Tardive Dyskinesia—Diagnostic Issues, Subsyndromes, and Concurrent Movement Disorders: A Study of State Hospital Inpatients Referred to a Movement Disorder Consultation Service


Abstract

Of 49 state hospital patients referred for movement disorder consultation for tardive dyskinesia (TD), 11 (23.9%) of 46 meeting inclusion criteria had movement disorders other than TD. These other disorders led to a false diagnosis of TD in 6 subjects (12.2%). Between-day dyskinesia variability affected TD ascertainment in only 3.2 percent of subjects. Prevalences of other neurological conditions in the 30 patients identified with definite TD were parkinsonism (90%), dystonia (25%), akathisia (16%), cerebellar signs (40%), dysmetria (23%), cerebellar tremor (17%), tardive dystonia (3.3%), and tardive akathisia (3.3%). Concurrence rates of parkinsonism with TD varied significantly according to which clinical signs were used to define parkinsonism. Using a rating score threshold of at least mild, rigidity occurred in 79.3 percent, bradykinesia in 55.2 percent, and resting tremor in 41.4 percent of subjects with TD; more significant rigidity occurred in 41.4 percent, bradykinesia in 31.0 percent, and resting tremor in 20.7 percent. Concurrence rates of neurological conditions with TD subsyndromes were distributed rather evenly according to condition prevalences, except for an association of cervicotruncal TD with bradykinesia (perhaps because of ventromedial striatal presynaptic and postsynaptic D2 blockade, respectively). These findings, as well as the occurrence of equal gender ratio and relative underrepresentation of bipolar and alcohol disorders in subjects with definite TD, are discussed.

Keywords: Tardive dyskinesia, parkinsonism, dystonia, akathisia, cerebellar signs, tremor.


Tardive dyskinesia (TD) has been a major concern in patients receiving antipsychotics. This is especially true in state hospitals, where many patients have psychotic disorders or psychotic manifestations requiring long intervals of treatment with antipsychotics. While TD may be becoming less of a risk with the advent of atypical antipsychotics, it is still of concern. Moreover, as the incidence of TD declines in the context of these newer drugs, the differential diagnosis of these movements becomes even more important in correctly determining movement disorder etiology. Some of these etiologies have important neuropsychiatric morbidities (e.g., Huntington's disease).

Although TD has been extensively studied, the present study offers a unique perspective and reports findings from a diagnostic consultation service. There are few studies in the literature that examine TD from the vantage point of a movement disorder consultation service. We are not aware of any consultation service studies that simultaneously and systematically determine alternative movement disorder diagnoses, distinct anatomical TD subsyndromes, specific features of parkinsonism, comprehensive concurrence rates of various movement disorders and cerebellar signs, and clinical correlates of both TD subsyndromes and movement disorders, including negative and positive symptoms of schizophrenia. Yet such information could enhance diagnostic assessment and improve our understanding of TD.

The authors were asked to provide diagnostic consultation for patients with suspected TD. Because dyskinesia variability (Kane et al. 1992) and alternative diagnoses that simulate TD complicate diagnostic assessment, study of the clinical impact of these confounding factors upon...
TD diagnosis was undertaken. The concurrence rates of other extrapyramidal syndromes and cerebellar signs with TD anatomical subsyndromes as well as the clinical correlates of these TD subsyndromes were also determined. Beyond its clinical utilities, identifying associations of TD with other motor signs may reveal additional clues to neural circuit pathophysiologies in TD.

We therefore assessed the following hypotheses: (1) between-day variability in TD significantly reduces clinical ascertainment when patients are evaluated for TD on 2 different days; (2) detailed clinical assessment using blinded examination and blinded chart review for alternative etiologies of movement disorders leads to a diagnosis other than TD in a significant number of cases; (3) the frequencies of association between various parkinsonian signs (e.g., rigidity and tremor) with TD differ significantly; and (4) various TD subsyndromes are associated with specific patterns of concurrent neurological conditions (i.e., parkinsonian rigidity, bradykinesia, tremor, dystonia, akathisia, terminal kinetic tremor, and dysmetria).

Methods

One of us (S.D.S.) reviewed Abnormal Involuntary Movements Scale (AIMS, American Psychiatric Association 1992) scores for the presence and severity of abnormal movements in 620 randomly selected patients at a 1,320-bed state hospital facility in Georgia. Hospital policy required annual AIMS assessments on all patients. Each chart was also reviewed for neuroleptic exposure and documentation of continued presence of abnormal movements. Fifty-four patients from an adult chronic inpatient ward were consecutively referred for consultation and chart review. Detailed scrutiny of the charts was employed; the investigator looked for medical conditions other than TD that are associated with movement disorders (Hyde et al. 1991; American Psychiatric Association 1987; Rodnitzky and Keyser 1992). Data from examination and chart review were then integrated (E.C.L. and W.G.C.) to determine the final diagnosis of TD. Features distinguishing TD from other movement disorders have been discussed elsewhere (Hyde et al. 1991; Rodnitzky and Keyser 1992).

After examinations on all patients had been completed, each subject's chart was then comprehensively reviewed with regard to admission evaluations, discharge summaries, consultation notes, laboratory studies, and medication records. Chart review was undertaken by an investigator (W.G.C.) blind to the findings of the examination protocol. Detailed scrutiny of the charts was reviewed; the investigator looked for medical conditions other than TD that are associated with movement disorders (Hyde et al. 1991; American Psychiatric Association 1992; Rodnitzky and Keyser 1992). Data from examination and chart review were then integrated (E.C.L. and W.G.C.) to determine the final diagnosis of TD. Features distinguishing TD from other movement disorders have been discussed elsewhere (Hyde et al. 1991; Rodnitzky and Keyser 1992).

