Incidence of Tardive Dyskinesia and Tardive Dystonia in African Caribbean Patients on Long-Term Antipsychotic Treatment: The Curaçao Extrapyramidal Syndromes Study V

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Objective: Tardive dyskinesia (TD) and tardive dystonia (TDt) syndromes represent severe side effects of first-generation antipsychotics (FGAs). Although second-generation antipsychotics (SGAs) confer a lower risk for tardive syndromes, many patients continue to use FGAs alone or in combination with SGAs. Some patients remain free of TD or TDt even after many years of antipsychotic treatment with predominantly FGAs. Do these patients remain at risk for TD or TDt and, consequently, should a switch to SGAs be considered? A longitudinal cohort study in patients on long-term antipsychotic treatment may answer this question.

Method: A 9-year cohort study (1992–2001) was conducted of the whole, mostly chronic, psychiatric inpatient population on the Caribbean island of Curaçao (N = 194). Almost all patients (95%) were of African Carribean origin. TD and TDt were assessed (1 baseline, 6 follow-ups) with the Abnormal Involuntary Movement Scale and the Fahn-Marsden rating scale, respectively. New cases of TD or TDt were diagnosed if they fulfilled the criteria at 2 successive follow-up visits.

Results: In patients with a mean antipsychotic use of approximately 18 years, the yearly incidence rates of TD and TDt were 10.2% (95% CI = 7.7 to 13.5) and 0.7% (95% CI = 0.4 to 1.5), respectively. The severity of TD was strongly associated with the severity of TDt ($\beta = 0.08$, 95% CI = 0.03 to 0.14) and vice versa ($\beta = 0.10$, 95% CI = 0.03 to 0.16). TD severity was positively associated with age and akathisia but negatively associated with parkinsonism.

Conclusions: Patients who are free of TD after many years of antipsychotic treatment still have a considerable risk for TD. Switching to an SGA may be warranted. The risk for incident TDt in this group was very low.

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Tardive dyskinesia (TD) and tardive dystonia (TDt) syndromes are frequent and severe side effects of antipsychotics, particularly first-generation antipsychotics (FGAs).[1] Both side effects can cause psychological or physical distress, and TDt especially may cause severe physical handicaps such as blepharospasm or torticollis.[2,3] The prevalence of TD and TDt in patients on long-term treatment with FGAs is 20% to 50% and 2% to 5%, respectively.[2,4]

However, some patients stay free of these tardive syndromes even after many years of treatment with FGAs. Do these patients remain at risk for TD and/or TDt and, consequently, should a switch to second-generation antipsychotics (SGAs) be considered in the context of lower risk for tardive syndromes but higher risk of other side effects such as weight gain, hyperlipidemia, new-onset diabetes mellitus, and cardiac complications?[5–10]

One incidence study showed that patients on long-term antipsychotic treatment do remain at risk for TD[11]; however, the population included came from referrals to a specialized clinic, giving doubts about the representativeness of the population. Also, the duration of the study was 5 years, which may not be long enough to capture the incident morbidity force of TD. Moreover, in that study, only TD was measured, and no data were available on

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TDt, akathisia, or parkinsonism. Thus, the relationship between TD and TDt or between the tardive syndromes and parkinsonism or akathisia could not be investigated.[11]

Therefore, we conducted a study with patients on long-term antipsychotic treatment in a well-defined catchment area, with a long follow-up (9 years), and with the aim to measure the incidence of TD and TDt and, additionally, akathisia and parkinsonism.

METHOD

Sample

The study was conducted in Curaçao, an island in the Caribbean with a predominantly African Caribbean population. In 1992, a cross-sectional survey (N = 194) was carried out with all inpatients of the Dr. D. R. Capriles Hospital, the only psychiatric hospital in Curaçao providing services for all patients with psychotic disorders. Almost all psychiatric inpatients (95%) were of African Caribbean origin.[12]

To be eligible for the study, a patient had to fulfill the following criteria: (1) no organic disorders that could cause movement disorders and (2) a history of use of antipsychotics for at least 3 months.[12]

The protocol was approved by the Curaçao Institutional Review Board, and informed consent was obtained from each patient after the purpose of the study was fully explained.

Demographic and Clinical Variables at Baseline and Follow-Up

The variables collected at baseline have been described previously. Briefly, age, sex, DSM-III-R diagnosis, presence of diabetes mellitus, and a history of leucotomy were assessed.[12]

Current use of medication was assessed at baseline and at each follow-up assessment. Antipsychotic doses were converted into chlorpromazine equivalents, anticholinergics into benztropine equivalents, and benzodiazepines into diazepam equivalents. Lithium and other medications were assessed as binary variables indicating presence or absence.[13]

The lifetime medication data were reviewed as previously reported. Lifetime medication data were considered valid when they were clearly indicated in the patients' charts for at least 90% of the time in which medication had been taken.[14]

Case Definition of Movement Disorders

Dyskinesia was defined as involuntary writhing and purposeless, irregular movements that may or may not be continuous.

