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A 5-Year Prospective Longitudinal Study of Tardive Dyskinesia: Factors Predicting Appearance of New Cases

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In a 5-year longitudinal study in a cohort of 169 schizophrenic outpatients treated with neuroleptics, we found a twofold increase (from 22% to 44%) in prevalence of tardive dyskinesia (TD) meeting the Schooler and Kane research diagnostic criteria. If we include cases of TD that were considered definite but did not meet the research criteria, the prevalence increased from 31% to 58%. In the cohort of 131 patients who did not present with the disorder in 1975, we found parkinsonism and increase in parkinsonism to be the best predictors of subsequent development of the disorder. Poor schizophrenic prognosis and long treatment duration also appeared to be risk factors. Another finding was the importance of changes in neuroleptic and antiparkinsonian dosage in both covering and uncovering TD.
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TARDIVE DYSKINESIA (TD), a neuroleptic-induced extrapyramidal hyperkinetic syndrome,[1–3] is characterized by involuntary, repetitive, and purposeless movements that vary in localization and form. The clinical manifestations involve eight main areas: tongue, jaw, cheeks and lips, trunk, upper extremities, lower extremities, face, and respiratory system. The most common manifestation is the buccolingual-facial-masticatory syndrome, which involves the muscles of the mouth, tongue, lips, cheeks, and jaws, and manifests itself by lateral jaw movements or tongue movements within the oral cavity, protrusion or torsion of the tongue, and slow lateral movements of the tongue. The syndrome also includes choreoathetoid movement of upper and lower extremities.

Early studies reported a prevalence of TD of 2% to 15% in neuroleptic-treated patients.[4] In 1980 the Task Force of the American Psychiatric Association[5] estimated the prevalence in patients at risk to be at least 10% to 20%, and 40% in elderly patients. Jeste and Wyatt[6] reviewed the changing epidemiology of TD and concluded that the prevalence had been progressively rising and had reached 25% during the period of 1976 to 1981. In 1982, Kane and Smith[4] reviewed 65 studies and found an average prevalence of 20% in neuroleptic-treated patients compared with 5% showing dyskinesia-like movements in untreated patients. More recent estimates[7–16] from 1981 to 1986 have been even higher, with an average prevalence of 30%. In contrast, the prevalence of spontaneous dyskinesia in healthy elderly volunteers was found to be 1.2%,[12] 1.5%,[17] and, in a geriatric medical population, 4.8%.[12] Also, in a series of studies conducted in Turkey with chronic schizophrenic patients who were treated with minimal doses of neuroleptics, Crane[1, 2] was able to distinguish between TD and schizophrenic stereotypies.

Concerning risk factors, there is agreement that TD is more prevalent in elderly patients.[4, 6–8, 18, 19] Although information on gender and TD is conflicting, there are studies suggesting that elderly female patients are more at risk than male patients.[4, 18, 20, 21] Other risk factors that have been reported are: (1) total exposure to neuroleptics,[8, 19] (2) neuroleptic treatment of affective disorder,[22] and (3) fluphenazine drugs.[12, 15, 18, 23–25]

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 of Psychiatry.[18] At that time, we reported the prevalence of TD in the clinic to be 31%

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(in fact, 22% met the research diagnostic criteria for TD proposed by Schooler and Kane[26]). Five years later, in the same clinic, we found the prevalence meeting these research criteria to be 45%, a twofold increase.[27] Of these 224 patients, 169 were examined both in 1975 and 1980. We report the 5-year follow-up of these 169 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 with the disorder in 1975.

