Tardive dyskinesia. Determinants of temporal dynamics of its emergence

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Abstract

BACKGROUND: The second generation antipsychotics (SGA) is considered to have contributed to the decrease of the risk of TD in comparison with the first generation antipsychotics (FGA). Using the multiple regression analysis, we compared the predictive strength of the FGA/SGA distinction with the predictive strength of the duration of treatment, patients' age and sex. The difference between sedative (sed) and incisive (inc) antipsychotics was added as the fifth predictor.

METHOD: A cohort of patients treated with antipsychotic drugs for less than 5 years and who were free from TD was followed for one year and examined regularly by the abnormal involuntary motor scale (AIMS).

RESULTS: From a sample of 98 patients, 6 patients developed TD after six months. The duration of treatment, age and sex of the patients were the main determinants of its emergence. The drugs used did not play a statistically significant role.

After one year, 15 patients developed TD. Age and sex lost their statistically provable influence on its emergence. The difference between the treatment with sedative or incisive antipsychotics became the variable with the highest statistical significance. The relationship of the risk of TD to the FGA/SGA distinction was not statistically significant. 14.4% of the variability in the increase of the risk of TD during the second half of the one year observational period could be explained by the predictors. The stepwise regression showed that both, SG/FG and sed/inc distinction remained statistically significant.

INTRODUCTION

Explanation of the origin of extrapyramidal adverse effects of antipsychotic drugs opened the door to the discovery of their mechanism of action and to the importance of the role of dopamine in the pathophysiology of schizophrenia (Carlsson 1978).

Extrapyramidal symptoms and tardive dyskinesia are produced when nigrostrial dopamine D2 receptors are blocked. Delusions and hallucinations are reduced when mesolimbic D2 receptors are inhibited while negative and cognitive symptoms are worsened as a consequence of D2 blockade of the mesocortical D2 receptors. Hyperprolactinaemia is the consequence of the blockade of tuberoinfundibular D2 receptors. First generation antipsychotics (FGA) block D2 dopamine receptors in all four dopamine pathways.

The estimates of the incidence of tardive dyskinesia varies between 0.5 and 65% (Wolf *et al*. 1990). This huge range is due to various diagnostic criteria and differences in the patients' samples and their treatment. The average prevalence is considered to be 15–20%.

Compared to FGA, second generation antipsychotics (SGA) have lower occupancy of the dopaminergic receptors, and high occupancy of the serotonergic receptors 5-HT2A (Meltzer *et al.* 1989). Serotonin 2A antagonism reverses dopamine 2 antagonism in the nigrostriatal pathway and promote dopamine release. This difference results in opposite morphological changes: the treatment with FGA is associated with an enlargement of the basal ganglia, whereas this enlargement does not occur, or can be even reversed, with SGA (Corson *et al.* 1987). An alternative explanation of the lower risk of extrapyramidal symptoms in patients treated with SGA is in their fast dissociation from the dopamine D2 receptor (Kapur *et al.* 2001).

The risk of developing TD increases with the duration of the use of antipsychotics. Epidemiological studies of patients on FGA have shown that the cumulative incidence of TD is 5% after 1 year, 10% after 2 years, and 25% after 4 years. The average overall prevalence of TD in persons on long-term antipsychotic treatment is 20% (Kane *et al.* 1982).

It was expected – and confirmed by first clinical experience (Chouinard *et al.* 1993, Marder *et al.* 1994, Peuskens *et al.* 1995, Beasley *et al.* 1996) – that compared to FGA, SGA would not induce any, or only minimal extrapyramidal adverse effects. Further clinical experience corrected unduly optimism about the advantage of SGA over FGA, nevertheless the risk of TD is considered lower with SGA than with FGA (Kane, 2004, Pierre 2005). Tardive dyskinesia only after perphenazine (a FGA) was found to be a reason for discontinuation in the CATIE study (Lieberman *et al.* 2005) – a rare exception to the finding that the relative effectiveness of SGA is not greatly better as compared to FGA in terms of the rates of discontinuation.