Dystonia was defined as a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures. If the dystonic movement was rated on the Fahn-Marsden scale,[15] it was not rated on the Abnormal Involuntary Movement Scale (AIMS).[16] Sometimes, if a body region had both dystonic and dyskinetic movements, both were rated as such.

A detailed description of case definitions of TD, TDt, akathisia, and parkinsonism was given previously[12,14] and is repeated briefly below.

Tardive dyskinesia. Assessment of TD was carried out with the AIMS, which includes orofacial dyskinesia and choreiform purposeless movements of the trunk and/or limbs.[4] The case definition was based on the criteria laid down by Schooler and Kane.[17] The severity of TD was calculated as the sum of the first 7 items of the AIMS, each of which measures the severity of abnormal movements in a different area.

Tardive dystonia. For TDt to be diagnosed, it had to fulfill Burke's criteria.[18] TDt was rated using the Fahn-Marsden rating scale[15] and was diagnosed if 1 body area was involved at a severity level of at least "mild" or if 2 or more body areas were involved at a level of at least "slight." If frequent eye blinking (a "mild" rating on the item "eyes") was the only symptom, at least a "moderate" (blepharospasm) involvement was required in order to obtain case status. The severity of TDt was calculated as the total score on the Fahn-Marsden rating scale.

Akathisia. *Akathisia* can be defined as subjective complaints of both restlessness and objective motor movements, typically movements of the legs. Akathisia was assessed with the Barnes Akathisia Rating Scale,[19] which comprises an objective and subjective item.

Parkinsonism. Parkinsonism was measured with the motor examination section of the Unified Parkinson's Disease Rating Scale.[20] Rest-tremor and rigidity are typical of parkinsonism; therefore, a "mild" involvement on one of these items led to the case definition. If no tremor or rigidity were rated, the cutoff point was at least 1 "moderate" or 2 "mild" scores on the other items. This more stringent criterion for items concerning bradykinesia and postural stability was chosen because these symptoms can also be caused by psychiatric syndromes or sedation.

Incidence

Over the course of the study, patients were reexamined 6 times by the same 2 raters (P.N.vH., G.E.M.) simultaneously. The same examination procedure was used as the one used in the cross-sectional study,[12] which aimed to reach a consensus diagnosis. An *incident case* was defined as a case meeting the criteria for TDt or TD for the first time for at least 2 consecutive assessments. This is in line with the Research Diagnostic Criteria for a persistent case.[17]

In order to measure incidence, at least 2 follow-up assessments were required; 28.2% of the patients had less than 2 follow-up assessments. For the risk factor analysis, at least 1 follow-up was required; 14.4% of the patients

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had no follow-up. A total of 43.8% of the patients participated in all 6 follow-up assessments.

Statistical Analyses

Incidence analyses. The 9-year period (1992–2001) incorporated a baseline assessment and 6 follow-up assessments. Because the requirements for an incident case were (1) being free of TD (or TDt) at baseline and (2) showing evidence of new TD (or TDt) for at least 2 consecutive follow-ups, the earliest moment at which a person could become a "case" was between the first and the second follow-up (no TD or TDt at baseline, emergence of TD or TDt between baseline and first follow-up, and persistence of TD or TDt between first and second follow-up). In order to calculate incidence rates, the time from the first follow-up to the end of the study was divided into 5 time bands. During each of the 5 time bands (follow-up 1 to follow-up 2, follow-up 2 to follow-up 3, follow-up 3 to follow-up 4, follow-up 4 to follow-up 5, follow-up 5 to follow-up 6), person-time was allocated to each patient. Person-time was the number of years between the first follow-up and the interview at which the person was diagnosed as having TD or TDt or between the first follow-up and the last interview if the person did not develop either syndrome. If a person missed an assessment on a given occasion, but was seen on the next occasion, the most recently updated status was used to assess the presence of TD or TDt, and person-time was assigned accordingly.

Incidence rates (of TD and TDt) were calculated for each time band by dividing the number of incident cases by the person-time of follow-up. Incidence rates were expressed as percentages. Cumulative incidence was expressed as the number of cases of TD (or TDt) over the follow-up divided by the total person years over the follow-up. Patients who developed TD (or TDt) at 1 screening point were censored, i.e., they were excluded from incidence rate analyses at the next screening points.