The chart-blind examination protocol was sequenced as indicated above because the authors anticipated that some patients would become tired during the lengthy examination period (60-120 minutes). The benefit of this is that fatigue can sometimes elucidate movement disorders that otherwise would not be apparent. The disadvantage of fatigue is failure to complete all study items. Consequently, we structured the protocol so that movement disorders would be evaluated first, followed by psychiatric items. Completion rates for each protocol item were as follows: neurological exam, 94% (n = 46); movement disorder exam, 96% (n = 47); AIMS, 94% (n = 46);...
UPDRS, 96% (n = 47); DMS, 76% (n = 37); akathisia scale, 63% (n = 31); and BPRS, 29% (n = 14). Using these data, the authors considered the following: (1) the variable presence of dyskinesia on different days; (2) the reliability of the diagnosis of presumed TD prior to referral; (3) the form of the movements, TD anatomic distribution, and concurrence rates of other movement and neurological disorders with TD; and (4) the clinical correlates of certain movement disorder syndromes, including negative symptoms of schizophrenia.

Definitions and Diagnosis of TD. **Definite TD** was diagnosed if the patient showed movements consistent with TD to both examiners, if chart review did not evidence any alternative etiologies, and if the movements met the criteria of Schooler and Kane (1982). Additionally, the presence of choreoathetoid movements was required to determine a diagnosis of definite TD, in contrast to other tardive diagnoses such as tardive dystonia (requiring dystonic movements) and tardive akathisia (requiring akathismic movements). **Withdrawal TD** was excluded by review of medication records. **Presumptive TD** was diagnosed if TD movements were apparent to one rater (K.M.R.) but not the other and chart review findings were compatible with TD. **Possible TD** was diagnosed if choreoathetoid movements consistent with TD were observed by both raters and chart review findings were compatible with TD but other causes of dyskinesia could not be definitively excluded. **Questionable TD** was diagnosed if movements were not seen by either examiner but TD-like movements previously had been documented in the chart.

Variability of Dyskinesia on Different Days. Agreement between the two raters on 2 different days as to the presence or absence of movements resembling TD for the 49 subjects was determined. The authors computed the rate of agreement for subjects with **presumptive TD**.

Reliability of the Diagnosis of TD Prior to Referral. The authors determined movement disorder diagnoses for the 49 subjects using evidence of medical and neurological disease taken from the chart (admission assessments, discharge summaries, consultant notes, laboratory studies, medications other than neuroleptics, etc.) and the neurological and movement disorder examinations. This information was integrated to verify the presence or absence of **definite TD**.

Movement Form, TD Anatomic Distribution, and Movement Disorder Prevalence and Concurrence Rates. Movements were inspected for evidence of chorea, athetosis, parkinsonism, dystonia, akathisia, tremor, myoclonus, and other movement disorders. Prevalences were determined. The authors assessed the anatomic distribution of TD and the frequency of association of other movements in subjects with **definite TD**.

Concurrence rates between TD anatomical subsyndromes—oro-buccofaciolingual (OBFL), upper extremity, lower extremity, and cervicotorcular—and extrapyramidal syndromes (parkinsonism, dystonia, and akathisia) and cerebellar signs (terminal kinetic tremor and dysmetria; no subjects had ataxia or dysdiadochokinesia) were determined. Because parkinsonism can be defined in various ways (by degree of symptom severity and by number of cardinal features), the authors determined neurological concurrence rates for subjects with at least mild features (UPDRS item score > 1) and for those with more severe features that were definitely present without activation procedures (UPDRS item score > 1). Concordance rates were determined for these different severity levels of rigidity, bradykinesia, and resting tremor. In summary, we evaluated concurrence rates of each neurological condition with each TD subsyndrome.

Hypothesis Testing. Hypothesis 1 was evaluated by comparing the rate of cases of definite TD determined by the two raters on 2 different days to the rate of cases of definite TD determined by the single rater on a single day. Hypothesis 2 was tested by comparing the rate of definite TD cases in the original sample of 49 subjects referred for consultation to the rate of definite TD cases in the 30 subjects completing consultation. Hypothesis 3 was evaluated by comparing the concurrence rates of parkinsonism rigidity with parkinsonian resting tremor among subjects with definite TD. McNemar's test (Fleiss 1981) was used to evaluate hypotheses 1, 2, and 3 because data were paired (95% confidence intervals are presented to assess differences in evaluations). The alpha level was adjusted from 0.05 to 0.0167 as appropriate for the three hypotheses assessed using this statistical test. Hypothesis 4 was assessed by means of odds ratios. Odds ratios with 95% confidence intervals were determined for associations in which the frequency of the neurological condition in a particular TD subsyndrome varied by at least 20 percent from the frequency of the neurological condition in the overall sample of subjects with definite TD. Because some cell sizes were less than five, odds ratios were then tested for significance using Fisher's exact test. The alpha level was adjusted from 0.05 to 0.0167 as appropriate for the three odds ratios assessed using this statistical test.

