A Five-Year Follow-up Study of Tardive Dyskinesia

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Introduction

Prevalence studies of tardive dyskinesia (TD) in neuroleptic-treated patients have investigated factors associated with the presence of the disorder. The most reliable finding is that TD is more prevalent in older patients. In 1975, we carried out a cross-sectional study of TD in all 256 schizophrenic patients receiving neuroleptic maintenance treatment in the outpatient clinic of the Allan Memorial Institute (Chouinard et. al, 1979b). At that time, we reported the prevalence of TD in the clinic to be 31% (in fact, 23% met the recently proposed Schooler and Kane research diagnostic criteria for TD) (1982). Stepwise multiple logistic regression analysis suggested the following risk factors for TD (in order of statistical significance): advanced age, long records of hospitalization, poor therapeutic response to neuroleptics, and fluphenazine medication [oral or intramuscular (i.m.)]. There was also an inverse relationship between parkinsonism and TD, patients tending to have one or the other disorder but usually not both.

We now report a 5-year follow-up of these patients, focusing in particular on an investigation of factors related to the subsequent development of TD in a cohort of 131 patients who did not present the disorder in 1975.

Method

In 1975 TD and parkinsonism were assessed by a neurologist (A.R.-C.) in all 256 schizophrenic outpatients receiving maintenance antipsychotic medication in the Special Follow-Up Clinic of the Allan Memorial Institute. The scale used was the Extrapyramidal Symptom Rating Scale (ESRS) of Chouinard and Ross-Chouinard (Chouinard et al., 1979a, 1980), and the presence of TD was determined according to the Schooler and Kane Research Criteria (1982) which require at least moderate dyskinetic movements in one body area or mild dyskinetic movements in two body areas. The presence of parkinsonism was also determined on a similar basis. Psychopathology was assessed by one of the authors (G.C.) who conducted a psychiatric interview. The schizophrenic illness of patients was classified as good or poor prognosis using the World Health Organization (WHO) scale for prognosis. Data were collected on demographic characteristics, treatment history, neuroleptic type and dosage converted to chlorpromazine equivalents (Davis, 1980), and antiparkinsonian drugs. Patients with a history of meningitis, brain trauma, neurosyphilis, or an abnormality on neurological examination associated with a neurological disease were classified by the neurologist as having brain damage.

In 1980, 169 of the original cohort of 256 patients (65%) were reassessed by the same neurologist and psychiatrist after 5 years of further neuroleptic treatment, using the same rating scales and criteria as before. At this time it was confirmed that all patients met the DSM-III criteria for schizophrenia. Eighty-seven of the original 256 patients (35%) were lost to follow-up because of either failure to return to the clinic, transfer elsewhere, or death. Table 1 compares the characteristics of patients lost to follow-up with those of patients who were reassessed in

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TABLE 1

Patient Characteristics (1975): Differences Between Follow-up Cohort of Patients and Those Lost to Follow-up

	Follow-up Cohort ($N = 169$)	Lost to Follow-up ($N = 87$)	Statistical Significance of Difference[a] p
Men/Women	83/86	54/33	0.07
Age	42 (23-67)[b]	39 (19-63)[b]	0.06
Treatment duration (yrs)	10.5 (0.1-22)[b]	8.0 (0.1-21)[b]	0.001
Dosage (CPZ equivalents)	487 (15-4000)[b]	506 (0-5000)[b]	0.82
Brain damage	25%	14%	0.05
Neuroleptic type			
p.o. only	61%	52%	0.20
i.m. only	18%	18%	0.96
p.o. and i.m.	20%	24%	0.48
Antiparkinsonian medication	55%	67%	0.10
Tardive dyskinesia (research criteria)[c]	22%	24%	0.89
Parkinsonism[d]	33%	44%	0.13

[a]Chi-square test with Yates correction for percentages. *t* test for means (two-sided).
[b]Mean (minimum-maximum).
[c]Schooler and Kane (1982).
[d]At least two items with scores ≥ 2 or one item with score ≥ 3.

1980. Patients lost to follow-up were more likely to be male ($p = 0.07$), younger (mean difference = 3 years, $p = 0.06$), treated for a shorter period of time (mean difference = 2.5 years, $p = 0.001$), less likely to have brain damage ($p = 0.05$), and more likely to be receiving antiparkinsonian medication ($p = 0.10$). There were no significant differences between the two groups, however, with respect to prevalence of TD or parkinsonism in 1975.

TABLE 2

Patient Characteristics: Cohort of 131 Patients With No TD in 1975

	1975		1980
Men/Women		61/70	
Age	40 (23-67)[a]		45 (27-72)[a]
Duration of treatment (yrs)	9.5 (0.1-22)[a]		14 (4.4-26)[a]
Dosage (mg/day CPZ equivalents)	300 (15-4000)[a]		338 (6-4200)[a]
Poor schizophrenic prognosis		72%	
Brain damage		24%	
Neuroleptic type			
p.o. only	66%		36%
i.m. only	18%		60%
p.o. and i.m.	16%		5%
Antiparkinsonian medication	53%		68%

[a]Median (minimum - maximum).

