Tardive Dyskinesia and the 3-Year Course of Schizophrenia: Results From a Large, Prospective, Naturalistic Study

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Objective: The objective of this study was to compare the 3-year course of schizophrenia between persons with tardive dyskinesia (TD) and persons without TD on multiple outcome measures.

Method: Data were drawn from a large, prospective, naturalistic study of persons treated for schizophrenia-spectrum disorders (DSM-IV criteria) in the United States, conducted between July 1997 and September 2003. Treatment outcomes were assessed at enrollment and at 12, 24, and 36 months postenrollment using measures of symptoms, functioning, productivity, activity, and quality of life. Participants who had TD at enrollment (fulfilling Schooler-Kane criteria, N = 637) were compared with those who did not (N = 1538) on clinical and functional measures at enrollment and across the 3 years of follow-up. Additional analyses examined those with persistent TD compared to those without persistent TD.

Results: With adjustment for known correlates of TD, participants with TD compared to those without TD had significantly more severe psychopathology, were less likely to experience symptom remission, had more severe extrapyramidal side effects, and had lower levels of quality of life and functioning, lower productivity, and fewer activities (all $p < .001$) across the 3-year follow-up. Findings were essentially unchanged when the subgroup of participants with persistent TD (at enrollment and at 1 year) was examined.

Conclusion: These results indicate that, in the long-term treatment of schizophrenia, persons with TD have a significantly more severe and more refractory course of illness than those without TD, suggesting poorer prognosis and the need for specialized interventions.

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Tardive dyskinesia (TD) is an abnormal involuntary movement disorder that was first observed in the late 1950s among patients receiving first-generation (typical) antipsychotic agents. Involuntary movements of extremities or the trunk can occur, but most common are orofacial movements involving the tongue or jaw. Before the advent of second-generation antipsychotic medications, prevalence studies suggested that approximately 20% to 24% of patients have dyskinesia, with about 5% occurring in untreated patients, yielding an estimate of neuroleptic-induced TD of about 15%–19%.[1,2] The prevalence of TD is higher in women and in the elderly.[1–3] TD tends to persist over time, with most patients experiencing a similar level of TD severity even after 10 years.[4] The risk for TD is now in decline with the use of atypical antipsychotics, which have lower rates of TD compared to typical antipsychotics.[5–7]

The effects of TD extend beyond the movement disorder. Patients with schizophrenia and TD, compared to those with schizophrenia but without TD, are more prone to physical illness, have increased mortality, and generally experience a lower quality of life.[8–10] The social acceptability of patients with TD is less than that for those without TD.[11] Patients with schizophrenia-related disorders who have TD are less likely to have a full-time job, be employed, or earn the minimum wage or above.[12] TD can also lead the physician, or the patient, to discontinue effective treatment.[13]

The large-scale Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial has reported on correlates of the presence of TD at baseline for a sample of patients with schizophrenia.[14] In addition to factors that have consistently emerged in previous research (age and treatment with typical vs. atypical antipsychotics), race, illness duration, comorbid diagnosis of substance use disorder, and use of anticholinergics in the 6 months prior to enrollment were associated with the presence of TD at baseline, but gender was not. Patients with TD also had higher ratings of psychopathology, extrapyramidal side effects, and akathisia, compared to those without TD.[14]

Although cross-sectional studies have uncovered several clinical and functional correlates of TD, such TD symptoms are known to fluctuate over time. Therefore, it

is important to systematically investigate both the factors that predict TD and the outcomes that are associated with it using longitudinal assessments of TD and clinical outcomes. In regard to the predictors of TD, the Schizophrenia Outpatient Health Outcomes (SOHO) study found that worsening of psychosis over time was associated with an increased incidence of TD, although medication dosage changes were not controlled in this study.[15] The SOHO study also reported that about half of those with schizophrenia who had extrapyramidal symptoms were found to have TD 1 year later.[16] Other studies have also linked poor premorbid functioning to the development of TD.[17] Thus, it may be that patients susceptible to TD have greater functional impairment or tendency for clinical deterioration independent of the TD, rather than the TD progressively contributing to such impairments and clinical deterioration. Recent evidence linking a gene polymorphism to TD and TD severity within a schizophrenic population might be consistent with preexisting differences that relate also to functional impairments, although such genetic factors would not rule out a progressive impact on functioning over time due to the TD symptoms themselves.[18]

The purpose of the current study is to compare the clinical and functional course of schizophrenia between persons with TD and persons without TD at enrollment and at 12, 24, and 36 months postenrollment. A broad range of measures was examined in order to document whether functioning, symptoms, drug and alcohol use, productivity, activities, quality of life, resource utilization, suicide attempts, arrests, or violent behaviors are correlated with the presence of TD over time.