Results

Variability of Dyskinesia on Different Days (Hypothesis 1). Between-day variability in TD did not significantly reduce clinical ascertainment when patients were evaluated
for TD on 2 different days (30/31 vs. 31/31; McNemar's test $\chi^2 = 0.0$, $df = 1$, $p = 1.00$; 95% confidence interval for the difference between evaluations was $[-0.031, 0.095]$). The two raters agreed on the presence of movements consistent with TD in all but one subject (30 of 31, 96.8%). In this single unconfirmed case, movements suggestive of TD were seen by only one examiner.

**Reliability of the Diagnosis of TD Prior to Referral (Hypothesis 2).** Detailed clinical assessment using blinded examination and blinded chart review for alternative etiologies of movement disorders led to a diagnosis other than TD in a significant number of cases (30/49 vs. 30/30; McNemar's test $\chi^2 = 17.05$, $df = 1$, $p = 0.00004$; 95% confidence interval for the difference in diagnosis was $[0.252, 0.524]$).

Integrating the blinded chart and examination data, the authors determined movement disorder diagnoses for the 49 subjects as detailed in table 1. Among the 30 subjects with confirmed TD, the mean age was 62.43 ± 14.60 years, and there were 15 women and 15 men. AIMS scores averaged 16.59 ± 4.69. The mean duration of movements was 56.87 ± 80.82 months (range 5–248 months). Mean duration of neuroleptic exposure was 224.60 ± 130.42 months (range 18–518 months). Three subjects had been on neuroleptics for less than 1 year. Seven were off antipsychotics when evaluated, but all had been on neuroleptics previously. Chart diagnoses for the 30 subjects included 24 with schizophrenia (14 chronic undifferentiated type, 5 chronic paranoid type, 3 catatonic type, 2 residual type) and 1 with delusional disorder. Other diagnoses sometimes overlapping with psychotic and mood disorders included primary degenerative dementia (5), mental retardation (7), and alcohol abuse (1). No subject carried a diagnosis of organic mood disorder, schizoaffective disorder, bipolar disorder, or anxiety disorders, in contrast to the original sample of 49 subjects. There were no significant differences between these 30 subjects and the original 49 subjects for any of the above variables (i.e., age, AIMS scores, movement duration, neuroleptic exposure, current administration of antipsychotics, or diagnoses) except for nonsignificant trends toward less bipolar disorder ($p = 0.08$) and alcohol abuse ($p = 0.05$) in subjects with TD (Fisher's exact test). However, among the 30 subjects with TD, men were younger than women (age $56.73 ± 13.40$ vs. $68.13 ± 13.88$ years, $t = -2.289$, $df = 28$, $p = 0.03$) and tended to have a shorter course of TD ($20.43 ± 23.87$ vs. $51.67 ± 63.88$ months, Mann Whitney $U = 63.0$, $p = 0.066$).

**Movement Form, TD Anatomic Distribution, and Movement Disorder Prevalence and Concurrence Rates (Hypotheses 3 and 4).** The frequencies of association between various parkinsonian signs with TD differed

### Table 1. Movement disorder diagnoses in the 49 subjects

<table>
<thead>
<tr>
<th>Condition</th>
<th>Subjects (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original sample</td>
<td>49</td>
</tr>
<tr>
<td>Subjects refusing neurological exam</td>
<td>2</td>
</tr>
<tr>
<td>TD not confirmed by second examiner</td>
<td>1</td>
</tr>
<tr>
<td>Subjects eligible for diagnosis of TD</td>
<td>46</td>
</tr>
<tr>
<td>Definite TD</td>
<td>30</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
</tr>
<tr>
<td>Moderate</td>
<td>2</td>
</tr>
<tr>
<td>Mild</td>
<td>22</td>
</tr>
<tr>
<td>Minimal</td>
<td>6</td>
</tr>
<tr>
<td>Possible TD (confirmed by 2 examiners and chart review)</td>
<td>5</td>
</tr>
<tr>
<td>Possible edentulous dyskinesia</td>
<td>2</td>
</tr>
<tr>
<td>Possible post–infarct dyskinesia</td>
<td>2</td>
</tr>
<tr>
<td>Possible post–head trauma or –hepatic dyskinesia</td>
<td>1</td>
</tr>
<tr>
<td>Questionable TD (not seen by either examiner but suggested by chart documentation)</td>
<td>5</td>
</tr>
<tr>
<td>Movement disorder other than TD (confirmed by 2 examiners and chart review)</td>
<td>6</td>
</tr>
<tr>
<td>Huntington's disease</td>
<td>2</td>
</tr>
<tr>
<td>Hyperthyroid chorea</td>
<td>1</td>
</tr>
<tr>
<td>Anticonvulsant-related chorea</td>
<td>1</td>
</tr>
<tr>
<td>Senile dyskinesia</td>
<td>2</td>
</tr>
</tbody>
</table>

Note.—TD = tardive dyskinesia.
significantly (23/29 vs. 12/29; McNemar’s test $\chi^2 = 7.69$, df = 1, $p = 0.0055$; 95% confidence interval for the difference between rigidity and tremor is [0.215, 0.543]). Various TD subsyndromes were not associated with specific patterns of concurrent neurological conditions (the only association found was bradykinesia with cervicotorcular TD).

Rating scale completion rates for the 30 subjects with definite TD were clinical neurological exam, 30 (100%); AIMS, 30 (100%); UPDRS, 29 (97%); DMS, 24 (80%); akathisia scale, 19 (63%); and BPRS, 10 (33%). The anatomic distribution of choreoathetoid dyskinesia in the 30 subjects with definite TD and point prevalences are shown in table 2. OBFL dyskinesia was present in some form in nearly all subjects, with upper extremity involvement in two-thirds, lower extremity involvement in nearly half, and axial (cervicotorcular) TD in about one-quarter (exact percentages given in table 2). Among OBFL components, lingual dyskinesia occurred in most, perioral in half, mandibular in one-third, and facial in one-fifth of the 30 subjects (exact percentages given in table 2). There were no significant differences in concurrence rates between the various TD subsyndromes.