The two most consistent risk factors for developing tardive dyskinesia while on chronic antipsychotic treatment are female sex and advanced age. This study is devoted to an exploration of the strength of the predictive value of the duration of treatment, age, gender and the kind (first or second generation) of antipsychotic drugs on the incidence of tardive dyskinesia in a one-year follow up of a naturalistic patients' sample. As a fifth predictor, the distinction between sedative and incisive antipsychotic drugs (sed/inc) was added.

Multiple regression analysis was the major method of statistical elaboration of the data.

Table 1. Incisive vs. sedative antipsychotic drugs

Incisive	sedative
haloperidol	levopromazine
perphenazine	chlorpromazine
flupentixol	clozapine
zuclopentixol	quetiapine
fluphenazine	olanzapine
risperidone	

METHOD

Sample:

Consecutively admitted patients to the wards and outpatient clinic of the psychiatric department of the Medical School of the Palacky's University in Olomouc from March 2002 to February 2005 were assigned to a program of a one year observational period that fulfilled the following criteria:

1. The patient is 18 years old or older.
2. There are no signs of tardive dyskinesia
3. The patient has been treated with an antipsychotic drug not longer than for 5 years.
4. The patient fulfills the criteria of the diagnosis according to ICD F 20 (schizophrenia), F 22 (delusional psychotic disorder) F 23 (acute psychotic disorder) or F 25 (schizoaffective disorder)
5. The patients signed an informed consent with the treatment

Exclusion criteria were:
1. Comorbidity with another mental disorder incl,. Drug dependence or alcohol abuse
2. Serious somatic disease incl. diabetes
3. Neurologic disease which could induce abnormal involuntary movements
4. Treatment with a combination of psychotropic drugs.

Each patient included the sample was treated with relatively constant dose of the same antipsychotic drug during the one-year follow-up.

Cases of TD were defined by the AIMS according to Schooler-Kane criteria, which require at least moderate dyskinetic movements in one body area or mild dyskinetic movements in two body areas.

For the purpose of statistical evaluation, the frequencies of patients where tardive dyskinesia appeared after 6 months and then after 12 months were considered as measures of incidence.

Multiple stepwise regression was the main method of statistical analysis. Duration of treatment, sex, age and drugs (FGA vs. SGA, their dosage and the distinction between sedative and incisive antipsychotic drugs) were independent variables (predictors), the incidence of tardive dyskinesia was the dependent (predicted) variable.

The drugs divided according to the inc/sed distinction can be seen in the Table 1.

RESULTS

98 patients fulfilled the inclusion criteria. The characteristics of the sample can be seen in the Table 2. From the 98 patients included in the sample, 6 did not finish the one-year follow-up. In four, the drug had to be changed,

one patient refused to take the drug and one patient died. His death was not related to the treatment.

Treatment: 35 patients were treated with FGA, 63 patients were treated with SGA. The drugs administered are shown in the Table 3.

Six months follow up:

Six months after the start of the study, tardive dyskinesia appeared in six patients (6.5% of 92 patients who finished the one year follow up). Three of them were treated with FGA and three with SGA. Because the total number of patients treated with SGA was higher (N = 63) than the total number of patients treated with FGA (N=35), the incidence of tardive dyskinesia after six months is 8.6% after FGA and only 4.8% after SGA.

Four of the six patients who developed tardive dyskinesia were older than 60 years. Two of them were treated with FGA and two with SGA.

One half (N=3) of the patients who developed tardive dyskinesia were female.

Multiple regression (Table 5): according to the complete model approximately 11% (adjusted $R^2 = 0.108$) of the variability of the emergence of TD after six months is due to the effect of predictors. The significance of the effects of some of the predictors (FGA vs. SGA, incisive vs. sedative, dosage) was weak (not statistically significant).

