Tardive Dyskinesia in Psychiatric Outpatients

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

Sukdeb Mukherjee, MD; Arnold M. Rosen, MD; Carlos Cardenas, MD; Virendra Varia, MD; Silvia Olarte, MD

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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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, high-potency neuroleptics, low-potency neuroleptics, use of antiparkinsonian drugs, and use of depot fluphenazine. However, other studies have failed to find an association between TD and duration of neuroleptic exposure or any particular neuroleptic or use of antiparkinsonian drugs.

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, 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 assess or control.

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, 163 patients were examined.

The mean age of the sample was 49.9 years (SD, 10.74 years); of the 112 women, 50.76 years (SD, 9.33 years); and of the 41 men, 45.97 years (SD, 13.08 years). Of the 163 patients, 62 (34%) had no history of psychiatric hospitalization, 38 (64%) had histories of hospitalizations for acute disorders, and 23 (18.3%) had histories of state hospitalizations of less than one year. Of the 101 with histories of hospitalization, the mean number of emergency...
Patients were examined for TD using the Abnormal Involuntary Movement Scale (AIMS) developed by the Psychopharmacology Branch of the National Institute of Mental Health,11 and variously reported to be reliable.11 The AIMS records the presence and severity of abnormal movements in seven body areas: facial muscles, lips, and perioral areas, jaw, tongue, upper extremities, lower extremities, and trunk. For each body area, movements are scored on a five-point severity scale in which 0 indicates no, 1 minimal (may be borderline normal); 2 mild; 3, moderate; 4 severe. Overall severity of abnormal movements, incapacitation resulting from movements, and the patient’s reported awareness and distress related to the abnormal movements are rated on a scale of 0 to 4. Presence of dentures and problems with dentures were also noted.

Patients were then examined for signs of parkinsonism and athetosis, by means of the Scale for Extrapyramidal Effects (SEE),12 which measures ten extrapyramidal signs: gait, arm appying, shoulder shaking, elbow rigidity, wrist rigidity, leg rigidity, head dropping, globella tap, tremor, and saliva- tion. To these signs we added a rating for akathisia. Each item was rated on a five-point scale, with 0 meaning the absence of a sign and 4 its extreme form.

After the ratings, patients were asked for the following information: years of medication therapy, number of periods without drugs lasting three months or more; and histories of acute stotnia, parkinsonism, akathisia, or anticholinergic effects. Data, in several of the studies on the Schedule for Affect Disorders and Schizophrenia (SADS), patients were asked about past or present symptoms suggesting diagnoses of schizophrenia or schizoaffective disorder by Research Diagnostic Criteria (RDC).13

The patients were examined by one of two raters, each of whom examined about half of the total sample. Then, the other rater, aware of the examination findings, reviewed the patient’s spinal records for demographic data, all diagnoses, psychotic symptoms noted at any time, previous treatment history, and presented side effects of medication. Detailed drug history was recorded for the past eight years, including individual drugs, daily dosages, and duration of treatment with each drug and dosage. Drugs prescribed for less than one month were excluded. Recorded data included neuroleptics, antiparkinsonian drugs, and antide- pressants. The rater examining a patient had no access to the examination findings, the examination, findings, the patient’s records, or the patient’s previous treatment history.

RESULTS

Prevalence of TD

The assessment of TD prevalence was based on the AIMS scores.14 AIMS gave three measures of involvement: individual subtest scores of the seven body areas; a total score, which was the sum of the seven body areas; and a global severity rating. A criterion level of TD was based on the individual subtest scores. It was defined as the minimum score the patient had to have on at least one of the subtests to qualify as having TD. The prevalence of TD at different criterion levels is shown in Table 1.

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

<table>
<thead>
<tr>
<th>Criterion Level</th>
<th>Total</th>
<th>Male Patients</th>
<th>Female Patients</th>
<th>M-F Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 (minimal)</td>
<td>45.8</td>
<td>48.8</td>
<td>45.6</td>
<td>0.91</td>
</tr>
<tr>
<td>2.0 (mild)</td>
<td>30.6</td>
<td>30.7</td>
<td>34.1</td>
<td>2.02</td>
</tr>
<tr>
<td>3.0 (moderate)</td>
<td>10.1</td>
<td>9.8</td>
<td>10.7</td>
<td>1.09</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean Total AIMS Scores</th>
<th>t</th>
<th>df</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalizations</td>
<td>2.73</td>
<td>1.46</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Grandiose delusions</td>
<td>4.93</td>
<td>1.99</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Incoherence when psychotic</td>
<td>3.40</td>
<td>1.60</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>5.10</td>
<td>1.88</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Akathisia</td>
<td>6.14</td>
<td>1.83</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Dystonic reactions</td>
<td>5.57</td>
<td>1.65</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Psychotic depression</td>
<td>4.18</td>
<td>2.13</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Neuroses</td>
<td>0.80</td>
<td>2.35</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>RDC schizophrenia or schizoaffective disorder</td>
<td>2.76</td>
<td>1.76</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Teeth or denture problems (AIMS)</td>
<td>4.25</td>
<td>1.95</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

Other psychiatric symptoms, diagnoses, and side effects, histories of emergency or state hospitalizations, electroconvulsive therapy, antiparkinsonian or antidepressant drugs, and sex were not significant (P > 0.07).

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

The number of significant variables was reduced with a stepwise multiple regression analysis (MRA). There were three sets of variables analyzed using t tests to compare mean AIMS scores, and correlation coefficients were calculated for the 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 (χ² = 4.89; χ² = 1; P = 0.03). This correlation became stronger when the continuous variables—total AIMS and total SEE scores—were used. Their product moment correlation was −0.465 (P < .0001), highly significant and accounting for more than 21% of the variance between the two scores.

Multivariate Analyses

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Multivariate Analyses

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independent variables. The first included neuroleptic dose and exposure factors (log maximum dose, 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, hydrochloro, thiophene,
thiothixene, haloperidol, and two drug groups—low and high
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, probability of RDC schizophrenia or
schizoaffective disorder, total SEE score, and problems with teeth
and dentures. Sex and psychotic depression were also included on
fluoxetine hydrochloride, fluphenazine decanoate, thiothixene

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%.

When the same variables used in the previous analysis, the second
MRA was performed using the dichotomous dependent variable of
TD at criterion level 3 (Table 4, group 3). When we calculated the
discriminant function with the seven variables that entered into
the three stepwise MRA, we were able to classify 32% of the
criteria correctly, with the chance expectation being 32%. We
could, therefore, 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 semistruc-
tured 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 (30.1%) 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 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. Our finding may be related to our sample’s lack of the
treatment of elderly patients. We have reported to be more prone to severe TD. 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.

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, 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. It has been
suggested 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 MRAs may have accentuat-
ed 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 preva-
lence and severity. This is in accordance with several
recent reports and raises questions about the routine
use of depot preparation of fluphenazine. High-
potency neuroleptics in general were significantly corre-
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