Disorders associated with TD (table 2), from most common to least common, were parkinsonism, dystonia, cerebellar dysmetria, terminal kinetic tremor, akathisia, tardive akathisia, and tardive dystonia. Parkinsonism occurred in most subjects, dystonia was infrequent (often occurring with parkinsonism), and akathisia was rare. Among parkinsonian features, rigidity was most common, followed by bradykinesia, and then tremor (table 2). Twenty-seven subjects with definite TD consented to the clinical evaluation of movement disorders other than TD, parkinsonism, dystonia, and akathisia. Of these, none

Table 2. Choreoathetoid TD syndromes: Anatomical distribution in 30 subjects with definite TD

<table>
<thead>
<tr>
<th>Condition</th>
<th>Subjects$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tardive dyskinesia (n = 30 of 30 definite TD subjects assessed)</td>
<td>30 (100.0%)</td>
</tr>
<tr>
<td>Orofaciolingual</td>
<td>29 (96.7%)</td>
</tr>
<tr>
<td>Facial</td>
<td>6 (20.7%)</td>
</tr>
<tr>
<td>Perioral</td>
<td>14 (48.3%)</td>
</tr>
<tr>
<td>Mandibular</td>
<td>11 (37.9%)</td>
</tr>
<tr>
<td>Lingual</td>
<td>25 (86.2%)</td>
</tr>
<tr>
<td>Upper extremity</td>
<td>20 (66.7%)</td>
</tr>
<tr>
<td>Lower extremity</td>
<td>14 (46.7%)</td>
</tr>
<tr>
<td>Cervicotorcular</td>
<td>7 (23.3%)</td>
</tr>
<tr>
<td>Parkinsonism (n = 29 of 30 definite TD subjects assessed)</td>
<td>26 (89.7%)</td>
</tr>
<tr>
<td>Rigidty (UPDRS ratings &gt; 0)</td>
<td>23 (79.3%)</td>
</tr>
<tr>
<td>(UPDRS ratings &gt; 1)</td>
<td>12 (41.4%)</td>
</tr>
<tr>
<td>Bradykinesia (UPDRS ratings &gt; 0)</td>
<td>16 (55.2%)</td>
</tr>
<tr>
<td>(UPDRS ratings &gt; 1)</td>
<td>9 (31.0%)</td>
</tr>
<tr>
<td>Resting tremor (UPDRS ratings &gt; 0)</td>
<td>12 (41.4%)</td>
</tr>
<tr>
<td>(UPDRS ratings &gt; 1)</td>
<td>6 (20.7%)</td>
</tr>
<tr>
<td>Rigidity + bradykinesia (UPDRS ratings &gt; 0)</td>
<td>14 (48.3%)</td>
</tr>
<tr>
<td>(UPDRS ratings &gt; 1)</td>
<td>4 (13.8%)</td>
</tr>
<tr>
<td>Rigidity + bradykinesia + tremor (UPDRS ratings &gt; 0)</td>
<td>8 (27.6%)</td>
</tr>
<tr>
<td>(UPDRS ratings &gt; 1)</td>
<td>2 (6.9%)</td>
</tr>
<tr>
<td>Dystonia (n = 24 of 30 definite TD subjects assessed)</td>
<td>6 (25.0%)</td>
</tr>
<tr>
<td>Akathisia (n = 19 of 30 definite TD subjects assessed)</td>
<td>3 (15.8%)</td>
</tr>
<tr>
<td>Cerebellar signs (n = 30 of 30 definite TD subjects assessed)</td>
<td>12 (40.0%)</td>
</tr>
<tr>
<td>Dysmetria</td>
<td>7 (23.3%)</td>
</tr>
<tr>
<td>Terminal kinetic tremor</td>
<td>5 (16.7%)</td>
</tr>
</tbody>
</table>

Note.—TD = tardive dyskinesia; UPDRS = Unified Parkinson Disease Rating Scale.

$^1$ The numbers and percentages of patients with movement disorders and their subsyndromes. Percentages are proportions of the number of subjects actually assessed for each feature.
manifested myoclonus or action-postural tremor. Tardive
dystonia and tardive akathisia each occurred in one sub-
ject, coexisting in the same patient. Other tardive phe-
nomena reported in the literature (tardive parkinsonism,
ymyoclonus, tremor, tic) were not apparent in this sample.
Some of the seven subjects off antipsychotics had TD and
parkinsonism, but none had dystonia or akathisia.

Concurrence rates of parkinsonism often varied by an
order of magnitude, depending upon how parkinsonism
was defined (table 2). In general, rigidity was most com-
mon, followed by bradykinesia and then resting tremor.
Except for bradykinesia, concurrence rates of neuro-
logical features did not significantly differ between the
various TD subsyndromes. Only three neurological condi-
tions met the criterion for odds ratio examination of their
relationship to TD subsyndromes. Each of these three
conditions varied by 20 percent from expected rates in
only one TD subsyndrome, cervicotruncal TD. Odds
ratios were determined for dystonia (odds ratio = 4.00,
95% confidence interval 0.42–37.78, p = 0.25), bradyki-
nesia > 1 (odds ratio = 11.2, 95% confidence interval
1.6–80.3, p = 0.0164), and tremor > 0 (odds ratio = 0.17,
95% confidence interval 0.017–1.62, p = 0.11). The asso-
ciation of bradykinesia with cervicotruncal TD remained
significant after Bonferroni correction of the alpha level to
0.0167.