Severity analyses. In order to compute an incidence rate, it is necessary to dichotomize the tardive syndrome. However, the scores on the tardive syndrome rating scales are more likely to be a reflection of a continuously varying phenotype than an arbitrarily defined cutoff point. Therefore, analyses of risk and protective factors are much more sensitive if carried out with the continuous outcome of the AIMS and the total scores on the Fahn-Marsden rating scale. As the mean continuous measure of tardive movements is assumed to vary across persons, 2 observations will be more similar if they pertain to the same person. Our design of repeated measures within the same person therefore compromised the statistical independence of the observations. In order to deal with this issue, multilevel random-regression models[21] were fitted using the XTREG procedure in the STATA statistical program.[22] In multilevel regression, dependency of observations within persons is taken into account by estimating a within-person as well as a between-person level variance. Thus, the model used had 2 levels: 7 measurement occasions (level 1: 1 baseline and 6 follow-ups) clustered within subjects (level 2). Effect sizes of explanatory variables were expressed as regression coefficients (β) from the multilevel models, which can be interpreted in the same way as the coefficients from regular multiple regression models (change in y with 1 unit change in x).

Two types of analyses of risk and protective factors were performed. First, effects of potential risk factors were calculated for change in AIMS and Fahn-Marsden rating scale scores for individuals with any baseline value on these 2 scales. Second, effects of potential risk factors were calculated for the onset of any AIMS and Fahn-Marsden rating scale abnormality for individuals, who, at baseline, had a score of zero on the AIMS or the Fahn-Marsden rating scale, respectively. The change analyses were performed by including all subjects in the analyses and adjusting for the baseline score on the AIMS or the Fahn-Marsden rating scale. The onset analyses were conducted by restricting the samples to those with a zero score on the AIMS or the Fahn-Marsden rating scale. All effects of predictors were adjusted for age and sex. In addition, associations between movement disorders were adjusted for medication variables at the time of assessment (dosage in chlorpromazine equivalents for antipsychotics and yes/no variables for anticholinergics, benzodiazepines, antidepressants, lithium, and other medication).

RESULTS

Sample Characteristics

Of the risk set of 117 patients who were free of TD at baseline, 84 (72%) had at least 2 assessments after baseline. Of the risk set of 168 patients who were free of TDt at baseline, 124 patients (74%) had at least 2 follow-up assessments after baseline. The characteristics of these incidence cohorts are shown in Table 1.

Incidence Rates

The overall yearly incidence rates of TD and TDt were 10.2% (95% CI = 7.7 to 13.5) and 0.7% (95% CI = 0.4 to 1.5), respectively. The incidence of TD decreased over time and was relatively high during the first 3 follow-up intervals compared with the incidence rates in the last 2 follow-up intervals (Table 2). The incidence of TDt over time remained stable but low (Table 2).

Severity Analyses: Prediction of Change and Prediction of Onset

The prediction of change for TD and TDt was analyzed in a risk set consisting of all patients at baseline (N = 194). (For characteristics of this cohort, see a previous article.[12]) The prediction of the onset of TD and TDt was analyzed in

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Table 1. Characteristics of the Incidence Cohorts at Baseline[a]

Characteristic	Cohort Without Tardive Dyskinesia (N = 84)	Cohort Without Tardive Dystonia (N = 124)
Age, mean (SD), y	50.7 (13.8)	53.8 (14.7)
Male, %	79.8	77.4
Age at first admission, mean (SD), y	23.2 (8.4)	24.8 (9.8)
Primary DSM-III-R psychiatric diagnosis, %		
Schizophrenia[b]	81.0	79.8
Affective disorder	6.0	4.0
Dementia	0.0	4.0
Mental retardation	1.2	2.4
Other	11.9	9.7
Secondary diagnosis, %		
Cocaine abuse[c]	9.5	10.5
Diabetes mellitus	7.1	9.7
Leucotomy in the past	11.9	13.7
Medication at baseline		
Antipsychotics, mean (SD), mg/d chlorpromazine equivalents	764.9 (859.5)	663.2 (793.9)
Anticholinergics, %	41.7	34.7
Benzodiazepines, %	22.6	21.0
Antidepressants, %	4.8	4.0
Lithium, %	15.5	12.1
Other, %	26.2	25.8
Lifetime medication[d]		
Lifetime intake of neuroleptics, mean (SD), kg chlorpromazine equivalents	4.61 (3.86) (N = 71)	4.1 (3.5) (N = 109)
Duration of antipsychotic use, mean (SD), y	18.7 (9.3) (N = 71)	18.3 (9.5) (N = 109)
No. of neuroleptic interruptions each longer than 3 mo, mean (SD)	1.1 (1.4) (N = 71)	1.4 (1.8) (N = 109)
Lifetime intake of anticholinergics, mean (SD), gram benztropine equivalents	30.4 (23.9) (N = 71)	26.9 (24.0) (N = 109)
Duration of anticholinergic use, mean (SD), y	10.9 (7.4) (N = 71)	9.8 (7.5) (N = 109)
Duration of lithium use, mean (SD), y	1.1 (3.6) (N = 70)	0.9 (3.2) (N = 108)
Movement disorders at baseline, %[e]		
Parkinsonism	38.1	36.3
Akathisia	8.3	10.5
Tardive dystonia	7.1	…
Tardive dyskinesia	…	37.1

