Risk of Tardive Dyskinesia in Older Patients

A Prospective Longitudinal Study of 266 Outpatients

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Background: Neuroleptic-induced tardive dyskinesia (TD) is a major iatrogenic disorder that is more prevalent among older patients. The objective of this study was to determine the incidence of and risk factors for TD in neuroleptic-treated patients over age 45 years.

Methods: We studied 266 middle-aged and elderly outpatients with a median duration of 21 days of total lifetime neuroleptic exposure at study entry. Most patients were treated throughout the study with either a high-potency or a low-potency neuroleptic and maintained on relatively low doses. The patients were followed up at 1- to 3-month intervals with "blind" assessment of psychopathologic condition, clinically as well as instrumentally (ie, using electromechanical sensors with computerized data reduction, including spectral analysis) evaluated movement disorder, and global cognitive function.

Results: Cumulative incidence of TD was 26%, 52%, and 60% after 1, 2, and 3 years, respectively. The principal risk factors for TD were duration of prior neuroleptic use at baseline, cumulative amount of high-potency neuroleptics, history of alcohol abuse/dependence, borderline or minimal dyskinesia, and tremor on instrumental assessment.

Conclusion: Use of higher amounts of neuroleptics, particularly high-potency ones, should be avoided in older patients, patients with alcohol abuse/dependence, or patients with a subtle movement disorder at baseline; these patients are at a higher risk of developing TD.

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ONE OF the most serious adverse effects of neuroleptic therapy is tardive dyskinesia (TD).[1,2] In a prospective study of more than 850 young adult patients (mean age, 29 years), the cumulative incidence of TD after exposure to neuroleptics was found to be 5% after 1 year, 19% after 4 years, and 26% after 6 years.[3] In a study population that consisted mainly of elderly institutionalized or inpatient subjects,[4] the cumulative incidence of TD was reported as 31% after 43 weeks of neuroleptic treatment.

Despite numerous studies spanning more than three decades, the understanding of risk factors for TD is still incomplete. Aging appears to be the predominant patient-related risk factor for TD.[2,5,6] Other patient-related risk factors, about which there is less evidence in the reported results, include female gender,[7] mood disorders,[4,8,9] alcohol or other substance abuse,[10,11] diabetes mellitus,[12-14] smoking,[15,16] African-American ethnicity,[17,18] and cognitive dysfunction.[19]

In terms of neuroleptic-related risk factors, no significant differences among different types of neuroleptics have been reported. A possible exception is clozapine, which reportedly has a much lower risk of TD.[20] Other suggested medication-related risk factors include a high amount of neuroleptics,[21-23] development of extrapyramidal symptoms (EPS) early in the course of neuroleptic treatment,[3,4,24-26] and use of anticholinergic agents.[27]

In an effort to overcome some of the problems associated with subjective ratings of EPS and to improve our skill at early detection of EPS, we have been using a battery of instrumental assessment procedures.[24,28] Instrumental motor measurement systems yield continuous rather than categorical or ordinal data, produce variables that show a linear positive relationship to the severity of the movement dis-

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METHODS AND MATERIALS

Over an approximately 4-year period, 266 consecutive outpatients over the age of 45 years met the following criteria for enrollment into our study: (1) psychiatric diagnoses (based on *DSM-III-R*[33] criteria and confirmed by at least two board-certified psychiatrists) for which neuroleptic therapy was indicated; (2) availability of reliable medical and pharmacological history from the patient, from medical records, and/or from significant others; (3) baseline evaluation prior to or early in the course of neuroleptic treatment; (4) absence of severe physical illness that would preclude study assessments; (5) not meeting criteria for TD (defined below); and (6) willingness to participate and to give informed consent in writing.

Patients were recruited from several sources, the majority coming from the San Diego (Calif) Veterans Affairs Medical Center. The patients' mean (SD) age was 65.5 (12.0) years; education level, 12.4 (3.3) years. Neuroleptics were prescribed to treat psychotic or other severe behavioral symptoms. The median cumulative duration of neuroleptic treatment at baseline was 21 days. We have several ongoing studies of late-onset psychosis, including schizophrenia. Hence, we received a number of referrals of patients over age 45 years who were either starting neuroleptic treatment or in the early stages of neuroleptic treatment. Of the 266 patients, 24.8% were neuroleptic-naive while 45.4% had 1 to 90 days of total lifetime neuroleptic exposure at baseline.