Discussion
In contrast to previous cross-sectional studies of state hos-
pital patient populations, this study provides the perspec-
tive of a movement disorder consultation service within a
state hospital. Ascertainment methodology involved a
blinded, lengthy, and comprehensive neuropsychiatric
assessment coupled with a blinded chart review. Interrater
agreement was high. The findings of this study should be
interpreted in light of several considerations. First,
although a large number of studies have considered the
relationship of other movement disorders to TD in a vari-
ety of different patient populations and clinical settings,
there appear to be no studies of patients selected for possi-
ble TD from movement disorder consultation services in
psychiatric hospitals. Thus, the study appears to be unique
and is not strictly comparable with the extant literature.
Some studies have addressed movement disorder preva-
lences in special populations incomparable to that of the
present study, including children (Richardson et al. 1991),
patients with particular diagnoses such as mental retarda-
tion (Rao et al. 1987) or affective disorders (Ghadirian et
al. 1996), patients on specific drugs (multiple studies),
and normal community populations (Green et al. 1993).
Second, patients were referred for evaluation of suspected
TD. This limits somewhat the generalizability of these
results to state hospital populations, because the study is
not strictly cross-sectional in nature. Third, most patients
in this study suffered mild dyskinesia, making the results
most relevant to patients with relatively less severe TD.
Fourth, all 49 subjects were right-handed, perhaps point-
ing to a somewhat atypical sample. There were, however,
more women than men and the mean age of the subjects
was 64 years, consistent with findings in other studies of
TD (Casey 1990; Morgenstern and Glazer 1993). The
average duration of suspected TD was 5 years but varied
considerably, consistent with what one might expect to
find in a state hospital population. Moreover, the duration
of chronic neuroleptic exposure and the array and fre-
quency of psychiatric diagnoses are also representative
of state hospital populations. Thus, overall, the features
of the sample are consistent with state hospital populations.
Fifth, the examination procedure was rather long, which
enhanced our ability to identify movement disorders. This
rigorous, blinded ascertainment methodology coupled
with blinded comprehensive chart reviews may reduce the
comparability of the findings to studies that employ only a
brief AIMS exam. Indeed, previous work has demon-
strated that methodological and observational rigor can
more than double ascertainment rates for TD and parkin-
sionism (Hansen et al. 1992a). Finally, the lengthy pro-
dure also reduced the sample sizes for some of the rating
scale assessments (dystonia and akathisia), because some
patients became tired by this point in the protocol. The
findings must be viewed in light of the limited size of the
sample and the special considerations enumerated above.

Hypotheses. The findings of this study suggest that
between-day variability in TD has little impact in case
ascertainment when patients are assessed in detailed fash-
ion. Such evaluation, however, identifies a significant
number of false positive TD cases, indicating the merits
of careful neurological examination and review of the past
medical history and laboratory data. Concurrence rates for
parkinsonism in TD can vary significantly depending
upon what clinical signs are used to ascertain cases. Rates
of concurrent neurological conditions with various TD
subsyndromes appear to reflect their underlying preva-
lence, with the exception of an apparent association
between cervicotruncal TD and bradykinesia. Thus, most
concurrence rates appear to represent true comorbidity
rates (i.e., rates between independent disorders). Attention
to these details, apparent only on careful clinical assess-
ment, can influence clinical diagnosis as well as our
understanding of the nature of TD.

Variability of Dyskinesia on Different Days. Rater
agreement was 96.8 percent as to presence of TD. This
suggests reliable ascertainment of TD and clinically
in significant between-day variability in this study. This lack of clinically significant variability contrasts with previous studies documenting significant intrapatient variability in TD movements assessed clinically (Richardson et al. 1982) and instrumentally (Stanilla et al. 1996; Baca-Garcia et al. 1999). The study by Richardson et al. employed 8-minute frequency counts over 11 weeks in six patients and found the degree of variability significant enough to lead to a false negative diagnosis of TD. Bergen et al. (1984), however, found within-rater variability to dominate within-patient variability in clinically assessed TD. Instrumentally assessed TD studies indicate that diurnal fluctuation (Stanilla et al.), time since waking, TD severity, and smoking (Baca-Garcia) contribute to within-patient variability. In addition, factors other than natural fluctuations in dyskinesia could have operated in the present study to produce TD variability. Although not apparent to the initial rater who was present at both ratings, it is possible that subtle changes in psychiatric or medication status may have occurred between ratings. However, such changes between ratings would only serve to increase the variability of TD, making it even more difficult to achieve good interrater agreement. The potential operation of these factors only adds credence to the conclusion that between-day variability does not significantly reduce clinical ascertainment when patients are evaluated for TD on 2 different days. The duration of the examination in the present study allowed protracted assessment and patient fatigue, improving ascertainment reliability. This also occasionally led to observing movements not otherwise apparent. For example, one patient manifested dystonia only after 30 minutes of examination. Careful clinical assessment in this manner may contribute to the observation of minimal variability, contrasting with findings using more sensitive instrumental methods and shorter periods of assessment.