[a]Patients in each cohort had at least 2 follow-up assessments.
[b]Includes 295.1, 295.2, 295.3, 295.4, 295.6, 295.7, and 295.9.
[c]In Curaçao, addiction to drugs refers almost exclusively to cocaine (base) and cannabis.
[d]Some lifetime medication data were missing (see text).
[e]According to case definitions (see text and reference 12).

a risk set of patients with zero points at baseline on the AIMS (N = 66) or the Fahn-Marsden rating scale (N = 135), respectively (Tables 3 and 4). The 66 patients with zero points on the AIMS at baseline had a mean age of 51.1 years (SD = 13.9) and 77.3% were men, 6.1% had diabetes mellitus, 12.1% had a history of leucotomy, and 9.1% used cocaine. The 135 patients with zero points on the Fahn-Marsden rating scale at baseline had a mean age of 54.5 years (SD = 15.6) and 74.8% were men, 8.1% had diabetes mellitus, 13.3% had a history of leucotomy, and 11.1% used cocaine.

The severity of TD was positively associated with age, leucotomy, akathisia, and the severity of TDt but was negatively associated with diabetes and the severity of parkinsonism (Table 3). The severity of TDt was related only to the severity of TD (Table 4).

DISCUSSION

Incidence of TD

This study clearly shows that patients on long-term antipsychotic treatment remain at risk for TD, with an incidence rate of 10.2% per year. There was some decrease in the incidence of TD after the fourth assessment. However, the number of subjects at risk after the fourth assessment was too small to draw a solid conclusion.

Most incidence studies of TD in populations using FGAs had only a baseline and endpoint assessment or were of relatively short duration (less than 3 years).[1] However, TD is a variable syndrome with a waxing and waning course, and therefore longer study and more frequent follow-ups are likely to increase the accuracy of TD incidence assessment. Furthermore, to define a side effect with clinical relevance, it is better to identify new cases on the basis of research criteria for persistent TD.

Two studies in a population with long-term use of antipsychotics had at least 2 assessments after baseline and used the research criteria mentioned. The Yale study[11] included whites and African Americans in a study population that, on average, was 10 years younger than the population in the current study. The researchers found an overall incidence of persistent TD of 5.3% and a relative risk of nearly 2 for African American patients.[11] Our incidence rate for TD (10.2%) is almost twice the overall rate (5.3%) of the Yale study but is comparable to the incidence among African Americans in the Yale study population. Therefore, it may well be that the high incidence found in the current study has ethnic specificity and that black ethnic groups are more vulnerable to TD than whites. However, no firm conclusion could be made about ethnicity as a risk factor because no white ethnic group was available for comparison.

Moreover, a study of a population with a mean age and duration of antipsychotic treatment comparable to our study, but conducted in white patients, reported half the incidence compared to our incidence rate.[23]

Incidence of TDt

This first incidence study of TDt showed a low incidence of 0.7% per year in patients on long-term antipsy-

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Table 2. Incidence of Persistent Tardive Dyskinesia and Tardive Dystonia[a]

	Tardive Dyskinesia				Tardive Dystonia			
Postbaseline Follow-Up[b]	Subjects, N	No. of Onsets	Person-Years	Rate,%	Subjects, N	No. of Onsets	Person-Years	Rate, %
1	…	…	…	…	…	…	…	…
2	82	26	193	13.5	120	4	278	1.4
3	48	9	82	11.0	101	0	173	0
4	41	6	53	11.4	101	2	116	1.7
5	32	3	53	5.7	87	0	145	0
6	32	5	102	4.9	89	1	251	0.4

[a]Definitions of persistent tardive dyskinesia and tardive dystonia are given in the text.
[b]Baseline was in 1992; postbaseline follow-up assessments were in 1993, 1994, 1996, 1997, 1998, and 2001.

