Tardive Dyskinesia in Psychiatric Outpatients

A Study of Prevalence and Association With Demographic, Clinical, and Drug History Variables

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• **We examined 153 psychiatric outpatients, on a maintenance regimen of neuroleptics, for tardive dyskinesia (TD) and parkinsonism. Demographic, clinical, and drug history data were collected to assess whether any of these factors were significantly associated with TD. After initial univariate screening, significant variables were analyzed by multivariate statistical methods. Tardive dyskinesia was significantly associated with the use of high-potency or high-dosage neuroleptics and depot fluphenazine, whereas low-potency neuroleptics were negatively correlated with moderate TD. Age, but not sex, correlated significantly with TD, as did histories of incoherence, grandiose delusions, and teeth or denture problems. Parkinsonism and TD were strongly associated. Although the prevalence of TD was quite high, there were no severe involvements of any of the Abnormal Involuntary Movement Scale body areas.**

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Since its first recognition and description two decades ago,[1,2] tardive dyskinesia (TD) has been extensively studied, and two comprehensive reviews[3,4] have recently been published. However, many basic issues regarding its diagnosis, epidemiology, and relation to neuroleptic drugs remain controversial. Reviews of the literature[3-7] have reported widely discrepant prevalence rates ranging from 0.5% to almost 60%. These discrepancies are probably due, in part, to differences in study design, population studied, methods of assessment, and criteria for diagnosis. Although it had been assumed in the past[8] that TD is less common in outpatients, recent studies[9-12] have reported otherwise.

Recent data[11-18] suggest a significant association between TD and age. A significant association with sex, women being more at risk, has also been reported.[14-16,19-21] However, other studies[10,22-25] have failed to find a significant association between TD and age or sex. It has been suggested that studies of older chronically ill populations are more likely to find sex differences in TD than those involving younger populations.[26,27]

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Even though a connection between neuroleptic drugs and the genesis of TD is generally accepted, the relative contributions of different drug variables, such as dosage, duration of treatment, and type of neuroleptic, are far from clear. There are reports of significant associations between TD and duration of neuroleptic treatment,[24,25] high-potency neuroleptics,[13] low-potency neuroleptics,[24,25] use of antiparkinsonian drugs,[20,28] and use of depot fluphenazine.[11,17,24,29,30] However, other studies have failed to find an association between TD and duration of neuroleptic exposure,[13,14,20,28] any particular neuroleptic,[14,20] or use of antiparkinsonian drugs.[11,14,24]

The proper study of these drug variables is made difficult by the fact that most patients have been exposed to many neuroleptics during the course of their treatment. Also, investigators studying different aspects of drug history have often used univariate statistical methods to analyze the data. This may lead to an increased probability of chance correlations, or lack thereof, especially in the study of a complex syndrome such as TD, in which multiple intercorrelated variables appear to be involved. Finally, most studies have been done on chronically and severely ill patients where the effects of organic changes or of long-standing psychosis are difficult to exclude or control for.

Our study was conducted to assess the prevalence and severity of TD in an outpatient clinic treating noninstitutionalized and less severely ill patients and to investigate the relationship of TD with demographic, clinical, and drug history variables using a multivariate statistical model.

PATIENTS AND METHODS

All patients regularly attending the outpatient clinic of New York Medical College–Metropolitan Hospital Center (New York) and receiving neuroleptics for a year or more were referred to the Psychopharmacology Program for evaluation. Those with organic brain syndromes, neurologic disorders other than neuroleptic-induced side effects, or history of severe alcohol or drug abuse were excluded. During a five month period ending in December 1980, 153 patients were examined.

The mean age of the sample was 49.8 years (SD, 10.74 years); of the 112 women, 50.75 years (SD, 9.53 years); and of the 41 men, 45.9 years (SD, 13.08 years). Of the 153 patients, 52 (34%) had no history of psychiatric hospitalization, 98 (64%) had histories of hospitalizations for acute disorders, and 28 (18.3%) had histories of state hospitalizations of less than one year. Of the 101 with histories of hospitalization, the mean number of emergency

spitalizations was 3.5 and of state hospitalizations, 1.0. The an age at first hospitalization was 36.1 years (SD, 11.6 years). the total sample, 30 patients (19.6%) had never received a gnosis of schizophrenia. All patients were on a neuroleptic intenance regimen with no dosage reduction during the three nths preceding the examination.