The characteristics of the cohort of 131 patients who did not present TD in 1975 and who were reassessed in 1980 are shown in Table 2. During this period the policy in the clinic was to switch patients from daily oral (p.o.) neuroleptics to long-acting i.m. neuroleptics (mostly fluphenazine enanthate or decanoate) if feasible. Antiparkinsonian medication was prescribed only if necessary and not prophylactically. Polypharmacy was avoided as far as possible. The principal changes in treatment may be summarized as follows: 1) there was a switch from p.o. to i.m. medication in 45% of patients; 2) a reduction in neuroleptic dosage (chlorpromazine equivalents) (Davis, 1980) in 48% of patients;

TABLE 3

Prevalence of TD and Parkinsonism in 1975 and 1980: Cohort of 169 Patients Assessed in 1975 and 1980

		1975 (Percent)	1980 (Percent)
Tardive dyskinesia (research criteria)[a]		22	44
Men	($N = 83$)	27	43
Women	($N = 86$)	19	45
Parkinsonism[b]		33	72
Men	($N = 83$)	39	76
Women	($N = 86$)	28	69

[a]Schooler and Kane (1982).
[b]At least two items with scores ≥ 2 or one item with score ≥ 3.

and 3) an increase in antiparkinsonian dosage in 45% of patients.

Results

Prevalence of TD in all reassessed patients (N = 169). Table 3 shows the prevalence of TD (Schooler & Kane, 1982) and parkinsonism in the 169 patients assessed in both 1975 and 1980. The prevalence of TD increased from 22% to 44% ($p<0.001$, McNemar's test) and that of parkinsonism from 33% to 72% ($p<0.001$, McNemar's test). There was no significant ($p<0.05$) difference between the sexes with respect to the prevalence of either TD or parkinsonism on either occasion. There was, however, a tendency ($p<.10$, $\chi^2 = 3.65$) for more parkinsonism in men than women in 1975, but not in 1980.

Development of TD in reassessed patients (N = 131). In the cohort of 131 patients who did not present TD in 1975, 46 patients (35%) developed TD, while the prevalence of parkinsonism increased from 32% to 71%. Stepwise multiple logistic regression analysis (Kleinbaum et al., 1982) was used to predict the development of TD (coded 0,1) during the period 1975 to 1980. The exploratory variables included for selection were of two types: those thought to be of possible etiological significance in the development of TD, and those known or suspected to uncover covert TD. The etiological variables included were: sex, age, duration of neuroleptic treatment (dichotomized and coded as follows: 0 = <5 yrs, 1 = >5 yrs), schizophrenic prognosis (0 = good, 1 = poor), brain damage (0 = none, 1 = present), and parkinsonism score (1975); the uncovering or confounding variables were: reduction in neuroleptic dosage, switch from daily p.o. to long-acting i.m. neuroleptic (the uncovering mechanism may be through a decline in blood level at the end of the injection interval when all patients were assessed), and an increase in antiparkinsonian dosage.

The model building strategy used was to start with all main effects in the model and then carry out forward selection to add any significant second-order product (i.e., interaction) terms (Kleinbaum et al., 1982). Second-order product terms were considered because we were unable to obtain a good fit with main effects only. An alpha level of 5% was used throughout. Because there were nine main effects and 36 second-order interaction terms as candidates for selection, this analysis should be regarded as exploratory, particularly where variables of marginal statistical significance were selected.

The results of the stepwise logistic regression analysis are shown in Table 4. Three main effects were significant at the 5% level: parkinsonism score (1975), poor schizophrenic prognosis, and treatment duration (>5 years). Also, two variables were significant at the 10% level: a switch from p.o. to i.m. medication and a neuroleptic dosage reduction. In addition to these main effects two interac-

TABLE 4

Variables Related to Development of TD (1975–1980): Results of Stepwise Logistic Regression Analysis (N = 131)

Variable	Coefficient	S.E.	χ^2	p
Intercept	−5.07	1.43	12.58	0.0004
Parkinsonism score (1975)	0.13	0.06	4.68	0.03
Poor schizophrenic prognosis	1.09	0.53	4.31	0.04
Treatment duration	1.42	0.73	3.75	0.05
p.o. to i.m. switch	1.12	0.61	3.37	0.07
Neuroleptic dosage reduction	0.80	0.45	3.18	0.07
Age	0.03	0.02	1.33	0.25
Antiparkinsonian dosage increase	−0.57	0.54	1.11	0.29
Sex	0.15	0.46	0.11	0.74
Brain damage	−0.01	0.66	0.00	0.98
p.o. to i.m. switch x parkinsonism score	−0.23*	0.09	7.08	0.008
Antipark. increase x brain damage	2.20	1.04	4.51	0.03

*Negative coefficient indicates that effect of presence of both risk factors is less than sum of each main effect (lack of additivity).