**Reliability of the Diagnosis of TD Prior to Referral.** Chart-blind examination and examination-blind chart review reduced the chances for potential bias in assessing movement disorders and chart data. Although chart diagnoses of TD can be notoriously unreliable (as demonstrated in table 1), we did not use chart data in this way. Rather, we used the chart to search for data supportive of movement disorder diagnoses other than TD. In this way, chart review improved the accuracy and specificity of TD diagnosis, although the duration of movements may have predated their documentation in the chart. Final integration of chart data with examination data can enhance diagnostic validity and reliability. Five subjects had movements that may have represented either TD or other conditions (Hyde et al. 1991; American Psychiatric Association 1992; Rodnitzky and Keyser 1992), including previous stroke, head trauma, non-Wilsonian hepatic cirrhosis, and edentulous dyskinesia (table 1). These findings highlight the need for careful vigilance about neuropsychiatric disorders that can lead to a false positive diagnosis of TD. Another six subjects had movement disorders other than TD, including Huntington's disease, hyperthyroid chorea, anticonvulsant-related chorea, and senile dyskinesia (table 1). Dyskinesias other than TD occurred in more than 20 percent of the sample, indicating that alternative attributions for dyskinesias besides TD should be considered in clinical populations, especially in subjects with mild TD as in the present sample. In addition to leading to proper diagnosis, exploration of alternative etiologies can lead to the elucidation of other conditions such as Huntington's disease and hyperthyroidism, which carry their own psychiatric morbidities.

**Sample Comparability: Equal Gender Ratio and Relative Absence of Bipolar and Alcohol Disorders in Definite TD.** Comparing the sample of 30 subjects with definite TD to the other 19 subjects of the original sample of 49, the equal number of males and females and the relative absence of bipolar and alcohol diagnoses among the 30 subjects with definite TD is striking. The equal sex ratio may relate to methodological differences (e.g., referral to study, ascertainment rigor, etc.) between this study and those employed in TD risk factor studies (Casey 1990). Referral bias in favor of males is possible because the only gender differences in definite TD were significantly younger age and a nonsignificant trend toward shorter TD duration in males. Nevertheless, females predominated in the original sample of 49 subjects, and earlier findings of female gender as a risk factor for TD may in part reflect inadequate exclusion of other movement disorders. Equal gender ratios and younger age and less neuroleptic exposure in patients with definite TD are consistent with previous findings. Studies of risk factors for TD in long-term outpatients (Morgenstern and Glazer 1993) and patients with minimal neuroleptic exposure (Harris et al. 1992) as well as a review of the African and Asian literature (Pandurangi and Aderibigbe 1995) have also found no significant effect of gender. Moreover, other studies in outpatients (Morgenstern et al. 1987; Joseph 1990), younger patients (van Os et al. 1999), and patients with minimal neuroleptic exposure (van Os et al. 1997) demonstrated that male gender rather than female gender was associated with TD. Female gender has actually been associated with less risk for TD in patients with minimal neuroleptic exposure (van Os et al. 1997). Subject age seems to affect gender-related risk for TD. In one study, TD severity was related to age in women but not in men (Moore et al. 1983), whereas in another study of subjects with TD aged 40 or younger, younger men were at risk for TD but women were not (Woerner et al. 1991). Thus, the findings of equal gender ratio and younger age and less
neuroleptic exposure in men with TD are consistent with previous findings in the literature, suggesting that younger men may be at particular risk for TD.

Affective disorders have been considered to represent a risk factor for TD (Rush et al. 1982; Wolf et al. 1987; Casey 1988; Kane et al. 1988; O'Hara et al. 1993; Kane 1999) and the absence of definite TD in the five subjects with bipolar disorders from the original 49 subjects is therefore surprising. The absence of bipolar disorders in subjects with TD may in part reflect multiple dyskinetic conditions in some subjects and TD variability in others: two subjects had “possible TD” (i.e., “definite TD” could not be diagnosed because the movements may have represented edentulous dyskinesia in one subject and poststroke dyskinesia in the other); one subject had “questionable TD” (not seen by either examiner but suggested by chart documentation); and two had no evidence of TD (other than referral to the study). It is possible that the two without evidence of TD may have had mood-dependent dyskinesias (Coleman 1989; Sandyk 1990) that were in remission at the time of the evaluation.

Similarly, the relative absence of alcohol disorders among subjects with definite TD is surprising, because alcohol disorders are also considered a risk factor for TD (Olivera et al. 1990; Dixon et al. 1992; Duke et al. 1994; Jeste et al. 1995; Paulsen et al. 1996; van Os et al. 1997). An alcohol disorder was documented in only one subject with TD (3.3%) in contrast to 12.25 percent of the initial 49 dyskinetic subjects, suggesting that careful screening of patients with alcohol diagnoses may elucidate sources of dyskinesia other than TD. O'Hara et al. (1993) actually found that recent use of alcohol was associated with lower AIMS total scores. One study found that alcoholism predicted TD in male patients with affective disorders (Wolf et al. 1987). Perhaps the absence of bipolar disorders in subjects with TD drove down the frequency of alcohol disorders in these subjects. Alternatively, rigorous exclusion of other movement disorders may contribute to the equal gender ratio and absence of bipolar and alcohol disorders in this study.

TD Anatomic Distribution. TD more commonly affected superolateral aspects of the body than inferoaxial aspects (table 2), consistent with previous observations in the literature (McCreadie et al. 1982; Altamura et al. 1990; Paulsen et al. 1996). Overall, the most frequent manifestations of TD were lingual and finger dyskinesia.