METHOD

Study Design

The U.S. Schizophrenia Care and Assessment Program (US-SCAP) study database was used to assess the relation between TD and functional impairment over time. US-SCAP was a prospective, naturalistic, nonrandomized, 3-year study designed to examine the effect of various clinical and treatment variables on long-term outcome in patients with schizophrenia-spectrum disorders. A total of 2327 patients at 6 large health care sites were enrolled. The study sites were chosen to provide a sample diverse in geography, ethnicity, and clinical setting (e.g., university and community mental health centers, Veterans Affairs Health Services, and community and state hospitals). Only sites that offered open and unrestricted formulary access to all available antipsychotic medications, and that did not rely on any algorithms for treatment decision-making, were chosen for the study. Study participants were enrolled from July 1997 to September 2003. The institutional review board at each site approved the study protocol prior to study initiation, and written informed consent was obtained from all participants.

A detailed description of study design and methods has been provided in previous publications.[19–21] Study enrollment was offered to all patients 18 years or older who had a DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or schizophreniform disorder. In order to obtain the broadest and most representative sample of schizophrenia-spectrum patients seen in clinical practice settings, there were no exclusions based on psychiatric or medical comorbidity, use of concomitant medications, presence of behavioral problems (criminal or otherwise), or pregnancy status.

Measures

Psychiatric history and background characteristics were collected at study entry as part of a semistructured interview. Medical history data, including mental health resource utilization information during the preceding 6 months, were extracted from the participant's medical record.

Throughout the 3-year study period, self-report and medical record data were collected at 6-month intervals, and clinical assessments were performed at 1-year intervals. Thus the maximum number of clinical assessments for an individual was 4 (baseline and 12-, 24-, and 36-month follow-ups), and the minimum number was 1. Data were abstracted from medical records by trained and certified examiners. Patients were queried about use of medical and psychiatric services outside of their regular treatment site. When such use occurred, systematic efforts were made to obtain and abstract off-site medical records.

The assessment of TD presence at study entry (enrollment) was based on participants meeting Schooler-Kane criteria.[22] These criteria include (1) a history of at least 3 months' cumulative antipsychotic exposure and (2) the presence of at least "moderate" abnormal involuntary movement in 1 or more body areas, or at least "mild" movements in 2 or more body areas (face, lips, jaw, tongue, upper extremities, lower extremities, trunk), based on the Abnormal Involuntary Movement Scale (AIMS).[23]

Thirty clinical and functional outcome measures were used, including the Positive and Negative Syndrome Scale (PANSS),[24] the Montgomery-Asberg Depression Rating Scale (MADRS),[25] the Global Assessment of Functioning (GAF),[26] the Heinrichs-Carpenter Quality of Life Scale (QLS),[27] Simpson-Angus extrapyramidal side effects rating scale (Simpson-Angus),[28] and the SCAP-Health Questionnaire (SCAP-HQ).[29] The SCAP-HQ is a validated self-report measure that assesses the status of 15 domains, including psychiatric symptoms, drug and alcohol use, productivity, activities, quality of life, resource utilization, suicide attempts, arrests, and violent behaviors. The SCAP-HQ includes items from previously

Table 1. Demographic and Clinical Characteristics of Patients With Schizophrenia at Enrollment[a]

Characteristic	With TD (N = 637)	Without TD (N = 1538)	p Value
Age, mean (SD), y	44.9 (11.3)	41.0 (11.0)	< .001
Gender, male	411 (64.5)	924 (60.1)	.053
Illness duration, mean (SD), y	23.7 (11.9)	20.8 (11.5)	< .001
High school education or less[b]	446 (70.3)	1026 (67.7)	.225
Race			.001
White	309 (48.5)	790 (51.4)	
African American	253 (39.7)	500 (32.5)	
Other	75 (11.8)	248 (16.1)	
Single (never married)[b]	385 (60.6)	943 (61.6)	.688
Medication use in prior 6 months			
Typical antipsychotics, any	431 (67.7)	861 (56.0)	< .001
Atypical antipsychotics, any	330 (51.8)	976 (63.5)	< .001
Anticholinergics, mean (SD), d	86.5 (86.2)	71.7 (84.3)	< .001
Anticholinergics, any	347 (54.5)	721 (46.9)	.001
Comorbid substance use disorder[b]	190 (29.9)	399 (26.1)	.073

[a]Values expressed as N (%) unless otherwise noted.
[b]Denominators vary based on availability of complete data.
Abbreviation: TD = tardive dyskinesia.