Table 3. Variables Related to the Severity of Tardive Dyskinesia (TD) to Predict Change and Onset of TD[a]

	Cohort of All Patients at Baseline (N = 194)			Cohort of Patients With Zero Points on the Abnormal Involuntary Movement Scale at Baseline (N = 66)		
Predictor Variable[b]	β[c]	95% CI	p	β	95% CI	p
Demographic variables						
Age at baseline, y	0.07	0.04 to 0.10	.000	0.08	0.013 to 0.15	.019
Sex	0.43	–0.65 to 1.50	.44	0.38	–1.94 to 2.70	.75
Age by sex, y	–0.01	–0.07 to 0.06	.82	0.04	–0.12 to 0.21	.63
Baseline diagnoses						
Diabetes mellitus	–0.75	–2.25 to 0.74	.32	–3.98	–7.56 to –0.41	.029
Leucotomy	1.86	0.48 to 3.24	.008	1.94	–1.02 to 4.90	.20
Cocaine abuse	–0.20	–1.71 to 1.30	.79	0.48	–3.06 to 4.02	.79
Baseline psychiatric diagnoses						
Schizophrenia	0.00[d]			0.00[d]		
Affective disorder	–0.50	–2.56 to 1.57	.64	1.65	–2.12 to 5.43	.39
Dementia	1.83	–0.55 to 4.22	.13	…[e]	…	…
Mental retardation	0.94	–2.39 to 4.28	.58	1.14	–6.10 to 8.38	.76
Other	–1.20	–2.63 to 0.22	.10	–1.71	–4.81 to 1.38	.28
Movement disorders at baseline						
Akathisia	–0.83	–2.26 to 0.60	.25	–0.80	–4.63 to 3.02	.68
Score on Fahn-Marsden rating scale	0.04	–0.01 to 0.09	.14	0.22	0.06 to 0.39	.007
Score on UPDRS	–0.009	–0.05 to 0.03	.65	–0.04	–0.13 to 0.04	.32
Movement disorders during follow-up						
Akathisia at time of assessment	1.59	0.47 to 2.70	.005	2.80	0.50 to 5.09	.017
Akathisia at previous visit	0.83	–0.38 to 2.03	.18	1.87	–0.26 to 3.99	.085
Score on Fahn-Marsden rating scale at time of assessment	0.08	0.03 to 0.14	.001	0.11	–0.03 to 0.25	.12
Score on Fahn-Marsden rating scale at previous visit	0.05	–0.01 to 0.10	.13	0.04	–0.09 to 0.18	.53
Score on UPDRS at time of assessment	–0.04	–0.07 to –0.01	.004	–0.04	–0.09 to 0.01	.13
Score on UPDRS at previous visit	–0.03	–0.06 to 0.007	.13	–0.06	–0.12 to –0.002	.044
Score of tremor at time of assessment	–0.22	–0.35 to –0.10	.000	–0.30	–0.49 to –0.12	.001
Score of tremor at previous visit	–0.09	–0.23 to 0.06	.23	–0.20	–0.39 to –0.01	.038

[a]Severity of TD was measured on a continuous scale. The range at baseline was 0–17; mean = 4.1; SD = 4.7.
[b]The associations between each variable (other than age and sex) and the severity of TD were adjusted for age and sex. The associations between movement disorders and the severity of TD were also adjusted for medication variables at time of assessment (dosage in chlorpromazine equivalents and yes/no variables of anticholinergics, benzodiazepines, antidepressants, lithium, and others).
[c]Analyses were adjusted for baseline score on the Abnormal Involuntary Movement Scale.
[d]Reference category.
[e]No cases for analyses.
Abbreviation: UPDRS = Unified Parkinson's Disease Rating Scale.

chotic treatment. A baseline prevalence rate of TDt of 13.4%[12] together with a very low incidence of TDt in the population that was free of TDt at baseline suggest that this side effect occurs relatively early during the course of antipsychotic treatment. This relatively early development of TDt during antipsychotic treatment was also reported in a review of 110 case reports; around 80% of patients developed TDt within 5 years of exposure to antipsychotics.[18]

Interpretation of the Incidence Rates

This study shows that the risk of TD remains high over time, whereas the risk of TDt appears to diminish over the years. This finding underlines that TDt is not a subgroup of TD but a separate disorder.[2] Other studies show that the mean age at onset of TDt is lower than the age at onset of TD.[18] It is tempting to link the age-dependent vulnerability of TDt and TD to the activity of the dopamine system.