We used the criteria of Schooler and Kane[34,35] to diagnose TD, except that the minimum duration of prior neuroleptic use was 1 month instead of 3 months, given the higher risk and the likelihood of earlier development of TD in older patients.

INITIAL EVALUATION

Medical and Pharmacologic History

We obtained medical and pharmacologic history to record information about pertinent medical illnesses (eg, hyperthyroidism, stroke), alcohol and other substance abuse, smoking, and medications (especially neuroleptics).

Neurological and Other Medical Assessment

A complete neurological and other medical examination was performed to help diagnose "organic" disorders. Appropriate laboratory tests, such as thyroid function tests and computed tomography or magnetic resonance imaging of the brain, were obtained when indicated.

Global Cognitive Assessment

We used the Mini-Mental State Examination (MMSE).[36]

Assessment of Psychopathology

We used the Brief Psychiatric Rating Scale (BPRS)[37] and the Hamilton Depression Rating Scale (HAM-D).[38]

Clinical Assessment of Movement Disorder

We used the Simpson-Angus Scale for early EPS,[39] the Abnormal Involuntary Movement Scale (AIMS),[35] and the Simpson Abbreviated Dyskinesia Rating Scale (ADRS).[40]

Instrumental Assessment of Movement Disorder

Below we describe briefly our methods of evaluating movement or muscle activity using electromechanical sensors with computerized data reduction, including spectral analyses. The details of these procedures have been published previously.[24,41]

Instability. Force instability was used to quantify hand and jaw dyskinesia.[28,42]

Tremor. Postural tremor of the upper extremity was quantified.[43] Spectral amplitudes within the 3- to 7-Hz range have been shown to be reliable indexes of neuroleptic-induced tremor.[24,28,44]

Movement Speed. Bradykinesia was evaluated by measuring the peak instantaneous velocity associated with simple ballistic movements of the wrists.[45]

Rigidity. The procedure for quantifying abnormalities in muscle tone involved measurement of wrist stiffness.[46-48]

Videotaping

A standard procedure was followed to obtain a 10-minute videotape for the AIMS[35] examination.

FOLLOW-UP EVALUATION

The patients were assessed 1 and 3 months after study entry and then every 3 months with review of pharmacotherapy administered since the last assessment, neurological assessment, MMSE,[36] BPRS,[37] HAM-D,[38] Simpson-Angus Scale for early EPS,[39] AIMS,[35] ADRS,[40] instrumental assessment of movement disorder, and videotaping.

The raters were "blind" to other clinical information, including earlier assessments of the same patients. Videotaped recordings of patients' AIMS examinations at various periods were mixed randomly and analyzed at a later date by "blind" evaluators. A high degree of interrater reliability (intraclass correlation coefficient $>.84$) was established for the AIMS[35] and other rating scales.

TREATMENT

Patients were treated with relatively low doses of neuroleptics, determined individually (often <150 mg/d of chlorpromazine equivalent[6]). Moderate to severe EPS were treated with benztropine mesylate, usually at dosages of 2 mg/d or less.

Our original goal was to randomize every patient entering the study to either haloperidol or thioridazine. We found, however, that this was not possible in patients with a history of allergy to or severe side effects with either medication; or in case of a refusal for randomization by the patient, caregiver, or physician; or in

Continued on next page

patients already receiving neuroleptics who did not wish to be switched to another antipsychotic agent. Similarly, randomization to haloperidol or thioridazine was considered to be contraindicated in patients who were thought to be at a relatively high risk of side effects from either of these medications (eg, patients with severe parkinsonian signs at baseline or those with glaucoma). Additionally, some randomized patients refused to continue the medication prescribed because of side effects, etc. Of the 266 patients entering the study, 107 continued to take haloperidol (n=68) or thioridazine (n=39) for at least a month. Regardless of randomization, we strove to keep every patient in the study on the same medication for the entire duration of the study; failing that, we tried to keep him or her taking only one class of neuroleptics—either high-potency or low-potency. We kept a total of 190 patients taking either high-potency neuroleptics only (n=126) or low-potency neuroleptics only (n=64) throughout the study.