Patients were examined for TD using the Abnormal Involuny Movement Scale (AIMS) developed by the Psychopharmacoly Branch of the National Institute of Mental Health,[31] and eviously reported to be reliable.[15] The AIMS records the presce and severity of abnormal movements in seven body areas: ial muscles, lips and perioral areas, jaw, tongue, upper extremes, lower extremities, and trunk. For each body area, movents are scored on a five-point severity scale in which 0 indicates ne; 1, minimal (may be borderline normal); 2, mild; 3, moderate; d 4, severe. Overall severity of abnormal movements, incapacion resulting from movements, and the patient's reported areness and distress related to the abnormal movements are ted on a scale of 0 to 4. Presence of dentures and problems with th or dentures were also noted.

Patients were then examined for signs of parkinsonism and athisia, by means of the Scale for Extrapyramidal Effects EE),[32] which measures ten extrapyramidal signs: gait, arm opping, shoulder shaking, elbow rigidity, wrist rigidity, leg ndulousness, head dropping, glabella tap, tremor, and saliva-n. To these signs we added a rating for akathisia. Each item was ted on a five-point scale, with 0 meaning the absence of a sign d 4 its extreme form.

After the ratings, patients were asked for the following infor-ation: years of medication therapy; number of periods without ugs lasting three months or more; and histories of acute stonia, parkinsonism, akathisia, or anticholinergic effects. nally, in semistructured interviews (not the Schedule for Affece Disorders and Schizophrenia [SADS]), patients were asked out past or present symptoms suggesting diagnoses of schizorenia or schizoaffective disorder by Research Diagnostic Crite-a (RDC).[33]

The patients were examined by one of two raters, each of whom amined about half of the total sample. Then the other rater, aware of the examination findings, reviewed the patient's spital records for demographic data, all diagnoses, psychotic mptoms noted at any time, previous treatment history, and ported side effects of medication. Detailed drug history was corded for the past eight years, including individual drugs, daily sages, and duration of treatment with each drug and dosage. ugs prescribed for less than one month were excluded. Recorded ugs included neuroleptics, antiparkinsonian drugs, and antidepressants. The rater examining a patient had no access to the formation in that patient's records. Interrater reliability, sessed on a separate sample of patients prior to the study, was und to be satisfactory for the two scales (Pearson's $r = +.72$ to 98).

In addition to the 153 patients on neuroleptic maintenance gimens, 15 patients with no history of neuroleptic exposure were ndomly included for examination, without the knowledge of the ters. This group, treated with benzodiazepines and/or tricyclic tidepressants, had a mean age of 47.6 years (SD, 10.7 years), re found to have no scores on either AIMS or SEE, and were cluded from further data analyses.

RESULTS

Prevalence of TD

The assessment of TD prevalence was based on the AIMS scores. ie AIMS gave three measures of involvement: individual subtest ores of the seven body areas; a total score, which was the sum of e seven subtests; and a global severity rating. A criterion level r TD was based on the individual subtest scores. It was defined the minimum score the patient had to have on at least one of e subtests to qualify as having TD. The prevalence of TD at fferent criterion levels is shown in Table 1.

TD and Associated Variables

We used a univariate model to screen each variable for a gnificant association with TD and then used a multivariate technique to analyze those variables that had demonstrated significance when examined independently. The total AIMS score was chosen as the screening dependent variable, as it was a continuous rather than a categorical variable and allowed the use of more sensitive parametric tests of association. The total AIMS score was strongly correlated with the AIMS global severity ratings ($r = .92$) and with the different measures by criterion levels ($r = .86$).

For each neuroleptic, the following data were coded: the length of time the drug was taken; consistency of usage; maximum dosage; and total cumulative dose (the latter two in chlorpromazine equivalents.)[34] From the patients' reports, drug-free intervals were coded. As many patients had been sequentially exposed to more than one neuroleptic, the number of neuroleptics was coded as a separate variable. None had been exposed to more than one simultaneously.

Categorical variables were analyzed using t tests to compare mean AIMS scores, and correlation coefficients were calculated for continuous variables. The results of the univariate screening are shown in Tables 2 and 3.

Based on a total score of 4 or more on the SEE (excluding the measure for akathisia), 19 patients (12.4%) were classified as having parkinsonism. There was a significant association between the dichotomous variables—TD and parkinsonism—when they were placed in a 2×2 contingency table ($\chi^2 = 4.89$; $df = 1$; $P = .027$). This correlation became stronger when the continuous variables—total AIMS and total SEE scores—were used. Their product moment correlation was .465 ($P < .0001$), highly significant and accounting for more than 21% of the variance between the two scores.