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Table 4. Variables Related to the Severity of Tardive Dystonia (TDt) to Predict Change and Onset of TDt[a]

	Cohort of All Patients at Baseline (N = 194)			Cohort of Patients With Zero Points on the Fahn-Marsden Rating Scale at Baseline (N = 135)		
Predictor Variable[b]	β[c]	95% CI	p	β	95% CI	p
Demographic variables						
Age at baseline, y	0.02	–0.01 to 0.05	.19	0.008	–0.009 to 0.02	.37
Sex	0.53	–0.49 to 1.55	.31	0.24	–0.34 to 0.82	.42
Age by sex, y	–0.04	–0.11 to 0.02	.18	–0.01	–0.05 to 0.03	.49
Baseline diagnoses						
Diabetes mellitus	–0.32	–1.84 to 1.19	.68	–0.41	–1.25 to 0.43	.34
Leucotomy	0.60	–.82 to 2.01	.41	0.57	–0.20 to 1.35	.15
Cocaine abuse	–0.04	–1.57 to 1.48	.96	–0.22	–1.08 to 0.65	.62
Baseline psychiatric diagnoses						
Schizophrenia	0[d]			0[d]		
Affective disorder	–0.94	–3.04 to 1.17	.39	–0.54	–1.93 to 0.85	.45
Dementia	0.43	–1.90 to 2.75	.72	0.66	–0.69 to 2.00	.34
Mental retardation	–0.14	–3.57 to 3.28	.94	–0.16	–1.78 to 1.45	.84
Other	0.07	–1.39 to 1.53	.92	–0.07	–0.94 to 0.80	.88
Movement disorders at baseline						
Akathisia	0.18	–1.35 to 1.70	.82	–0.48	–0.31 to 1.27	.23
Score on AIMS	0.06	–0.04 to 0.17	.26	0.04	–0.01 to 0.10	.14
Score on UPDRS	–0.01	–0.05 to 0.03	.55	0.003	–0.02 to 0.03	.80
Movement disorders during follow-up						
Akathisia at time of assessment	0.62	–0.51 to 1.75	.28	0.76	–0.03 to 1.56	.059
Akathisia at previous visit	0.66	–0.48 to 1.81	.26	0.48	–0.25 to 1.21	.20
Score on AIMS at time of assessment	0.10	0.03 to 0.16	.002	0.07	0.02 to 0.11	.002
Score on AIMS at previous visit	–0.02	–0.09 to 0.05	.54	0.006	–0.04 to 0.05	.78
Score on UPDRS at time of assessment	–0.004	–0.03 to 0.03	.79	0.009	–0.01 to 0.03	.38
Score on UPDRS at previous visit	–0.003	–0.03 to 0.03	.87	0.003	–0.02 to 0.02	.78
Score of tremor at time of assessment	0.00	–0.12 to 0.13	.99	0.008	–0.07 to 0.08	.82
Score of tremor at previous visit	–0.05	–0.18 to 0.09	.51	0.007	–0.07 to 0.08	.86

[a]Severity of TDt was measured on a continuous scale. The range at baseline was 0–61; mean = 2.5; SD = 8.1.
[b]The associations between each variable (other than age and sex) and the severity of TDt were adjusted for age and sex. The associations between movement disorders and the severity of TDt were also adjusted for medication variables at time of assessment (dosage in chlorpromazine equivalents and yes/no variables of anticholinergics, benzodiazepines, antidepressants, lithium, and others).
[c]Analyses were adjusted for baseline score on the Fahn-Marsden rating scale.
[d]Reference category.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, UPDRS = Unified Parkinson's Disease Rating Scale.

Indeed, it has been found that D_2 activity decreases with age, and it could be hypothesized that individuals with an active dopamine system are more at risk of developing dystonic features during a long-term blockage of the D_2 receptor, whereas those with a less active dopamine system are more at risk of developing dyskinetic features.[24,25]

Interpretation of Interrelationships Over Time Between TD, TDt, Parkinsonism, and Akathisia

The severities of TD and TDt were significantly associated with each other, and the severity of TD was significantly associated with akathisia. These 3 movement disorders all have hyperkinetic characteristics. From a pathophysiologic point of view, hyperkinetic movement disorders have been associated with receptor supersensitivity, and this may represent a common pathway for these 3 hyperkinetic side effects.[26] The differences in phenomenology and risk factors may be related to a difference in the receptor involved. Genetic studies have found associations between various candidate receptor genes and each of these hyperkinetic side effects.[27]

The severity of parkinsonism was inversely related to the severity of TD. Parkinsonism is a hypokinetic movement disorder and is directly related pathophysiologically to a blockage of the dopamine receptor and not to the supersensitivity of a receptor. Previous work has also reported a negative association between parkinsonism and TD.[28,29] However, parkinsonism does not exclude TD. Indeed, both syndromes are very common, and they occur simultaneously in 6% to 24% of patients.[30] In the 9-year period of our study, the mean prevalence of the simultaneous occurrence of TD and parkinsonism was 21% (range, 12%–23%).