Neurological Condition Prevalence and Concurrency Rates. Myoclonus, tic, action-postural tremor, tardive parkinsonism, and tardive tremor were not encountered. Rates of tremor and all three parkinsonian signs were similar to those of Myslobodsky et al. (1986) in 49 patients with TD. Rates for bradykinesia with rigidity were substantially higher, likely due to lack of inclusion of isolated bradykinesia in ascertaining parkinsonism by Myslobodsky et al.

The authors are unaware of any studies that specifically and comprehensively determined prevalences and rates of concurrent parkinsonism, dystonia, akathisia, and cerebellar signs in patients with TD. Previous studies have examined the occurrence of movement disorders among samples of psychiatric patients without deliberately selecting for TD (Wolf et al. 1985; Grohmann et al. 1990; Hansen et al. 1992b; O'Hara et al. 1993; van Harten et al. 1996; Muscettola et al. 1999). Some have evaluated special populations of patients (Toenniessen et al. 1985; Rao et al. 1987; McCreadie et al. 1992). Other prevalence studies have looked at the sequelae of individual drugs. Still other studies have considered the prevalence of movement disorders in community samples not selected for psychiatric disorders (Green et al. 1993). In the present study, drug-induced parkinsonism was quite common, followed by dystonia and akathisia, which is similar to results seen in a sample of 1,107 psychiatric patients (Grohmann et al. 1990), despite methodological differences. Consistent with the high prevalence of parkinsonism in the present study, rates of TD and drug-induced parkinsonism were nearly identical in two studies of psychiatric inpatients (Hansen et al. 1992b; van Harten et al. 1996); TD was significantly associated with drug-induced parkinsonism in 141 psychiatric patients in day care (O'Hara et al. 1993) and 99 consecutive Department of Veterans Affairs male patients (Wolf et al. 1985). The prevalence of akathisia in the present study is similar to that of 194 inpatients with chronic psychiatric illnesses, where TD was present in 39.7 percent and akathisia occurred in 9.3 percent (van Harten et al. 1996). Akathisia was absent in patients with cervicotruncal TD in the present study, consistent with linkage of drug-induced akathisia to choreoathetoid orofacial and limb dyskinesia (Barnes and Braude 1985). Thus, although the methodology of the extant literature is not strictly comparable, the relative frequencies of TD, parkinsonism, dystonia, and akathisia are similar to those observed in the present study.

Concurrence rates of parkinsonism can vary by an order of magnitude, depending upon how parkinsonism is defined. Regardless, rigidity was most common, followed by bradykinesia and then tremor (table 2). Table 3 displays concurrence rates of movement disorders in patients with TD calculated from the reported literature. Van Harten et al. (1997) required at least mild tremor, rigidity, or bradykinesia; Hoffman et al. (1991) required at least mild ratings on two cardinal symptoms or moderate on one symptom; McCreadie et al. (1982) and Andreassen et
Table 3. Concurrence rates (%) of movement disorders in TD, from the literature

<table>
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<tr>
<th>Conditions</th>
<th>Studies&lt;sup&gt;1&lt;/sup&gt;</th>
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<tr>
<td>TD with P&lt;sup&gt;2&lt;/sup&gt;</td>
<td>(1) (2) (3) (4) (5) (6) (7) (8) (9) (10) (11) (12) (13)</td>
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<tr>
<td>TD with P&lt;sup&gt;3&lt;/sup&gt;</td>
<td>90 17 46 45 57 88</td>
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<td>TD with P&lt;sup&gt;2&lt;/sup&gt;</td>
<td>48</td>
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<tr>
<td>P with TD&lt;sup&gt;2&lt;/sup&gt;</td>
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<td>P with TD&lt;sup&gt;3&lt;/sup&gt;</td>
<td>100 57 53 57 73</td>
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<td>D with TD</td>
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<td>16 6.5</td>
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<td>A with TD</td>
<td>100 28</td>
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Note.—A = akathisia; D = dystonia; P = parkinsonism; TD = tardive dyskinesia.

<sup>1</sup> Columns refer to the following studies: (1) current study in 30 patients with TD, age 62.4 ± 14.6 yrs, 50% male; (2) van Harten et al. (1997) in 77 patients with TD, age 53.1 ± 16.7 yrs, 72.7% male; (3) McCreddie et al. (1982) in 26 patients with TD and schizophrenia living in Nithsdale; (4) Andreassen et al. (1997) in 51 Nithsdale patients with TD, age 57 ± 16 yrs, duration of illness 25 ± 16 yrs; (5) Myslobodsky et al. (1986) in 49 Caucasian chronic inpatients with TD, mean age 62.5, 51% male and 47% with organic brain disorder; (6) O'Hara et al. (1993) in 16 long-term psychiatric patients with TD, age 48.7 ± 14.4 yrs, 57.5% male; (7) Hoffman et al. (1991) in 30 patients with DSM-III-R akathisia; against age older than 55, treated with neuroleptics for at least 10 yrs, without previous neurological disease, including severe head injury; (8) subsample of 22 patients from (7); (9) subsample of (8) followed up 2–4 yrs later; (10) Gureje (1989) in 47 Nigerian psychiatric patients with TD showing the concurrence rates with tardive dystonia; (11) Raja & Azzoni (1996) in 42 consecutive psychiatric inpatients with TD, age 50.5 ± 13.3 yrs, 40% male; (12) Yassa et al. (1992) in 35 elderly patients with TD followed up 5 yrs after their first exposure to neuroleptics, showing the concurrence rate with tardive dystonia; (13) Ganesh et al. (1989) in 5 mentally retarded patients with chronic akathisia on neuroleptics for at least 3 yrs.