Methods

The Allan Memorial Institute of Psychiatry maintains a special follow-up clinic for the long-term maintenance treatment of schizophrenic outpatients. One of the authors (G.C.) is the psychiatrist in charge of this clinic. During the study period (1975 to 1980), patients were accepted in the clinic if the primary hospital diagnosis of schizophrenia was confirmed by the psychiatrist in charge using the DSM-III criteria. Schizophrenic patients who were not likely to need long-term pharmacotherapy were not accepted in the clinic. Pharmacotherapy was under strict control and the following principles were applied: the minimal therapeutic dose of neuroleptic was given; a single neuroleptic, injectable depot fluphenazine or oral fluphenazine, was prescribed whenever possible; orally administered drugs were prescribed in a single daily dose or twice-daily regimen; procyclidine (Kemadrin) was the only antiparkinsonian drug used; attempts were made to withdraw the antiparkinsonian after 3 months of treatment; injectable fluphenazine decanoate or enanthate was given to patients who were resistant to other neuroleptics, those who could not be relied on to take medication, and those with frequent relapses; polypharmacy was avoided and antidepressant drugs, mood stabilizers, minor tranquilizers, and hypnotics were not prescribed; medication was reviewed by the psychiatrist in charge of the clinic each time the patient visited the clinic.

In 1975, TD and parkinsonism were assessed by a neurologist (A.R.-C.) in all 256 schizophrenic outpatients attending the clinic. The scale used was the Extrapyramidal Symptom Rating Scale (ESRS) of Chouinard and Ross-Chouinard,[28, 29] and the presence of TD was determined according to the Schooler and Kane Research Criteria.[26] 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 WHO scale for prognosis. Data were collected on demographic characteristics, evidence of brain damage, treatment history, neuroleptic type and dosage converted to chlorpromazine equivalents,[30] and antiparkinsonian drugs. 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.

During the neurological examination, the neurologist completed a structured medical questionnaire. Care was taken to differentiate TD from other neurological disorders that have similar manifestations (Huntington's chorea, Sydenham's chorea, Wilson's disease, brain-damaged chorea, and senile chorea) and from stereotyped movements and mannerisms that are often associated with chronic schizophrenia. TD was assessed according to a standard procedure that included the following routine neurological tests: (1) the patient's spontaneous behavior was observed while seating, standing, or walking; (2) because abnormal movements are increased by voluntary movements of other muscle groups, the oral-facial region was observed while the patient carried out the pronation-supination tests of both hands as fast as possible and performed rapid alternate movements of both wrists; (3) the patient was asked to walk without shoes so that any choreoathetoid movements of the limbs could be noted; and (4) the patient was asked to copy a spiral with both hands and to sign his or her name (because the test is performed under emotional tension, this procedure may activate dyskinetic movements and thus sometimes uncover covert dyskinesias). Questionable cases of TD were not considered to be positive. The psychiatrist and the neurologist did not have access to each others' findings, nor to their previous ratings.

Fifty-four of the original 256 patients (21.1%) were classified by the neurologist as having evidence of brain damage: 32.1% as a result of head trauma, 11.3% involving frontal signs of unknown etiology, 7.6% congenital, 5.7% related to epilepsy, 5.7% to mental retardation, 5.7% to syphilis, and the remainder of miscellaneous or unknown etiology. Eighty-seven of the original 256 patients (35%) were lost to follow-up because of failure to return to the clinic, transfer elsewhere, or death. The characteristics of patients lost to follow-up with those of patients who were reassessed in 1980 are compared in Table 1. Patients lost to follow-up tended to be 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 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 (years)	10.5 (0.1–22)	8.0 (0.1–21)	0.001
Dosage (chlorpromazine equivalents)	487 (15–4000)	506 (0–5000)	0.82
Brain damage	25%	14%	0.05
Neuroleptic type			
Oral only	61%	52%	0.20
Intramuscular only	18%	18%	0.96
Oral and intramuscular	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; numbers in parentheses, minimum–maximum.
[c]Schooler and Kane (1982)
[d]At least two items with scores ≥2 or one item with score ≥3.