Parkinsonism is characterized by bradykinesia, tremor, and rigidity. Bradykinesia can have many causes such as depression, negative symptoms, or sedation, and rigidity can also be found in catatonia or can be misdiagnosed in nervous patients with muscle tension. Rest tremor, on the other hand, is more specifically related to parkinsonism. Therefore, the association between the severity of TD and the severity of rest tremor was analyzed separately. The significant inverse relationship between rest tremor and TD confirms that parkinsonism is inversely related to TD.

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Demographic and Clinical Factors

Age is a well-known risk factor for TD, and this study shows that, in patients who are on long-term antipsychotic treatment, age remains a risk factor for TD.[31] Sex was not found to be a risk factor.

Another risk factor, independent of age, which was corrected for, was leucotomy. With the exception of 1 patient, all leucotomies in Curaçao were carried out between 1950 and 1954. Several previous studies reported that leucotomy was a risk factor for TD.[26]

A negative association was found between diabetes mellitus and TD in the cohort with zero points on the AIMS at baseline; the small number of cases with diabetes mellitus (N = 4) in this cohort, however, does not permit a broader interpretation.

In contrast to the TD findings, no demographic or clinical variables were associated with the onset and the severity of TDt. This finding supports the suggestion that TDt is a separate disorder, although the comparatively low statistical power may also have played a role.

Strengths of This Study

A 9-year study with 1 baseline and 6 follow-up assessments will give a more accurate incidence estimate than studies of relatively short duration or studies with only a few assessments.

The interrater reliability in follow-up studies is often compromised in that a string of changing investigators is involved. In this study, the same 2 investigators carried out all follow-up assessments simultaneously, ensuring continuing reliability and comparability of assessments over time.

The Netherlands Antilles, where this study was conducted, is a very suitable location for epidemiologic research because, with only 1 psychiatric hospital, the population under study includes all psychiatric inpatients of the Netherlands Antilles. Furthermore, the catchment area is well defined because the Netherlands Antilles are islands. Another advantage is that island patients can easily be tracked after discharge from the hospital, resulting in low attrition rates.

Limitations

It could be argued that incidence studies should include patients who have started only recently with an antipsychotic treatment instead of patients chronically exposed to antipsychotics. However, the main goal of this study was to assess the incidence of TD and TDt in a patient group characterized by many years of antipsychotic treatment and still free of TD and/or TDt.

The study covered 9 years, and it could be that a longer follow-up would be more appropriate in order to differentiate between those patients who will develop TD or TDt versus those who will not. However, this is the first incidence study of TD and TDt in a population on long-term antipsychotic treatment of such long duration and with multiple assessments.

The number of patients in our study is relatively small compared with the numbers in classic studies such as, for example, the Yale study.[11] However, we were able to include all inpatients in a well-defined catchment area and could assess them during a long follow-up period (almost twice as long as in the Yale study), and this increased the power of the study by providing more person-years.

It can be questioned whether the raters were able to make a clear distinction between the various extrapyramidal syndromes, in particular, between TD and TDt. However, the raters were clinical experts in movement disorders and rated dyskinesia when patients had continuous involuntary, purposeless movements and rated dystonia when movements were twisted and the dystonic features lasted at least for 1 second.[12,18]

In the patient group, 28.2% had less than 2 follow-up assessments and therefore did not contribute to the TD/TDt incidence study. This group was more often female, older at first admission, more often using cocaine, and without history of leucotomy compared with the group with at least 2 follow-up assessments. Of these variables, only leucotomy was a risk factor, and therefore, it could be hypothesized that, in the patients who did not contribute to the TD incidence study, the TD rate would have been slightly lower.

Clinical Consequences

It is clear that patients on long-term treatment with FGAs remain at risk for TD, and the risk factor age does not abate with time. Therefore, clinicians should consider preventive strategies in these patients, such as prescribing SGAs with a lower risk of TD.[4,5]

Furthermore, in patients diagnosed with a hyperkinetic syndrome (TD, TDt, or akathisia), clinicians should be alerted to examine for another hyperkinetic syndrome because they are significantly interrelated.

Drug names: benztropine (Cogentin and others), chlorpromazine (Thorazine, Sonazine, and others), diazepam (Valium), lithium (Eskalith, Lithobid, and others).