The method of stepwise regression was used to assess the subset of predictors with significant effect (duration of treatment, age and sex). 12% of variability (adjusted $R^2 = 0.122$, *p* .02) was explained by the effect of predictors.

It can be predicted that the AIMS score increase by one is connected with one month duration of treatment by 0.0144 (CI 0.02–0.026). The risk of TD increases with age by 0.0089 with one year of age, and by 0.301 if the patient is woman.

Twelve months follow-up

After one year, 15 patients developed TD. Age and sex lost their statistically provable influence on its emergence. The difference between the treatment with sedative vs. incisive antipsychotics became decisive. The results of the stepwise regression can be seen in the Table 5.

Predictors of the increase of the risk of TD between six and twelve months

The prediction of the emergence of TD by the duration of treatment loses statistical significance. The SGA/FGA distinction becomes statistically significant.

Table 2. Characteristics of the sample

Characteristics of the sample	No
Included at the start	98
Finished the one-year follow-up	92
Men	39
Women	53
Age: mean	53.4
standard deviation	17.1
range	19–82
Number of persons older than 60 years	52

Table 3. Duration of the treatment with antipsychotic drugs in months before the start of the study

treatment	FGA	SGA
mean	11.2	13.1
standard deviation	8.6	9.2
range	0–30	0–40

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Table 4. Drugs administered

	Number of patients	Mean dosage in mg
risperidone	24	2.9
olanzapine	18	9.7
quetiapine	12	317.0
haloperidol	10	4.2
clozapine	7	228.0
flupentixol	5	26.5/4 weeks
levopromazin	3	166.8
zuclopentixol	7	186.0/4weeks
flufenazin	4	7.6
perfenazin	3	20.5
chlorpromazin	3	192.6

Duration: the increase of the AIMS score by one grows by 0.0144 with one months of treatment at six months and by 0.031 with one months of treatment at twelve months.
Age: the increase of the AIMS score by one grows byx 0.0089 with one year of age.
Sex: the increase of the AIMS score by one grows by 0.301, if the patient is woman.
Sed/inc: the decrease of the AIMS score one grows by 0.624, if the patient is treated with a sedative antipsychotic at 12 months and by 0.47, when the change between the state at 12 and 6 months is considered.
SG/FG: if the patient is treated with an antipsychotic of the second generation, the emergence of TD is decreased by 0.548, when the change between the state at 12 and 6 months is considered

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Table 5. Multiple regression. **Dependent (predicted) variable**: emergence of TD expressed in the AIMS score. **Independent varibales (predictors)**: duration of treatment; age sex; incisive vs. sedative antipsychotics; first vs. second generation antipsychotics

	Adjusted R^2	% of variability explained	significance
6 months	0.108	11	NS
12 months	0.19	19	.001
difference 12–6 months	0.13	13	. 009

Stepwise regression

	Adjusted R^2	% of variability explained	significance	Effect of				
				duration	age	woman	sed/inc	SG/FG
6 m	0.122	12	.02	0.0144	0.0089	0.301	NS	NS
12 m	0.174	17.4	.0.14	0.031	NS	NS	– 0.624	NS
dif 12–6	0.164	14.4	.047	NS	NS	NS	−0.47	−0.548

DISCUSSION

The results of the study cannot be considered as exploration of the incidences of tardive dyskinesia in antipsychotic naive patients. The majority of the patients had been treated with antipsychotic drugs already when entering the follow-up.

Our results do not differ substantially from the results of a systematic review (Correll *et al.* 2004) of 11 studies of treatment with SGA lasting approximately 1 year, the weighted mean annual incidence of TD was 6.8% in the mixed adult and elderly population. Estimates on the prevalence of TD in patients treated with FGA vary between 0.5 and 62% with an average prevalence of 30% (Llorca *et al.* 2002).