<sup>2</sup> Mild parkinsonism as criterion threshold for ascertaining cases.

<sup>3</sup> Moderate parkinsonism as criterion threshold for ascertaining cases.

al. (1997) required mild ratings on a global scale of parkinsonism; and Myslobodsky et al. (1986) determined parkinsonism as either present or absent. Given these definitions, the concurrence rates of TD with parkinsonism found by van Harten et al., McCreddie et al., Andreassen et al., and Myslobodsky et al. are lower than those of the present study, perhaps due to younger age in the van Harten et al. study, outpatient status in the McCreddie et al. and Andreassen et al. studies, and lack of inclusion of isolated bradykinesia in the Myslobodsky et al. study. In contrast, the concurrence rates of TD with parkinsonism of O'Hara et al. (1993) are higher despite much younger age. The concurrence rates of TD with parkinsonism of Hoffman et al. are also higher, perhaps due to more severe TD in their sample. Comparisons of concurrence rates of parkinsonism with TD, dystonia with TD, and akathisia with TD to those of the present study are not appropriate because our sample was selected for the presence of TD. Given the variance in prevalence of parkinsonism, which depends upon case ascertainment definitions, evaluation of a single sign should not be relied upon for ascertaining parkinsonism. The most valid ascertainment strategy requires vigilance for each of the cardinal parkinsonian signs.

The co-occurrence of parkinsonism and TD is to be expected because both occur with neuroleptic treatment. Whereas parkinsonism has been associated with dopaminergic insufficiency and chorea with dopaminergic excess, the relation of dopamine to chorea actually appears to be more complex, because the dopamine agonist apomorphine decreases chorea in Huntington's disease (Albanese et al. 1995). The presence of dystonia in patients with parkinsonism and choreothetotic movements (TD) is consistent with the ability of dystonia to occur both in parkinsonian conditions (e.g., Segawa's syndrome) and in choreiform disorders (e.g., Huntington's disease). Akathisia has similarly been observed in patients with TD (Ganesh et al. 1989; Sachdev 1993a and 1993b) as well as in patients with parkinsonism (Comella and Goetz 1994) and dystonia (Sachdev 1993a and 1993b).

Several anatomic subsyndromes of TD have been discriminated (Glazer et al. 1988; Gureje 1988; Kane et al. 1992; Paulsen et al. 1996; Muscettola et al. 1999). We therefore anticipated varying concurrence rates of neurological conditions for distinct TD subsyndromes, in contrast to the present findings in which the only association appeared to be bradykinesia with cervicotruncal TD. It is possible that the small sample size of this study obscured additional associations. Although other extrapyramidal syndromes and cerebellar signs were rather evenly distributed among TD anatomical subsyndromes according to their prevalences, it remains possible that larger samples may identify selective associations. Nevertheless, the even distribution among syndromes was not anticipated and, absent specific associations, suggests that different
Associations of Bradykinesia With Cervicotruncal TD.
The association of bradykinesia with cervicotruncal TD is consistent with other investigations finding a direct relationship between parkinsonism and TD severity (Mukherjee et al. 1982; O'Hara et al. 1993; Muscettola et al. 1999). Gerlach (1977) and Sachdev et al. (1996) found similar correlations between parkinsonism and limb truncal TD. In particular, Gerlach noted a quite strong relationship with bradykinesia, consistent with the present finding. However, other studies have found either an inverse relationship (Chouinard et al. 1979; Toenniessen et al. 1985; Kucharski et al. 1987; Gerlach 1988; Gerlach et al. 1993; van Harten et al. 1997) or no relationship (Caligiuri et al. 1991; Hansen et al. 1992b) between parkinsonism and TD. Consequently, the relation of TD to parkinsonism may depend upon the anatomic region of TD and the parkinsonian symptom specified. A relation between bradykinesia and TD may be based in ventromedial striatal neurons, which have been linked to both bradykinesia (Amalric et al. 1995; Jellinger 1999) and TD (Gerlach 1985). Blockade of D2 receptors in the ventromedial striatal territory associated with bradykinesia would disinhibit ventral tegmental dopamine release through presynaptic D2 blockade and would thus increase dopaminergic stimulation of ventromedial striatal dopamine D1 receptors, thereby increasing cervical TD (Peacock et al. 1990; Trugman et al. 1994) in the context of enhanced bradykinesia. This is consistent with the suggestion that D2 blockade may be requisite for TD (Peacock et al. 1990; Trugman et al. 1994). Such a mechanism may explain why only bradykinesia was associated with TD in only this body region, and why different studies observe contradictory relationships between parkinsonism and TD.

Conclusions
Although the subjects in this study were referred to a movement disorder consultation service, some of these findings generalize to state hospital patients with mild tardive dyskinesia. The more rigorous the evaluation, the greater the diagnostic certainty. It is important to exclude other causes of dyskinesia when diagnosing TD. Patients with definite TD should be monitored for other extrapyramidal syndromes, which are treatable conditions with their own morbidities. Although rates of concurrence of TD subsyndromes with other neurological disorders depend substantially on how these other neurological disorders are clinically defined, bradykinesia may be associated with cervicotruncal TD. Otherwise, these data seem to indicate a relative independence of movement disorders in terms of co-occurrence. Given the sample size of this study, further research is needed to replicate these findings.

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Joseph, A.B. Non-right-handedness and maleness correlate with tardive dyskinesia among patients taking neu-


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