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 neuroleptics to long-acting intramuscular neuroleptics (mostly fluphenazine enanthate or decanoate) if feasible and desirable, and attempts were made to decrease neuroleptic dosage. Antiparkinsonian medication was prescribed only if necessary and not prophylactically. The principal changes in treatment may be summarized as follows: (1) there was a switch from oral to intramuscular medication in 45% of patients; (2) there was a reduction in neuroleptic dosage (chlorpromazine equivalents[30]) in 48% of patients; (3) there was an increase in antiparkinsonian dosage in 45% of patients.

Results

Prevalence of TD in all reassessed patients (N = 169)

The prevalence of TD and parkinsonism in the 169 patients assessed in both 1975 and 1980 is shown in Table 3. The prevalence of TD meeting the research diagnostic criteria 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 ($p < 0.10$, $\chi^2 = 3.65$) for more parkinsonism in men than women in 1975 but not in 1980. The prevalence of definite cases of TD that did not meet the research diagnostic criteria (which require symptoms in two areas) increased from 31% to 58% in the same period.

Development of TD in reassessed patients (N = 131)

In the cohort of 131 patients who did not present with TD in 1975, 46 patients (35%) developed TD, while the prevalence of parkinsonism increased from 32% to 71%. Stepwise multiple logistic regression analysis[31] 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

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)
Duration of treatment (years)	9.5 (0.1–22)	14 (4.4–26)
Dosage (mg/day chlorpromazine equivalents)	300 (15–4000)	338 (6–4200)
Poor schizophrenic prognosis	72%	
Brain damage	24%	
Neuroleptic type		
Oral only	66%	36%
Intramuscular only	18%	60%
Oral and intramuscular	16%	5%
Antiparkinsonian medication	53%	68%

[a]Median; numbers in parentheses, minimum–maximum.

TABLE 3. Prevalence of TD and parkinsonism in 1975 and 1980: cohort of 169 patients assessed in 1975 and 1980

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

[a]Schooler and Kane (1982).[26]
[b]All values represent percentages.
[c]At least two items with scores ≥2 or one item with score ≥3.

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 years, 1 = ≥5 years), 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 oral to long-acting intramuscular 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.[31] 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 oral to intramuscular medication and a neuroleptic dosage reduction. In addition to these main effects, two interaction 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 oral only or intramuscular) in 1980; (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 ($r = 0.44, p < 0.001$). We examined the goodness of fit of this model by comparing the predicted cases ($p > 0.5$) with the true cases of TD: 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 (Table 5) 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 of 131). This is equivalent to a

TABLE 4. Variables related to development of TD (1975 to 1980): results of stepwise logistic regression analysis (N = 131)

Variable	Coefficient	SE	χ^2	p
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
Oral to intramuscular switch	1.12	0.61	3.37	0.07
Neuroleptic dosage reduction	0.80	0.45	3.18	0.07
Age	0.02	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
Oral to intramuscular switch × parkinsonism score	−0.23[a]	0.09	7.0[a]	0.00[a]
Antiparkinsonian increase × brain damage	2.20	1.04	4.51	0.03

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

TABLE 5. Alternative model including change in parkinsonism score (1975 to 1980) as predictor of TD development (1975 to 1980)

Variable	Coefficient	SE	χ^2	p
Increase in parkinsonism score	0.71	0.22	10.59	0.001
Parkinsonism score (1975)	0.29	0.09	9.58	0.002
Oral to intramuscular switch	1.32	1.37	5.96	0.02
Sex (female)	1.63	0.73	4.98	0.03
Treatment duration	1.35	0.81	4.20	0.04
Dosage reduction	0.96	0.49	3.93	0.05
Poor schizophrenic prognosis	1.04	0.57	3.39	0.07
Antiparkinsonian dosage increase	−0.65	0.57	1.31	0.25
Age	0.01	0.03	0.25	0.62
Brain damage	0.20	0.70	0.08	0.78
Medication switch × parkinsonism (1975)	−0.40[a]	0.13	10.06	0.002
Sex × increase in parkinsonism	−0.34[a]	0.11	8.65	0.003
Parkinsonism (1975) × increase in parkinsonism	−0.02[a]	0.01	7.05	0.008
Antiparkinsonian increase × brain damage	2.55	1.18	4.70	0.03