TABLE 5

Predictive Ability of Multiple Logistic Regression Model

		Predicted (1980) No TD	TD	Total
	No TD	75	10	85
True	TD	23	23	46
(1980)	Total	98	33	131

Sensitivity (true positives) = 50%
Specificity (true negatives) = 88%

tion terms were added to the model: 1) that between the medication switch and parkinsonism score with a negative coefficient ($p = 0.008$), indicating that the risk of TD with both factors present is less than the sum of their separate risks and, more specifically, that the patients most at risk for developing TD were those with high parkinsonism scores in 1975 who remained on the same medication type (either p.o. only or i.m.) in 1980; and 2) that between an antiparkinsonian dosage increase and brain damage with a positive coefficient ($p<0.05$), indicating that brain-damaged patients were more vulnerable to the effect of antiparkinsonian increase. The effects of age and sex were not significant ($p>0.10$), although it is worth noting that age and duration of treatment were correlated somewhat ($r = 0.44$, $p<0.001$). We examined the goodness-of-fit of this model by comparing the predicted cases ($p>0.5$) with the true cases of TD (Table 5): sensitivity (true positives) was 50% which is fair, and specificity (true negatives) was 88%, which is good.

Because the 1975 parkinsonism score appeared to be the best predictor of subsequent TD development, we repeated the stepwise logistic regression analysis including the change in parkinsonism score (1975 to 1980) as an additional variable. The results of this analysis were that the new variable, change in parkinsonism score, became the best predictor of TD development ($p = 0.001$) with 1975 parkinsonism score second. The new model increased the sensitivity of prediction to 54% while the specificity remained at 88%.

Annual incidence rate of TD. The 5-year cumulative incidence rate of TD in the cohort of 131 patients who did not present TD at the 1975 assessment was 35% (46/131). This is equivalent to a mean annual incidence rate of 8.4% (Kleinbaum et al., 1982). However, this does not consider remissions (or misclassifications) among patients who presented TD in 1975 but not in 1980 of which there were 9/38 cases representing a 5-year cumulative remission rate of 24% or a mean annual remission rate of 5.5%. Thus the mean annual incidence rate of TD corrected for remissions was 2.9%.

Discussion

These results suggest that three etiologic factors may be important in the development of TD. The presence of severe parkinsonism which cannot be suppressed by antiparkinsonian medication appeared to be a precursor of TD development. There was also evidence that worsening of parkinsonism was associated with TD development. Whereas in 1975 we observed an inverse relationship between parkinsonism and TD, in 1980 both disorders were commonly present simultaneously. During this interval the patients had both grown older and been exposed to more neuroleptic treatment, so that a more advanced stage of extrapyramidal movement disorder had probably been reached. One contribution to the changed relationship may have been the decrease in dopamine synthesis with aging, especially in male patients, as found in PET scan studies.

The second risk factor for TD was poor schizophrenic prognosis, which tends to confirm our earlier finding (Chouinard et al., 1979b) of an association between poor therapeutic response to neuroleptics and TD. Duration of neuroleptic treatment also appeared to be a risk factor with 5 to 10 years of exposure being a critical period. This finding has intuitive appeal but has not generally been substantiated in prevalence surveys. The correlation between treatment duration and age in the present population probably explains why we failed to find age an important predictor here, although it was the first variable selected in our 1975 prevalence survey (Chouinard et al., 1979b). Another factor to be considered is that these patients may constitute a special subgroup inasmuch as they were those patients in the clinic who did not present TD in 1975, despite presence of risk factors in some cases.

Three variables that may perhaps be characterized as uncovering or, in statistical terminology, confounding factors rather than etiologic factors were also identified as associated with the manifestation of TD: a switch from p.o. to i.m. medication in those without parkinsonism, a neuroleptic dosage reduction, and an increase in antiparkinsonian medication in brain-damaged patients. The explanation for the appearance of the medication switch as a risk factor may be that blood levels tend to decline toward the end of the injection interval (when all these patients were assessed), and a decline in dopamine receptor blockade at this point would tend to uncover any covert dyskinesia. This may be the explanation for our previous finding of an association between fluphenazine treatment and TD (Chouinard et al., 1979b) as many patients were receiving i.m. fluphenazine. A study in two patients using neuroleptic radioreceptor assay measurements of neuroleptic blood levels at different points during the injection period supports this view (Chouinard et al., 1982). The uncovering effect on TD of neuroleptic dosage reduction is well-known; that of anticholinergic antiparkinsonian dosage increase has also been documented (for example, Chouinard et al., 1979c), but the finding of increased vulnerability of brain-damaged patients in this respect is new. In our earlier prevalence study of TD (Chouinard et al., 1979b) in this population, we found that brain-damaged patients tended to have more severe forms of TD than those without brain damage. Thus, there seems to be some evidence to suspect that brain-damaged patients are at greater risk for the disorder.

The estimated 2.9% annual incidence rate of TD corrected for remissions is similar to that reported by Kane et al. (1982) from a prospective study of TD development, although the latter study is of a younger and heterogeneous population of patients with schizophrenia or manic-depressive disorder.

We believe that a large-scale prospective study of TD development in a homogeneous population of newly-treated schizophrenic patients would clarify further the risk factors.

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