REFERENCES

1. Glazer WM. Review of incidence studies of tardive dyskinesia associated with typical antipsychotics. J Clin Psychiatry 2000;61 (suppl 4):15–20
2. van Harten PN, Kahn RS. Tardive dystonia. Schizophr Bull 1999;25:741–748
3. Fernandez HH, Friedman JH. Classification and treatment of tardive syndromes. Neurologist 2003;9:16–27
4. American Psychiatric Association. Tardive Dyskinesia: A Task Force Report of the American Psychiatric Association. Washington, DC: American Psychiatric Association; 1992
5. Correll CU, Leucht S, Kane JM. Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. Am J Psychiatry 2004;161:414–425
6. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry

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1999;156:1686–1696
7. Koro CE, Fedder DO, L'Italien GJ. Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-controlled study. BMJ 2002;325:243
8. Coulter DM, Bate A, Meyboom RHB. Antipsychotic drugs and heart muscle disorder in international pharmacovigilance: data mining study. BMJ 2001;322:1207–1209
9. Koro CE, Fedder DO, L'Italien GJ. An assessment of the independent effects of olanzapine and risperidone exposure on the risk of hyperlipidemia in schizophrenic patients. Arch Gen Psychiatry 2002;59:1021–1026
10. Lieberman JA, Stroup TS, McEvoy JP, et al, and the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005;353:1209–1223
11. Morgenstern H, Glazer WM. Identifying risk factors for tardive dyskinesia among long-term outpatients maintained with neuroleptic medications: results of the Yale Tardive Dyskinesia Study. Arch Gen Psychiatry 1993; 50:723–733
12. van Harten PN, Matroos GE, Hoek HW, et al. The prevalence of tardive dystonia, tardive dyskinesia, parkinsonism and akathisia: the Curaçao Extrapyramidal Syndromes Study 1. Schizophr Res 1996;19:195–203
13. Davis JM. Comparative doses and costs of antipsychotic medication. Arch Gen Psychiatry 1976;33:858–861
14. van Harten PN, Hoek HW, Matroos GE, et al. Intermittent neuroleptic treatment and risk for tardive dyskinesia: Curaçao Extrapyramidal Syndromes Study 3. Am J Psychiatry 1998;155:565–567
15. Burke RE, Fahn S, Marsden CD, et al. Validity and reliability of a rating scale for the primary torsion dystonias. Neurology 1985;35:73–77
16. Psychopharmacology Research Branch, National Institute of Mental Health. Abnormal Involuntary Movement Scale (AIMS). In: Guy W, ed. ECDEU Assessment Manual for Psychopharmacology, Revised. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:534–537
17. Schooler NR, Kane JM. Research diagnoses for tardive dyskinesia. Arch Gen Psychiatry 1982;39:486–487
18. Burke RE. Neuroleptic-induced tardive dyskinesia variants. In: Lang AE, Weiner WJ, eds. Drug-Induced Movement Disorders. Mount Kisco, NY: Futura Publishing Co.; 1992:167–198
19. Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672–676
20. Martinez-Martin P, Gil-Nagel A, Gracia LM, et al. Unified Parkinson's Disease Rating Scale characteristics and structure. The Cooperative Multicentric Group. Mov Disord 1994;9:76–83
21. Goldstein H. Multilevel Models in Educational and Social Research. London, England: Charles Griffin, Oxford University Press; 1987
22. Stata Base Reference Manual: Release 8. College Station, Tex: Stata Press; 2003
23. Yassa R, Nair V. Incidence of tardive dyskinesia in an outpatient population. Psychosomatics 1984;25:479–481
24. van Harten PN, Hoek HW, Kahn RS. Acute dystonia induced by drug treatment. BMJ 1999;319:623–626
25. Volkow ND, Gur RC, Wang GJ, et al. Association between decline in brain dopamine activity with age and cognitive and motor impairment in healthy individuals. Am J Psychiatry 1998;155:344–349
26. Khot V, Egan MF, Hyde TM. Neuroleptics and classic tardive dyskinesia. In: Lang AE, Weiner WJ, eds. Drug-Induced Movement Disorders. Mount Kisco, NY: Futura Publishing Co.; 1992:121–166
27. Lerer B. Pharmacogenetics of psychotropic drugs. Cambridge, Mass: Cambridge University Press; 2002
28. Lang AE, Weiner WJ. Drug-induced movement disorders. Mount Kisco, NY: Futura Publishing Co.; 1992
29. van Harten PN, Hoek HW, Matroos GE, et al. The inter-relationships of tardive dyskinesia, parkinsonism, akathisia and tardive dystonia: the Curaçao Extrapyramidal Syndromes Study 2. Schizophr Res 1997;26:20 35–242
30. Gardos G, Cole JO. Drug-induced parkinsonism and concomitant tardive dyskinesia. In: Joseph AB, Young RR, eds. Movement Disorders in Neurology and Neuropsychiatry. Malden, Mass: Blackwell Science; 1999: 52–57
31. van Os J, Fahy T, Jones P, et al. Tardive dyskinesia: who is at risk? Acta Psychiatr Scand 1997;96:206–216

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