STATISTICAL METHODS

Life-table survival analysis[49] was employed to assess the cumulative incidence of TD for the total sample and for selected subgroups.

The analysis of the data on risk factors for TD was of two types: (1) *Univariable analysis* used either life-table survival analysis[49] or univariable Cox regression analysis.[50] The proportional hazards method (also called survival analysis with covariates or Cox regression) was used to investigate the effects of predictor variables and risk factors on the occurrence of TD.[50] Differences in subgroup survival curves were tested for significance by means of either improvement χ^2 analysis in the Cox regression analysis or the Breslow or Mantel-Cox statistic.[51] (2) The model for *cumulative multivariable analysis* (backward stepwise Cox regression) included more than one significant predictor at a time. Partialing for the effects of other predictors enabled one to assess the unique contribution of a given variable to the risk of TD.

Fixed and Time-Dependent Covariates

The potential risk factors for TD were considered to be either fixed or time-dependent[52] covariates. Fixed covariates were those variables, measured at baseline, that were fixed for the duration of the study (eg, age at intake or gender). Time-dependent covariates were the variables that were reassessed at subsequent visits and whose values could thus change as a function of the survival time (eg, AIMS score). The time-dependent variables for cumulative high-potency and low-potency neuroleptic amount were redefined repeatedly from the baseline visit to the visit at which TD had occurred or, in non-TD patients, from the baseline visit to the last visit; these were the contemporary time-dependent covariates. Thus, to estimate the risk of TD at the 9-month visit, we used a patient's total amount of high-potency neuroleptics received through the 9-month visit as the contemporary time-dependent covariate. All other time-dependent covariates were redefined repeatedly from the baseline value to the value at the visit prior to the occurrence of TD or to the visit prior to the last visit; these were the one-visit-back time-dependent covariates. For example, to estimate the risk of TD at the 9-month visit, we used a patient's MMSE total at the 6-month visit as the one-visit-back time-dependent MMSE covariate.

Cox Regression Analysis

A few continuous variables (eg, cumulative high-potency neuroleptic amount) with large range and skewed distribution of values were subjected to a base 10 logarithmic transformation prior to the Cox regression analysis to obtain useful $\hat{\beta}$ coefficients.[52]

One difficulty encountered in analysis was missing data, the amount of which differed across variables. To maximize the sample size, hence, power, for examining each variable in concert with others, we devised a staged approach to cumulative multivariable Cox regression analysis. We organized the variables into conceptually defined groupings and then ordered them beginning with the set of variables with the largest sample sizes (set 1) and ending with the set of variables with the smallest sample sizes (set 4).

- *Set 1* (N=230 to 266) comprised a basic set of fixed demographic (age, gender, ethnicity, education), fixed diagnostic grouping, fixed health index (history of diabetes, smoking, alcohol abuse/dependence), fixed and time-dependent MMSE score, fixed neuroleptic duration at baseline, and fixed and time-dependent high-potency and low-potency neuroleptic amount variables.
- *Set 2* (N=220 to 266) comprised a set of fixed and time-dependent clinical measures of motor abnormalities (Simpson-Angus EPS scale total score, AIMS global score, and ADRS total score).
- *Set 3* (N=191 to 202) comprised a set of fixed and time-dependent psychopathology rating scale scores (BPRS subscale scores and HAM-D total score).
- *Set 4* (N=153 to 178) comprised a set of fixed and time-dependent instrumental motor measures (instability, tremor, movement speed, and rigidity).

Univariable and cumulative multivariable Cox regression analyses[52,53] were run at each of the four stages corresponding to the four sets of variables. A cumulative multivariable Cox regression was run for the risk factor set corresponding to that stage plus the significant variables from each of the preceding stages. Within a stage, new variables had to meet nominal significance at $\alpha \leq .05$, while previously significant variables had to maintain nominal significance at $\alpha \leq .10$. All the tests for new main effects and new interactions were evaluated at the nominal criterion of $\alpha = .05$.