Table 2. Demographic and Clinical Characteristics of Tardive Dyskinesia Patients With Versus Without Extrapyramidal Symptoms (EPS) at Enrollment[a]

Characteristic	With EPS (N = 155)	Without EPS (N = 332)	p Value
Age, mean (SD), y	46.1 (11.3)	43.8 (10.3)	.032
Gender, male	103 (66.5)	227 (68.4)	.673
Illness duration, mean (SD), y	25.0 (12.3)	21.7 (10.4)	.004
High school education or less[b]	109 (70.8)	237 (71.6)	.852
Race			.033
White	78 (50.3)	152 (45.8)	
African American	52 (33.5)	147 (44.3)	
Other	25 (16.1)	33 (9.9)	
Single (never married)[b]	100 (64.5)	194 (58.8)	.229
Medication use in prior 6 months			
Typical antipsychotics, any	103 (66.5)	231 (69.6)	.489
Atypical antipsychotics, any	85 (54.8)	158 (47.6)	.136
Anticholinergics, mean (SD), d	86.2 (88.3)	89.3 (85.5)	.712
Anticholinergics, any	80 (51.6)	188 (56.6)	.300
Comorbid substance use disorder	40 (25.8)	110 (33.1)	.112

[a]Values expressed as N (%) unless otherwise noted.
[b]Denominators vary based on availability of complete data.

validated measures like the Short-Form 12-Item Health Survey (SF-12)[30] and the Lehman's Quality of Life Interview.[31] Symptom remission was defined using the expert consensus criteria (severity criterion), based on 8 PANSS items.[32]

All outcome assessments in US-SCAP were administered by trained and annually certified examiners.

Statistical Analyses

The analytic sample consisted of all US-SCAP participants who were outpatients at enrollment and had a history of at least 3 months' cumulative antipsychotic exposure during the 6 months prior to enrollment (93.5% of all participants, 2175/2327). Comparisons between the TD and non-TD groups on sociodemographic and clinical characteristics at enrollment were made using χ^2 tests for categorical variables and t tests for continuous variables.

An initial analysis compared those with TD to those without TD on all clinical and functional outcome measures collected at enrollment using linear regression for continuous variables and logistic regression for categorical variables. Additional longitudinal analyses were used to examine group differences (TD vs. non-TD) on the outcome measures over the course of the full study (enrollment and 12-, 24-, and 36-month assessments post-enrollment). The longitudinal analyses were conducted using a mixed model with repeated measures (MMRM) approach for continuous variables and a generalized estimating equations (GEE) approach for binary variables. The longitudinal analyses examine group differences in mean scores across the 3-year study. In both the MMRM and GEE longitudinal models, TD status, assessment (enrollment and follow-up year 1, 2, or 3), and interaction between TD status and assessment were fixed effects. Subject was a random effect in the models with an unstructured covariance for the MMRM. All analyses were performed adjusting for known correlates of TD[14] in the models, including age, gender, race, illness duration, comorbid diagnosis of substance use disorder, and treatment with typical antipsychotics (yes/no), atypical antipsychotics (yes/no), and anticholinergics (number of days) in the 6 months prior to enrollment. To further assess robustness of the findings, all analyses were repeated using more stringent criteria by comparing patients with persistent TD (meeting Schooler-Kane criteria at enrollment and at the end of the first year of follow-up) and patients without TD (across all 4 assessments during the 3-year study).

Group differences were tested using a 2-sided α level of .05. Because the analyses included 30 comparisons, Bonferroni corrections for multiple comparisons ($p < .05/30 = .0017$) are also discussed. SAS version 8.2 (SAS Institute, Inc., Cary, N.C.) was used to perform all statistical analyses.

RESULTS

Baseline Characteristics

The total patient sample used consisted of 2175 patients, 637 (29.3%) with TD and 1538 (70.7%) without TD (Table 1). At the time of enrollment, the typical patient was between 30 and 50 years of age, with a mean duration of illness of over 20 years. The TD and non-TD groups differed significantly on almost all baseline demographic and clinical characteristics tested. Relative to the non-TD group, the TD group was significantly older, more likely to be African American, had a longer duration of illness, scored higher on the PANSS, had lower functioning as measured by the GAF, had more extrapyramidal side effects (Simpson-Angus

Table 3. Comparisons of Patients With and Without Tardive Dyskinesia (TD) on Outcome Variables at Enrollment and Across the 3-Year Study[a]