Multivariate Analyses

The number of significant variables was reduced with a stepwise multiple regression analysis (MRA). There were three sets of

Table 1.—Prevalence of Tardive Dyskinesia at Different Criterion Levels

Criterion Level	Prevalence, % Total	Male Patients	Female Patients	M-F Ratio
1.0 (minimal)	45.8	48.8	44.6	0.91
2.0 (mild)	30.7	34.1	29.5	0.87
3.0 (moderate)	10.4	9.8	10.7	1.09

Table 2.—Categorical Variables (t Tests) in Univariate Screening Test Results*

Variable	Mean Total AIMS† Scores +‡	−‡	P
Hospitalizations	2.73	1.46	.02
Grandiose delusions	4.93	1.99	.04
Incoherence when psychotic	3.40	1.60	.007
Parkinsonism	5.10	1.96	.02
Akathisia	6.13	1.83	.01
Dystonic reactions	5.57	1.95	.02
Psychotic depression	4.18	2.13	.07
Neuroses	0.80	2.35	.001
RDC† schizophrenia or schizoaffective disorder	2.78	1.76	.07
Teeth or denture problems (AIMS)†	4.25	1.95	.01

*Other psychotic symptoms, diagnoses, and side effects, histories of emergency or state hospitalizations, electroconvulsive therapy, antiparkinsonian or antidepressant drugs, and sex were not significant ($P > .07$).

†AIMS indicates Abnormal Involuntary Movement Scale; RDC, Research Diagnostic Criteria.

‡Plus indicates patients with history or presence of variable; minus, those without.

Table 3.—Continuous Variables (Correlation Coefficients) in Univariate Screening Test Results*

Variable	r	r^2	P
Age	.188	.035	.02
Total dose of neuroleptics (chlorpromazine equivalent)	.180	.032	.02
Maximum dosage of neuroleptics (chlorpromazine equivalent)	.239	.057	.003
Years of neuroleptic therapy	.184	.034	.02

*Number of hospitalizations, emergency hospitalizations, state hospitalizations, duration of hospital stays, and drug-free periods were not significant.

Table 4.—Stepwise Multiple Regression Analysis

Dependent Variables	Incremental r^2	Total r^2
1. Tardive dyskinesia (TD) criterion level 2		
Maximum dose of neuroleptic (log)	.036*	.036*
Fluphenazine decanoate	.027*	.062†
Age	.043†	.106†
Grandiose delusions	.031*	.137‡
Teeth or denture problems	.023*	.160‡
2. TD criterion level 3		
Number of neuroleptics	.028*	.028*
Low-potency neuroleptics§	.036*	.064†
Thiothixene	.024*	.088†
Sum of SEE scores‖	.100‡	.188‡
Age	.055†	.244‡
Incoherence	.033*	.277‡
Teeth or denture problems	.022*	.299‡
3. Sum of AIMS scores (TD severity)‖		
Maximum dose of neuroleptic (log)	.061†	.061†
Number of neuroleptics	.017*	.079†
Haloperidol	.040*	.118‡
Fluphenazine decanoate	.036*	.154‡
Sum of SEE score‖	.126‡	.280‡
Age	.053†	.333‡
Grandiose delusions	.018*	.351‡
Teeth or denture problems	.019*	.370‡

*$P < .05$.
†$P < .01$.
‡$P < .001$.
§Negatively correlated.
‖SEE indicates Scale for Extrapyramidal Effects; AIMS, Abnormal Involuntary Movement Scale.

independent variables. The first included neuroleptic dose and exposure factors: (log) maximum dose, (log) total dose, number of neuroleptics taken, and duration of treatment with neuroleptics. The second set included the type of neuroleptic used, divided into eight individual drugs—chlorpromazine hydrochloride, thioridazine hydrochloride, trifluoperazine hydrochloride, perphenazine, fluphenazine hydrochloride, fluphenazine decanoate, thiothixene hydrochloride, and haloperidol—and two drug groups—low potency (chlorpromazine and thioridazine) and high potency (the other six). The third set contained significant demographic and clinical variables, including age, past hospitalizations, grandiose delusions, incoherence, neuroses, probable RDC schizophrenia or schizoaffective disorder, total SEE score, and problems with teeth or dentures. Sex and psychotic depression were also included on the chance that they might emerge as significant variables once suppressing intercorrelations were removed.

The sets were then regressed against the dichotomous dependent variable of TD at criterion level 2. Any significant variables were carried into the next set and entered into the equation first. A significant association for a particular variable then had to be demonstrated over and above the effects of the earlier ones. The results are shown in Table 4, group 1. The discriminant function was then calculated, using the simultaneous MRA model, with the five variables that entered into the equation after the stepwise MRA. We were able to classify correctly 70% of the patients using the discriminant function. Since we could expect to classify 57% correctly by chance alone, the results, although significant, were not impressive. However, we could correctly identify 60% of the patients with TD, as opposed to a chance expectation of 32%.