We also carried out some post hoc analyses, which are described in the "Results" section.

order, and can measure abnormalities below the threshold of human detection.[29] The instruments chosen for the proposed studies are relatively inexpensive, and the testing requires less than 30 minutes.[29]

We undertook the following study to determine the incidence of and risk factors for TD in middle-aged and elderly neuroleptic-treated outpatients because of the paucity of similar work in this population. Furthermore, we

wished (1) to include patients prior to or relatively early in the course of their neuroleptic treatment, (2) to assess the subjects at relatively short intervals (1 to 3 months), (3) to employ appropriate rating scales and instrumental motor evaluations, (4) to compare the risk of TD with low-potency vs high-potency neuroleptics given in relatively low dosages, and (5) to analyze the data in ways that would enable us to evaluate the individual and unique contributions of different risk factors for TD. Some of the risk factors reported in the literature are fixed (eg, gender), while others change over time—ie, are time-dependent (eg, cumulative amount of neuroleptics administered). Furthermore, there are varying degrees of associations among certain variables—eg, older age is likely to be associated with a longer duration of therapy and a greater cumulative amount of neuroleptics. Hence, we proposed to undertake univariable and multivariable analyses involving both the fixed and time-dependent variables.

We hypothesized that a number of fixed variables, such as older age, diagnoses of mood disorder and dementia, female gender, and duration of prior neuroleptic use at baseline, as well as time-dependent variables, such as the severity of EPS and cumulative amount of neuoleptics, would be significant univariable predictors of TD. We also hypothesized that older age, longer baseline duration of neuroleptic use, and greater cumulative amount of neuroleptics would emerge as risk factors for TD in the multivariable analysis.

We have previously published data on the 6-month and 1-year cumulative annual incidence of TD and some univariable analyses based on earlier results from the present, ongoing study.[30-32] This report represents our first attempt to examine the cumulative 3-year incidence of TD and risk factors for TD using a larger sample and multivariable as well as univariable data analyses.

RESULTS

At 1 year, the survival rate was 73.9%; hence, the 1-year incidence of TD was 26.1% (95% confidence interval [CI], 19.3% to 32.9%). The cumulative proportion developing TD by the end of 24 months was 51.7% (95% CI, 41.3% to 62.1%) and by the end of 36 months was 59.8% (95% CI, 47.6% to 72.0%) (**Figure 1**). From the life-table analysis we obtained 69 events or cases of TD per 211.9 person-years, or 0.33 events per person-year.

Table 1 shows that the following categorical or artificially dichotomized continuous variables at baseline were significant risk factors for TD: age under 65 years, duration of prior neuroleptic use of greater than 90 days at baseline, history of alcohol abuse/dependence, and baseline AIMS global score greater than 0. Although anticholinergic use was also a significant predictor, the proportion of patients treated with these drugs was small (11%). **Figure 2** shows the incidence of TD in patients with vs without a history of alcohol abuse/dependence.

Table 2 gives the results of univariable analysis using all the time-dependent variables and all the fixed variables for which there were no time-dependent values, but, unlike Table 1, Table 2 does not dichotomize continuous variables (such as age) artificially. The findings are similar to those in Table 1, except for the addition of the following time-dependent variables as significant predictors of the risk of TD: cumulative amount of high-potency neuroleptics, MMSE score, AIMS global score, and ADRS score, with trends for tremor and movement speed on instrumental assessment.

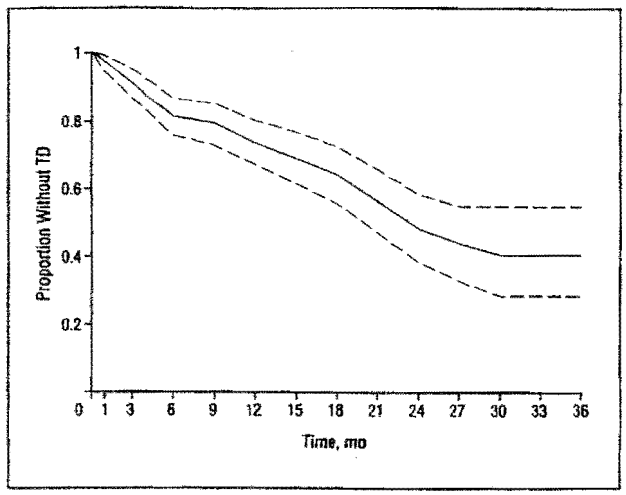

Figure 1. *Survival curve for tardive dyskinesia (TD) onset, with 95% confidence intervals (broken lines) (N=266).*