	Enrollment			Mean Across 3 Years		
Outcome Variable	With TD (N = 637)	Without TD (N = 1538)	p Value[b]	With TD (N = 621)	Without TD (N = 1482)	p Value[c]
Symptoms						
PANSS total score	74.9 (18.2)	67.1 (17.9)	< .001	74.8 (18.3)	67.1 (17.8)	< .001
PANSS positive score	17.5 (6.1)	15.5 (5.9)	< .001	17.4 (6.1)	15.5 (5.8)	< .001
PANSS negative score	19.4 (6.4)	17.9 (6.7)	< .001	19.5 (6.4)	18.0 (6.7)	< .001
PANSS general psychopathology	38.3 (10.0)	34.0 (9.2)	< .001	38.2 (10.0)	34.0 (9.1)	< .001
MADRS score	14.7 (10.1)	13.4 (10.2)	.582	14.6 (10.1)	13.4 (10.2)	.590
Remission, N (%)[d]	96 (15.1)	427 (28.3)	< .001	93 (15.0)	407 (28.0)	< .001
EPS (per Simpson-Angus Scale), N (%)[d]	155 (31.8)	229 (20.9)	< .001	150 (31.6)	221 (20.9)	< .001
Productivity						
Any productive activity, N (%)[d]	371 (58.3)	1082 (70.6)	< .001	362 (58.4)	1041 (70.5)	.189
Paid employment, N (%)[d]	113 (17.8)	3451 (22.9)	.108	110 (17.7)	343 (23.2)	.014
Income, $	744.4 (593.0)	679.3 (587.3)	.074	746.7 (594.4)	678.6 (586.2)	.016
Activities						
Daily activities	3.2 (1.2)	3.5 (1.2)	.008	3.2 (1.2)	3.5 (1.2)	< .001
Leisure activities	2.6 (1.2)	2.7 (1.0)	.001	2.6 (1.2)	2.7 (1.0)	< .001
Safety in the community, N (%)						
Violent behaviors[d]	45 (7.1)	103 (6.7)	.705	43 (6.9)	97 (6.6)	.361
Arrested/jailed[d]	38 (6.0)	93 (6.1)	.952	38 (6.1)	88 (6.0)	.903
Suicidal attempt	11 (1.7)	41 (2.7)	.476	11 (1.8)	41 (2.8)	.229
Victimized[d]	81 (12.8)	148 (9.7)	.316	78 (12.6)	139 (9.4)	.071
Suicidal thoughts/threats[d]	101 (15.9)	235 (15.4)	.981	98 (15.8)	230 (15.6)	.451
Quality of life						
QLS total score	54.7 20.3)	62.2 (22.6)	< .001	54.7 (20.3)	62.0 (22.4)	< .001
QLS interpersonal relations score	19.5 (9.7)	21.7 (10.6)	.016	19.6 (9.7)	21.6 (10.5)	.010
QLS instrumental role score	8.6 (6.5)	10.7 (6.8)	.002	8.6 (6.6)	10.7 (6.8)	.011
QLS intrapsychic foundations score	20.4 (8.0)	22.9 (8.5)	.001	20.3 (8.1)	22.8 (8.4)	< .001
QLS common objects and activities score	6.0 (2.2)	6.5 (2.3)	< .001	6.0 (2.2)	6.5 (2.3)	< .001
SF-12 mental health functioning score	27.3 (9.9)	27.2 (9.6)	.747	27.3 (9.9)	27.2 (9.6)	.110
SF-12 physical health functioning score	50.5 (14.5)	52.6 (14.0)	.099	50.7 (14.3)	52.8 (13.9)	.014
SCAP-HQ general life satisfaction score	4.6 (1.0)	4.6 (1.0)	.267	4.7 (1.0)	4.6 (1.0)	.225
GAF score	39.3 (11.9)	44.4 (13.1)	< .001	39.4 (11.9)	44.3 (13.2)	< .001
Substance use						
Alcohol use, N (%)[d]	167 (26.3)	359 (23.5)	.582	164 (26.5)	351 (23.9)	.476
Illicit drug use, N (%)[d]	72 (11.3)	103 (6.7)	.236	70 (11.3)	98 (6.7)	.561
Resource utilization						
Any psychiatric hospitalization, N (%)	79 (12.4)	265 (17.2)	.336	77 (12.4)	258 (17.4)	.490
Any use of emergency services, N (%)[d]	8 (13.6)	61 (16.1)	.272	7 (13.2)	61 (17.0)	.456

[a]Values expressed as mean (SD) unless otherwise noted.
[b]p Values from linear regressions (continuous variables) or logistic regressions (binary variables) adjusting for age, gender, race, site, substance use disorder (except when substance use was the outcome), illness duration, and prior treatment with atypical antipsychotics (yes/no), typical antipsychotics (yes/no), and anticholinergics (number of days).
[c]p Values from mixed model with repeated measures (continuous variables) or generalized estimating equations (binary variables) adjusting covariates as listed above.
[d]Denominators vary based on availability of complete data.
Abbreviations: EPS = extrapyramidal symptoms, GAF = Global Assessment of Functioning, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, QLS = Quality of Life Scale, SCAP-HQ = Schizophrenia Care and Assessment Program-Health Questionnaire, SF-12 = Short-Form 12-Item Health Survey.

scale), were more likely to be treated with a typical antipsychotic in the prior 6 months (67.7% of the TD group, 56.0% of the non-TD group), and were more likely to be treated with anticholinergic agents (Table 1).

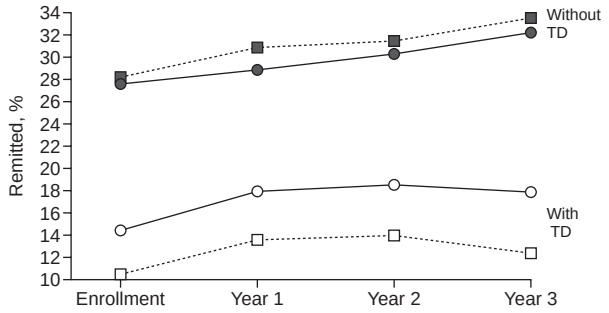
Since the TD was associated with EPS and because EPS was previously found to be predictive of later development of TD,[16,33–36] we also compared, within the TD group, the patients with EPS versus those without EPS. Compared to the TD patients without EPS (Table 2), the group with TD and EPS (31.8%) was significantly older, with longer illness duration and lower likelihood of being African American.

