapy is an antipsychotic with a relatively low risk of tardive dyskinesia.

Conclusions:

1. The prevalence of tardive dyskinesia in patients with schizophrenia treated with olanzapine was 16.4%.
2. The annual incidence of tardive dyskinesia was 3.9%.
3. The use of polytherapy with antipsychotic agents more than tripled the risk of tardive dyskinesia.
4. The introduction of treatment with olanzapine in monotherapy is associated with a low risk of tardive dyskinesia, the annual incidence is 1.96%.

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Acknowledgement: *The author would like to thank Piotr Łapa for the statistical analysis. He would also like to thank to all the doctors who participated in the implementation of the study. The study was conducted within LEKAM company research grant and it was coordinated by Moneopharma company.*

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