Table 3 presents the results of cumulative multivariable analysis at four successive stages. The stage 4 analysis may be viewed as the "final" result in that it suggests predictors whose unique contributions to the risk of TD were above and beyond what could be explained by their potential associations with other variables. The five significant predictors that emerged at the final stage were fixed duration of prior neuroleptic use at baseline, time-dependent cumulative amount of high-potency neuroleptics, fixed history of alcohol abuse/dependence, time-dependent AIMS global score, and time-dependent tremor on instrumental assessment. None of the first-order interaction effects among the variables was significant.

INTERPRETATION OF MODEL

From a clinical standpoint, an especially interesting value in Tables 1 through 3 is the risk ratio. Alcohol abuse/dependence may be considered as an example. In Tables 1 and 2 (stage 1), the risk ratio for this variable was 1.7—ie, when considered by itself, a history of alcohol abuse/dependence increased the risk of TD by a factor of 1.7. Table 3 examines the relative impact of the variable on the TD risk, considered in concert with other variables. In stage 1, the risk ratio for alcohol abuse/dependence (as a predictor of TD) was 2.0. In stage 2, the risk ratio for that variable was 1.9, and it remained unchanged in stage 3. In stage 4, the risk ratio for alcohol abuse/dependence was 1.7.

The other predictors identified in Tables 2 and 3 were continuous. Except for age, all the risk ratios for all the continuous variables (Tables 2 and 3) were greater than

Table 1. Life-Table Analysis of 1-Year Incidence Rates and Univariable Cox Regression Risk Ratios for Tardive Dyskinesia (TD)*

Variable	% of Subjects	Life-Table Analysis 1-Year Incidence of TD (95% CI)	Cox Regression Risk Ratio† (95% CI)	P‡
Age, y (n=264)				.03
<65	44.0	26.1 (16.1-36.2)	Reference group	
≥65	56.0	25.6 (16.2-34.9)	0.6 (0.4-0.9)	
Gender (n=265)				.36
F	18.5	21.2 (4.2-38.2)	Reference group	
M	81.5	26.6 (19.2-34.1)	1.4 (0.7-3.1)	
Ethnicity (n=265)				.20
White	81.9	23.2 (16.0-30.4)	Reference group	
Nonwhite	18.1	36.8 (19.0-54.7)	1.5 (0.8-2.6)	
Diagnostic group (n=266)				.23
Schizophrenia	21.4	28.6 (14.6-42.5)	1.4 (0.6-3.3)	
Mood disorder	21.1	27.0 (13.2-41.1)	1.0 (0.4-2.4)	
Other nonorganic disorder	16.2	29.3 (6.6-51.9)	Reference group	
Alzheimer's disease	24.4	27.3 (13.7-41.0)	0.7 (0.3-1.6)	
Other organic disorder	16.9	17.5 (3.0-31.9)	0.9 (0.4-2.5)	
Alcohol abuse or dependence (n=266)				.03
No	68.8	20.2 (12.6-27.8)	Reference group	
Yes§	31.2	37.7 (24.6-50.9)	1.7 (1.1-2.9)	
History of smoking (n=230)				.18
No	74.8	26.1 (17.8-34.4)	Reference group	
Yes	25.2	25.0 (11.0-39.1)	1.5 (0.9-2.5)	
Diabetes mellitus (n=266)				.33
No	84.6	25.9 (18.5-33.2)	Reference group	
Yes	15.4	27.6 (9.5-45.7)	1.4 (0.7-2.7)	
Baseline MMSE total (n=257)				.28
<28	57.6	29.5 (17.8-41.2)	Reference group	
≥28	42.4	24.5 (14.4-34.7)	1.3 (0.8-2.1)	
Duration of prior neuroleptic use at baseline, d (n=262)				.001
≤90	70.2	18.8 (11.5-26.1)	Reference group	
>90	29.8	39.7 (26.4-52.9)	2.4 (1.5-3.9)	
Neuroleptic treatment group (n=190)				.11
Low-potency	33.7	24.4 (8.9-39.8)	Reference group	
High-potency	66.3	34.3 (24.0-44.6)	1.7 (0.9-3.4)	
Anticholinergic use (n=147)				.005
No	89.1	20.4 (12.6-28.2)	Reference group	
Yes	10.9	64.4 (38.6-90.2)	3.5 (1.6-7.3)	
Baseline AIMS global score (n=265)				.007
0	67.9	19.8 (12.7-27.0)	Reference group	
>0	32.1	43.2 (27.9-58.6)	2.1 (1.3-3.6)	
Baseline ADRS total (n=244)				.37
<19	59.4	21.8 (13.3-30.3)	Reference group	
≥19	40.6	33.3 (20.9-45.8)	1.3 (0.8-2.2)	