Comparison of TD and Non-TD Groups on Outcomes

At enrollment, participants with TD were significantly ($p < .05$) different from those without TD on 15 of the 30 outcomes examined (Table 3). Of the 17 variables, all but 3 also were significant at the Bonferroni-corrected α level of .0017.

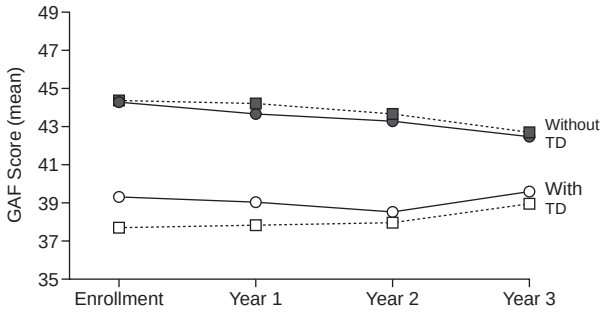
Similar results were apparent for the MMRM and GEE analyses examining the average over the 4 yearly assessments. In particular, participants with TD compared to those without TD had, across the 4 yearly assessments, significantly more severe psychopathology as measured by the PANSS total score, positive symptoms, negative

Figure 1. Proportion of Remitted Participants With Tardive Dyskinesia (TD) Versus Without TD[a]



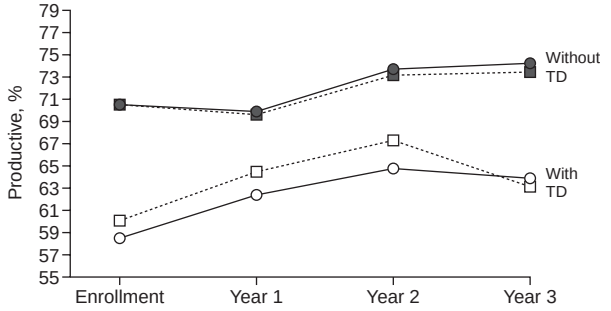
[a]Participants without TD at enrollment (continuous line, N = 1482) vs. with TD at enrollment (continuous line, N = 621), p < .001; participants without TD at all 4 assessments (broken line, N = 1164) vs. with TD at enrollment and 1 year (broken line, N = 252), p < .001. Analyses adjusted for age, gender, race, site, substance use disorder, illness duration, and prior treatment with atypical antipsychotics (yes/no), typical antipsychotics (yes/no), and anticholinergics (number of days). Remission defined using 8 PANSS items per expert concensus criteria.[32]
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Figure 2. Mean Global Assessment of Functioning (GAF) Scores for Participants With Tardive Dyskinesia (TD) Versus Without TD[a]



[a]Participants without TD at enrollment (continuous line, N = 1482) vs. with TD at enrollment (continuous line, N = 621), p < .001; participants without TD at all 4 assessments (broken line, N = 1164) vs. with TD at enrollment and 1 year (broken line, N = 252), p = .001. Analyses adjusted for age, gender, race, site, substance use disorder, illness duration, and prior treatment with atypical antipsychotics (yes/no), typical antipsychotics (yes/no), and anticholinergics (number of days).

Figure 3. Proportion of Productive Participants With Tardive Dyskinesia (TD) Versus Without TD[a]



[a]Participants without TD at enrollment (continuous line, N = 1482) vs. with TD at enrollment (continuous line, N = 621), p < .001; participants without TD at all 4 assessments (broken line, N = 1164) vs. with TD at enrollment and 1 year (broken line, N = 252), p = .22. Analyses adjusted for age, gender, race, site, substance use disorder, illness duration, and prior treatment with atypical antipsychotics (yes/no), typical antipsychotics (yes/no), and anticholinergics (number of days). Productivity defined as any self-reported productive activity in the past 4 weeks on the Schizophrenia Care and Assessment Program-Health Questionnaire (eg, work for pay, student, volunteer).

symptoms, and general psychopathology (all, p < .001) (Table 3). In addition, compared to the non-TD group, the TD group had significantly more severe extrapyramidal symptoms (EPS) (p < .001), less activity (daily and leisure activity, both p < .001), and poorer quality of life (Quality of Life Scale total score, p < .001; Quality of Life intrapsychic foundations subscale, p < .001; Quality of Life common objects and activities subscale, p < .001) across the 4 assessments (Table 3). Five additional variables were significant at the .05 level, but not at the .0017, Bonferroni-corrected α level: paid employment, income, Quality of Life interpersonal relations subscale, Quality of Life instrumental role subscale, and SF-12 physical health subscale. All of these findings were in the direction of participants with TD having lower functioning and poorer quality of life compared to those without TD.