Using the same variables, ordered in the same sets, a second MRA was performed using the dichotomous dependent variable of TD at criterion level 3 (Table 4, group 2). When we calculated the discriminant function with the seven variables that entered into the equation after the stepwise MRA, we were able to classify 92% of the patients correctly, with the chance expectation being 81%. We could, however, correctly identify 63% of the patients with moderate TD, as opposed to a chance expectation of only 10%.

Finally, using the measure of TD severity—the total AIMS score—as the dependent variable, a third stepwise MRA was performed (Table 4, group 3).

COMMENT

Compared with those in most studies, our sample was unusual in certain respects: one third of the patients had no history of psychiatric hospitalization; none had a history of repeated long-term institutionalizations; none was undergoing neuroleptic withdrawal; and, in semistructured interviews, half of them did not meet RDC criteria for schizophrenia or schizoaffective disorder.

As might be expected, the prevalence rate was a function of the criterion level for inclusion. At a criterion level of 2 on AIMS, 47 patients (30.7%) were found to have TD. When minimal scores were included, the prevalence rose to 70 (45.8%). The latter figure is similar to those in two outpatient studies[9,11] in which patients with minimal scores were included. It was interesting to note the absence of severe involvement of any of the body areas in our patients. A similar finding was recently reported in a study of Hungarian outpatients.[25] Our finding may be related to our sample's lack of elderly patients, who have been reported to be more prone to severe TD.[18] Moreover, 16 of the 47 patients with TD, at the criterion 2 level, showed significant concomitant parkinsonism. This may have partially masked the TD severity, as parkinsonism and TD are assumed to have an inverse pharmacologic relationship.[35-37]

Age was found to be significantly correlated with TD prevalence and severity in the MRAs, irrespective of criterion levels used for inclusion. Sex, however, was not a significant variable. This, as others have suggested,[27] could be related to the lower age of our sample, with only three patients over 70 years of age.

There was a significant correlation between TD and parkinsonism. Even though the two syndromes are assumed to be reciprocally related pharmacologically, their coexistence has been reported.[12,30,36,37,38] It has been suggested[38-40] that TD is more likely to develop in patients with parkinsonism than in those without, and that this association may have a predictive or etiologic significance.

Although duration of exposure to neuroleptics and consistency of use failed to show significant associations, the group with TD had histories of exposure to higher doses of neuroleptics, greater numbers of them, and higher mean total doses. Although the use of MRA may have accentuated one or the other of these variables, they were all highly intercorrelated. Chance may have emphasized the effect of one over the other. Of the individual drugs, fluphenazine decanoate stood out as a discriminator for both TD prevalence and severity. This is in accordance with several recent reports[11,17,24,29,30] and raises questions about the routine use of depot preparation of fluphenazine. High-potency neuroleptics in general were significantly corre-

ated with TD measures in the MRAs, although most were o strongly intercorrelated that it may have been a random peration that caused a particular drug to enter into the quation at the exclusion of the others. We were unable to uplicate the findings of two discriminant function analysis reports[24,25] of low-potency neuroleptics contributing to he risk of TD. On the contrary, the use of low-potency neuroleptics was negatively correlated with TD (criterion evel 3) in the MRA in our study.

The correlation of a history of grandiose delusions with TD is difficult to explain. We could not find any previous reports of this association in the literature. However, some recent reports[41-44] have suggested that patients with affective disorders may be a high-risk group for TD. In subsequent SADS-Lifetime interviews, ten of the 15 patients with histories of grandiose delusions were found to meet RDC for bipolar disorder. We are examining this association further. Problems with teeth or dentures consistently appeared as a significantly associated variable in the MRAs. This area needs further study, as dental problems, with consequent proprioceptive input, may contribute to the genesis or maintenance of orofacial or lingual dyskinetic movement disorders.

Our findings suggest that TD in an outpatient population is quite common, but that the degree of involvement is milder than that seen in patients undergoing long-term hospitalization, in whom psychosis-associated changes may be a contributing factor. As Bebbington[45] has pointed out, caution should be exercised in making causal interpretations. Our findings suggest that exposure to neuroleptics is necessary but not sufficient for the development of TD. It appears that TD results from multiple variables acting simultaneously and/or sequentially as moderating or confounding variables. As this study was based on point ratings, it does not allow discrimination between persistent and reversible dyskinesia. However, until the various factors involved in the genesis and outcome of TD are better understood, it would be prudent to limit the use of neuroleptics to conditions where definite indications and evidence of benefit exist, as has been recommended by the American Psychiatric Association's Task Force on TD.[3] We believe that the routine use of high doses of high-potency neuroleptics should be avoided, and the use of depot fluphenazine should be limited to those cases where neuroleptics are definitely indicated and compliance with oral medication is a problem.

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