*CI indicates confidence interval; MMSE, Mini-Mental State Examination; AIMS, Abnormal Involuntary Movement Scale; and ADRS, Simpson Abbreviated Dyskinesia Rating Scale.

†All dichotomous variables were coded 0 and 1. For diagnostic group, four dichotomous variables were coded 0 and 1, with 1 associated with the diagnostic category named.

‡Improvement χ^2 analysis.

§Eleven of these 83 patients were abusing alcohol at baseline; the other 72 patients had a history of only alcohol abuse or dependence.

1; therefore, the higher the value of the continuous variable, the greater the risk of TD.

EVALUATION OF MODEL

Testing the Proportionality Assumption

The only significant categorical predictor of the risk of TD was alcohol abuse/dependence (Tables 1 through 3). Results of the test of the assumption of proportionality for alcohol abuse/dependence were nonsignificant, justifying that assumption.

Testing the Model

The P values on global χ^2 analysis for each fixed or time-dependent covariate in univariable Cox regression analysis had to be similar to the backward stepwise improvement χ^2 P values for an individual variable to be entered or removed. The P values on global χ^2 analysis for both

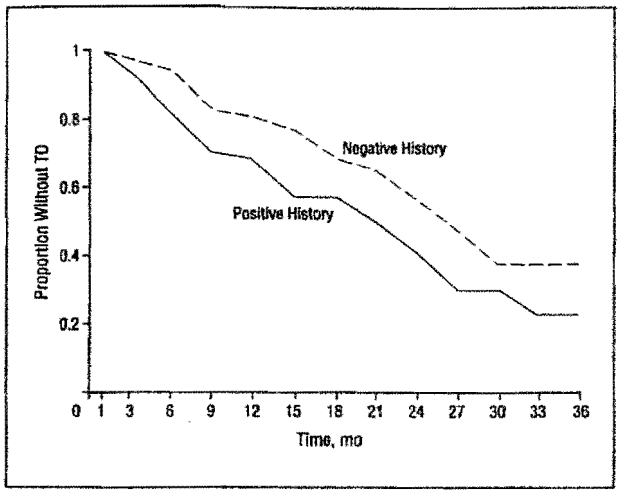

Figure 2. *Survival curves for tardive dyskinesia onset for patients with positive (n=83) vs negative (n=183) history of alcohol abuse or dependence (P=.01 by the Breslow test).*

fixed and time-dependent covariates in cumulative multivariable models were all .001 or less.

Assessing Accuracy of the Model

We computed the number of events (occurrences of TD) per predictor variable and compared the obtained ratio with that recommended by Concato et al.[54] The number of events for all cases over the 39-month period of follow-up was 69. We therefore had the recommended minimum ratio of events to predictors.

Assessing Possible Bias in Dropouts

There was an average 20% dropout rate per year. Using univariable Cox stepwise regression survival analysis, the dropouts did not differ from the study completers on any of the final significant predictors of TD except for alcohol abuse/dependence ($P=.007$). The 1-year dropout rate for nonabusers was 31.7% (95% CI, 24.2% to 39.1%) and for alcohol abusers was 16.3% (95% CI, 7.2% to 25.3%).