Symptom remission rates were significantly (p < .001) lower across the 4 yearly assessments for the TD group compared to the non-TD group (Figure 1). The overall functioning of TD patients, as measured by the GAF, was also significantly (p < .001) lower than that for non-TD patients across time (Figure 2). The mean proportion of TD patients that had any productivity was 58.4% over the 4 yearly assessments, compared to 70.5% for the non-TD group (p < .001 from GEE analyses) (Figure 3).

No significant differences were found between the TD and non-TD groups on depressive symptoms, safety in the community variables (violent behaviors, arrested/jailed, victims of crime, suicide attempts, and suicidal thoughts), general life satisfaction, relapse-related resource utilization (psychiatric hospitalization and use of emergency psychiatric services), alcohol use, or drug use (Table 3).

The results were essentially unchanged when the outcomes of patients with persistent TD (N = 252) and patients consistently without TD (N = 1164) were compared. One exception was for overall productivity (Figure 3). For this variable, the p value was no longer significant when comparing those with and without persistent TD.

Overall, there was little change in outcome measures over time. For the most part, differences between TD and non-TD groups existed at the enrollment assessment and continued for each subsequent yearly assessment.

Table 4. Comparisons of Tardive Dyskinesia Patients With and Without Extrapyramidal Symptoms (EPS) on Outcome Variables at Enrollment and Across the 3-Year Study[a]

	Enrollment			Mean Across 3 Years		
Outcome Variable	With EPS (N = 155)	Without EPS (N = 332)	p Value[b]	With EPS (N = 150)	Without EPS (N = 325)	p Value[c]
Symptoms						
PANSS total score	79.7 (19.1)	72.7 (16.8)	< .001	79.8 (19.4)	72.6 (16.9)	< .001
PANSS positive score	18.5 (6.5)	16.8 (5.7)	.022	18.5 (6.6)	16.9 (5.7)	.011
PANSS negative score	20.7 (6.2)	19.1 (6.4)	.006	20.8 (6.2)	19.1 (6.4)	.025
PANSS general psychopathology	40.7 (10.7)	36.9 (8.9)	.001	40.6 (10.8)	36.8 (9.0)	< .001
MADRS score	14.5 (10.0)	14.8 (10.3)	.687	14.3 (9.9)	14.6 (10.3)	.295
Remission, N (%)	11 (7.1)	61 (18.4)	.009	10 (6.7)	59 (18.2)	< .001
Productivity						
Any productive activity, N (%)[d]	78 (50.7)	201 (60.5)	.064	76 (50.7)	196 (60.3)	.080
Paid employment, N (%)[d]	21 (13.6)	66 (19.9)	.239	20 (13.4)	64 (19.7)	.803
Income, $	754.8 (671.6)	739.6 (552.0)	.882	765.4 (680.5)	735.6 (549.4)	.643
Activities						
Daily activities	3.0 (1.2)	3.3 (1.2)	.021	3.0 (1.2)	3.3 (1.2)	< .001
Leisure activities	2.5 (1.1)	2.7 (1.1)	.306	2.5 (1.1))	2.7 (1.1)	.583
Safety in the community, N (%)						
Violent behaviors[d]	7 (4.6)	28 (8.4)	.050	7 (4.7)	26 (8.0)	.982
Arrested/jailed[d]	7 (4.6)	21 (6.3)	.485	7 (4.7)	21 (6.5)	.791
Suicidal attempt[d]	5 (3.3)	4 (1.2)	.077	5 (3.4)	4 (1.2)	.275
Victimized[d]	17 (11.0)	46 (13.9)	.528	15 (10.1)	46 (14.2)	.635
Suicidal thoughts/threats[d]	25 (16.2)	51 (15.4)	.913	24 (16.1)	49 (15.1)	.123
Quality of life						
QLS total score	49.9 (20.1)	56.2 (19.2)	.018	50.1 (20.1)	56.1 (19.3)	.047
QLS interpersonal relations score	18.4 (9.7)	19.9 (9.7)	.399	18.5 (9.6)	19.9 (9.7)	.320
QLS instrumental role score	7.2 (6.5)	9.0 (6.3)	.018	7.3 (6.5)	9.0 (6.4)	.001
QLS intrapsychic foundations score	18.7 (7.8)	20.8 (7.7)	.030	18.7 (7.8)	20.8 (7.7)	.065
QLS common objects and activities score	5.5 (2.2)	6.2 (2.1)	< .001	5.6 (2.2)	6.2 (2.1)	.046
SF-12 mental health functioning score	28.6 (9.6)	26.4 (9.8)	.023	28.8 (9.5)	26.3 (9.8)	.105
SF-12 physical health functioning score	51.0 (14.0)	51.4 (14.1)	.164	51.1 (13.7)	51.7 (13.9)	.639
SCAP-HQ general life satisfaction score	4.7 (1.0)	4.6 (1.0)	.078	4.7 (1.0)	4.6 (1.0)	.025
GAF score	35.7 (11.3)	41.4 (11.8)	< .001	35.9 (11.4)	41.5 (11.8)	.002
Substance use, N (%)						
Alcohol use[d]	37 (24.0)	97 (29.2)	.416	37 (24.8)	95 (29.2)	.645
Illicit drug use[d]	12 (7.8)	48 (14.5)	.168	12 (8.1)	47 (14.5)	.129
Resource utilization, N (%)						
Any psychiatric hospitalization[d]	17 (11.0)	45 (13.6)	.148	17 (11.3)	45 (13.9)	.280
Any use of emergency services	4 (25.0)	2 (7.1)	NA[e]	4 (30.8)	2 (7.7)	NA[e]