The results of the multiple regression analysis show that the predictors (duration of treatment, sex, age, sed/inc and FGA/SGA distinctions) explain only 11–19% of variability. We did not evaluate the influence of affective symptoms, alcohol abuse and diabetes of the type II, which are other known risk factors. Heredity alone might explain the major part of the risk of TD. The importance of genetic factors compared to the risk of the treatment with antipsychotic drugs can be seen already in the Kraepelin's description of TD, i.e. at the time, when no antipsychotic drugs could be suspected as their cause.

Our finding that the distinction between incisive vs. sedative antipsychotics might be more important than the SGA/FGA distinction can be due to a close correlation between the influence of sedative and second generation antipsychotic drugs. If corroberated by larger clinical data, neurophysiological mechanisms of the interaction between the duration of treatment and the changing importance of other predictors deserves further study.

REFERENCES

1 Beasley CM, Jr, Tollefson G, Tran P, Satterrlee W, Sanger T, Hamilton S (1996). Olanzapine versus placebo and haloperidol. Acute phase results of the North ASmerican double-blind olanzapine trial. Neuropsychopharmacology **14**: 111–123.
2 Carlsson A (1978). Antipsychotic drugs, neurotransmitters, and schizophrenia. Am J Psychiat. **135**: 165–173.
3 Chouinard G, Jones B, Remington G, Bloom D, Addington D, McEwan GW, Labgelle A, Beauclair L, Arnott (1993). A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. J Clin Psychopharmacol. **13**: 25–40.
4 Corell CU, Leucht SD, Kane JM (2004) Lower isk for tardive dyxsikinesia associated with second-gneration antipsychotics: a systematic review of 1-year study. Amer J Psychiat. **161**: 414–425.
5 Corson PW, Noupulos P, Miller DD, Arndt S, Andreansen NC (1999). Change in basal ganglia volume over 2 years in patients with schizophrenia: typical versus atypical neuroleptics. Am J Psychiat. **156**: 1200–1204.
6 Kane JM, Smith JM (1982). Tardive dyskinesia. Prevalence and risk factors, 1959–1979. Arch Gen Psychiat. **39**: 473–481.
7 Kane J (2004). Tardive dyskinesia rates with atypical antipsychotics in adults: prevalence and incidence. J Clin Psychiat. **65** (suppl 9): 15–20.
8 Kapur S, Seeman P(2001). Does fast dissociation from the dopamine D2 receptor explain the action of atypical antipsychotics? A new hypothesis. Amer J Psychiat. **158**: 360–369.
9 Kinon BJ, Stauffer VL, Wang L, Thi KT (2002). Olanzapine improves tardive dyskinesia in patiens with schizophrenia. Schizophr Res **53** (3suppl 1): 190–191.
10 Lieberman JA, Stroup S, McEvoy J, Swartz M, Rosenheck R, Perkins D, Keefe RSE, Davis S, Davis CE, Hsiao J, Severe J, Lebowitz B, for the CATIE investigators (2005). Effectiveness of antipsychotic drugs in patiens with chronic schizophrenia. N Engl J Med. **353**: 1209–1223.
11 Llorca P-M, Chereau I, Bayle (F-J Lancon (2002). Tardive dyskinesias and antipsychotics: a review. Eur Psychiat. **17**: 129–138.
12 Marder SR, Meibach RC (1994). Risperidone in the treatment of schizophrenia. Am J Psychiat. **151**: 825–835.
13 Meltzer HY, Matsubara S, Lee JC (1989). Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin 2 pKi values. J Parmacol Exp Ther. **251**: 238–246.
14 Peuskens J and the Risperidone Study Group (1995). Risperidone in the treatment of patients with chronic schizophrenia: a multinational, multi-center, double-blind, parallel group study versus haloperidol. Brit J Psychiat. **166**: 712–726.
15 Pierre JM (2005). Extrapyranmidal symptoms with atypical antipsychotics: incidence, prevention and management. Drug Safety **28**: 191–208.
16 Wolf MA, Villeneuve A (1990). Les effets indésirables des neuroleptiques. L'Encéphale **16**: 111–124.