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

mean annual incidence rate of 8.4%.[31] However, this does not consider remissions (or misclassifications) among patients who presented TD in 1975 but not in 1980, of which there were 9 of 38 cases, which represents 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

There have been few prospective longitudinal studies of TD. One such is being carried out by Kane and associates[19, 22] in New York. However, Kane's study population differs from ours in that it is more heterogeneous and includes other diagnostic groups than schizophrenia, such as affective and schizoaffective disorder. Another difference is that in our study the neuroleptic treatment was standardized as far as possible. Nevertheless, it is interesting to note that the cumulative incidence of TD in the study by Kane and associates[22] was 12% after 4 years and 40% after 8 years of neuroleptic exposure, which is similar to our own finding of an annual incidence rate (corrected for remissions) of 3%. Barnes and associates,[7] in a 3-year follow-up study in the United Kingdom, reassessed 99 of 182 patients and found 22 new cases and 14 remissions; age and akathisia emerged as significant predictors of TD development.

The present study suggests that three etiological factors may be important in the development of TD. Parkinsonism appeared to be a precursor of TD development, and there was evidence that an increase in parkinsonism was associated with TD development. Whereas in 1975 we observed an inverse relationship between parkinsonism and TD, by 1980 both disorders were often present simultaneously. TD increased from 0% to 33% while the increase in parkinsonism was evident both on the neurologist's evaluation (an increase in prevalence from 32% to 71%) and the treating psychiatrist's prescription of antiparkinsonian medication (an increase in dosage in 45% of patients). 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 increase in both disorders may have been the decrease in dopamine synthesis with aging. Kane and colleagues[22] examined a subgroup of 52 patients who were identified as having significant parkinsonism and found that TD was significantly more prevalent in this subgroup than in the rest of the patients examined.

The second risk factor for TD was poor schizophrenic prognosis, which tends to confirm our earlier finding[18] of an association between poor therapeutic response to neuroleptics and TD. It is likely that poor prognosis schizophrenics, who have also a greater schizophrenic deficit, are more likely to have greater structural brain damage, thus explaining their increased risk.

Duration of neuroleptic treatment also appeared to be a risk factor, with more than 5 years of exposure being a critical period. Another study also found a relation between years of exposure (more than 6 years) and prevalence of TD.[15] The correlation between treatment duration and age in the present population could explain why we failed to find age an important predictor here although it had been in our 1975 prevalence survey.[18] Another factor to be considered is that these patients may constitute a subgroup inasmuch as they were those patients in the clinic who did not present with TD in 1975, despite presence of risk factors in some cases.

The great majority of patients in the present study had been treated with fluphenazine (orally or injectable decanoate). Thus, we could not assess the role of fluphenazine treatment. In our first study,[18] we found

fluphenazine treatment to be a risk for TD. This finding has been reported by at least five other studies.[12, 15, 23–25] However, prospective comparative studies will be necessary to solve this issue.

Three variables that may perhaps be characterized as uncovering factors were also identified as associated with the manifestation of TD: a switch from oral to intramuscular 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 covert dyskinesia. 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 and coworkers[32]), but the finding of increased vulnerability of brain-damaged patients in this respect is new. In our earlier prevalence study of TD[15] in this population, we found that brain-damaged patients tended to have more severe forms of TD than did those without brain damage. Thus, there seems to be some evidence to suspect that brain-damaged patients are at greater risk to develop the disorder, especially when given antiparkinsonian medication. Thus, antiparkinsonian medication may need to be used more cautiously in patients with a history of brain damage.

In conclusion, the principal findings of this study are that the following appear to be important risk factors for the development of TD: vulnerability to severe parkinsonism, poor schizophrenia prognosis, and long duration of neuroleptic treatment (over 5 years).

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