[a]Values expressed as mean (SD) unless otherwise noted.
[b]p Values from linear regressions (continuous variables) or logistic regressions (binary variables) adjusting for age, gender, race, substance use disorder (except when substance use was the outcome), illness duration, and prior treatment with atypical antipsychotics (yes/no), typical antipsychotics (yes/no), and anticholinergics (number of days).
[c]p Values from mixed model with repeated measures (continuous variables) or generalized estimating equations (binary variables) adjusting covariates as listed above.
[d]Denominators vary based on availability of complete data.
[e]Not applicable due to substantial missing values.
Abbreviations: GAF = Global Assessment of Functioning, MADRS = Montgomery-Asberg Depression Rating Scale, NA = not applicable, PANSS = Positive and Negative Syndrome Scale, QLS = Quality of Life Scale, SCAP-HQ = Schizophrenia Care and Assessment Program-Health Questionnaire, SF-12 = Short-Form 12-Item Health Survey.

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Comparison of Tardive Dyskinesia Patients With and Without EPS on Outcomes

Within the TD group, we also compared those with EPS versus those without EPS on outcome measures during the first year of the study and again across the 3-year study. Results (Table 4) show the TD with EPS group to have significantly poorer outcomes, including greater illness severity (PANSS total score, positive symptoms, negative symptoms, and general psychopathology), lower remission rate, lower level of daily activity, poorer quality of life (QLS total, instrumental role, and common objects and activities scores), and lower GAF scores. Level of general life satisfaction was reported, however, to be better for TD patients with EPS.

DISCUSSION

The primary finding of this large, multicenter, prospective observational study conducted in clinical practice settings was that individuals with schizophrenia and TD, compared to those with schizophrenia but without TD, had a more severe course of illness across a broad range of outcome measures, and that TD patients with EPS had the worst treatment outcomes. Specifically, those with TD

(29.3%) had more severe levels of symptomatology, were less likely to experience symptom remission, had more severe EPS, and had poorer levels of functioning and quality of life with reduced productivity and fewer activities. These impairments were apparent at enrollment and were relatively constant across the 4 yearly assessments conducted in the US-SCAP study. Findings were largely the same when the analysis was restricted to the subgroup of those with persistent TD versus those consistently without TD. Furthermore, TD patients with EPS were found to comprise a relatively large subgroup (32% of the TD patients) that is particularly disadvantaged and vulnerable due to their more severe symptomatology, lower remission rates, poorer quality of life, and lower level of functioning compared to those with TD but without EPS. Current findings suggest that EPS may be a valuable prognostic indicator in the long-term treatment of patients with schizophrenia, a potential clinical marker that warrants additional future study.

The present findings regarding symptoms are consistent with results from the large-scale CATIE study in which TD patients were also found to have more positive symptoms, negative symptoms, and general psychopathology.[14] Other, smaller studies[37–39] have yielded mixed results.

Findings in regard to EPS and TD are consistent with previous research,[16,33–36] including the CATIE study.[14] The relationships between TD and EPS will require further study considering that EPS was previously shown to predict subsequent development of TD[16] while also signaling a potential prognostic indicator due to its link to poorer treatment outcomes. Furthermore, although EPS and TD were previously hypothesized to reflect somewhat overlapping indicators of extrapyramidal dysfunction,[14] it is also possible that certain movement ratings may have been rated on both the AIMS and the EPS measure (Simpson-Angus).[14]

It is interesting to note that many of the current findings are consistent with the CATIE[14] study, despite differences in the definition of TD. Although both studies used the modified Schooler-Kane criteria for probable TD, the CATIE study excluded from the analysis patients with a history of TD (a detail not available in US-SCAP) and also those with a score of 1 or higher (mild or worse) on at least 1 item of the Simpson-Angus scale. These differences have very likely driven the different baseline TD prevalence rates (15% in CATIE, 29% in US-SCAP). Despite these differences, the TD patients in both studies significantly differed from non-TD patients on similar parameters (e.g., age, illness duration, level of symptomatology, current treatment with anticholinergics, and EPS).

Unlike in the CATIE study,[14] no relation between a comorbid diagnosis of substance use disorder and the presence of TD was found here. It may be that the relation of TD to substance use disorders depends on the particular drug and/or duration of use. In fact, the CATIE study found that only abuse of, or dependence on, stimulants, but not opiates or marijuana, was significantly related to TD.[14] Differences between the samples in prevalence and/or duration of stimulant use may explain this discrepancy, especially considering that methamphetamine use has large regional variation in the United States.[40]

There are few larger-scale studies examining the impact of TD on a broader range of outcomes, such as productivity, activities, and quality of life. One exception is the recent article by Rosenheck,[41] who reported TD and quality-of-life data from 2 large treatment trials. Only results for the total score from 1 instrument, the Heinrichs-Carpenter Quality of Life Scale, were provided. The percent reduction in QLS total scores at enrollment for those with moderate to severe TD compared to those without TD was 12.3% in one study and 7.3% in another.[41] In the current study, this same measure at enrollment showed a 12.1% reduction for the TD group compared to the non-TD group. However, the overall mean scores on the QLS in the Rosenheck[41] studies were low, with the non-TD groups in the 2 studies having scores of 43.2 and 49.0 compared to 62.2 (SD = 22.6) in the current study. The low level of functioning and quality of life, even among the non-TD patients in the Rosenheck[41] studies, may have made it difficult to detect any impact of TD on quality of life, except in the most severe cases. In addition, Rosenheck[41] did not examine the impact of TD on the broad range of outcomes measured here.

Taken as a whole, the current investigation extends the results of previous studies by documenting that individuals with schizophrenia and TD, compared to those with schizophrenia but without TD, had continued impairments over the course of this 3-year study. Moreover, the present study indicates that impairments found for those with TD, and especially for those with TD and EPS, are broad, with poorer productivity, activity levels, and general quality of life. These impairments were largely present at enrollment; thus, the data do not suggest that TD is associated with deterioration over time. In fact, previous research has indicated that prior clinical deterioration and prior EPS are associated with an increased incidence of TD over the subsequent year.[15,16] However, because medication dosage changes were not controlled in that study, cause-and-effect relations are difficult to determine.

The broad and persistent impairments found here for those with TD are consistent with the idea that TD vulnerability may be a constitutional feature of a more severe schizophrenia phenotype. This feature is hypothesized to be expressed when the individual is exposed to typical antipsychotic drugs[42] and may be connected to the gene polymorphism associated with TD and TD severity within a schizophrenic population that has recently been identified.[18] The ongoing vulnerability may also be evident in

neurobiological systems. Recent research has implicated neurocircuit abnormal function in the frontal-subcortical region and the basal ganglia in TD.[43]

The clinical implications of this and previous research on the correlates of TD are clear. As a marker of a more severe subtype of schizophrenia with greater impairment in functioning and more severe symptoms, clinicians need to plan long-term treatment accordingly. Specialized interventions may be needed to address the range of impairments that can be expected within this subpopulation. Medication choice, including the use of atypical antipsychotics, needs to be carefully considered in those at risk for TD, especially given the differential long-term efficacy of typical antipsychotics compared to atypical antipsychotics[44–47] as well as some differential effectiveness among atypical antipsychotics.[48]

The strengths of this study are the inclusion of a wide range of typical practice settings, large sample size, longitudinal assessment of TD and outcomes, and broad range of outcome measures. However, several limitations also need to be considered. First, these analyses were formulated and implemented post hoc. Although analyses were conducted controlling for known covariates of TD, it is possible that other variables not used as covariates here may have influenced the obtained differences between the TD and non-TD groups. Additional research is needed to replicate the present findings (although the main findings remained intact even with a conservative Bonferroni-corrected α level). A second limitation is that the current analyses did not address possible changes in patients' TD status postenrollment across the 3-year study. Some patients with TD at enrollment may not have met TD criteria later. We attempted to minimize this limitation by comparing patients with persistent TD over a 1-year period and patients who were consistently without TD across the 3-year study. A third limitation is that, although we adjusted for known risk factors for TD, and our findings suggest that TD is a prognostic marker, additional longitudinal research is needed to differentiate risk factors from prognostic indicators. A fourth limitation is that no interrater reliability on the AIMS was conducted. Finally, our study offers no information on cumulative dose of antipsychotics prior to baseline, a parameter that might be related to risk for TD. However, due to their older age and longer illness duration, the TD patients were assumed to have had a higher lifetime cumulative dose of antipsychotics.

In conclusion, during the long-term treatment of schizophrenia, the presence of TD, and particularly TD with EPS, is associated with significantly more severe psychopathology, more severe EPS, a lower level of productivity, and poorer functioning and quality of life. These findings indicate that individuals with TD have a significantly more severe and more refractory course of illness than those without TD, suggesting poorer prognosis and the need for specialized interventions.

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