Results of Post Hoc Analyses

Diagnosis. Although a diagnosis of schizophrenia had a risk ratio of 1.4 (Table 1), overall psychiatric diagnosis was not a significant predictor of TD in either univariable or multivariable analysis (Tables 1 through 3). The apparently increased risk of TD in patients with schizophrenia was likely to have been secondary to the use of neuroleptics for longer periods and in higher amounts.

Age. Age was correlated significantly with logarithmic cumulative neuroleptic amount (Pearson's $r=-0.24$, $df=261$, $P<.001$). Age was a significant predictor of the incidence of TD in the univariable analysis (Tables 1 and 2) but not in the cumulative multivariable analysis (Table 3). This suggested that the apparent effects of age on the risk for TD were secondary to the effects of other significant predictors, such as the cumulative amount of neuroleptics.

AIMS Global Score. Fixed baseline AIMS global score was a significant predictor of TD (Table 1). Patients with a score greater than 0 had a 2.1 times higher risk of developing TD than those with a score of 0. Compared with the patients who had a fixed baseline AIMS global score of 0, those with a score greater than 0 (almost always 1) were significantly younger, were more likely to have schizophrenia or another "nonorganic" disorder, had lower scores on the BPRS positive symptom subscale and HAM-D, had higher scores on the ADRS, and had a longer duration of neuroleptic use at baseline. The cumulative multivariable analysis revealed that the time-dependent AIMS global score (which included the baseline score) was still a significant predictor of TD risk, suggesting that the contribution of AIMS global score to TD incidence was above and beyond what could be explained by other possible predictors (including the duration of neuroleptic use at baseline).

The cumulative incidence of TD for the 165 patients who had an AIMS global score greater than 0 at baseline or at some point during follow-up and who did not concurrently have TD was as follows: 9.9% (95% CI, 4.6% to 15.3%) at 3 months, 31.4% (95% CI, 22.5% to 40.2%) at 6 months, 34.9% (95% CI, 25.7% to 44.1%) at 9 months, and 48.2% (95% CI, 37.5% to 58.9%) at 12 months. The time to occurrence of TD (or dropout or censoring) was measured from the time of the first AIMS global score greater than 0.

Anticholinergic Use. Anticholinergic use was a significant predictor of TD risk in univariable analysis (Table 1) but not in the final stage of the cumulative multivariable analysis (Table 3). This might be in part because only 11% of the patients were receiving anticholinergic therapy. Furthermore, patients receiving anticholinergic therapy had significantly greater mean cumulative logarithmic amounts of high-potency neuroleptics than those not treated with anticholinergics ($P<.001$, Mann-Whitney U test).

Neuroleptic Potency. The data on neuroleptic potency as a risk factor for TD were analyzed three ways.

1. The 107 patients treated with haloperidol or thioridazine compared with the other 159 patients. The two groups were similar on all the baseline variables except that the haloperidol/thioridazine group was older, had a greater proportion of patients with Alzheimer's disease or other "organic" disorders, had a lower MMSE score, and had a shorter duration of prior neuroleptic use at baseline ($P<.001$ for all). The two groups did not differ, however, either in the rate of dropouts or in the incidence of TD.

2. Haloperidol-treated (n=68) vs thioridazine-treated (n=39) patients. The two groups did not differ on any of the baseline measures except that the haloperidol-treated group had a greater proportion of patients with Alzheimer's disease or other "organic" disorders and had lower scores on the MMSE and BPRS depression subscale ($P<.05$ for all). The rate of

Table 2. Univariable Analysis for Several Cox Proportional Hazards Models for Onset of Tardive Dyskinesia for All Cases With Relevant Data*

Variable	Type of Variable†	$\hat{\beta}$ Coefficient	$\hat{\beta}$/SE ($\hat{\beta}$)	Risk Ratio‡	P
Stage 1					
Age (y)	*f*	−0.02	−2.3	1.0	.02
Neuroleptic duration (logarithmic days)	*f*	0.34	3.6	1.4	<.001
Cumulative high-potency neuroleptic amount (logarithmic mg of CPZE)	*t*	0.19	2.7	1.2	.004
MMSE total score	*t*	0.04	2.0	1.0	.04
Alcohol (abuse/dependence)	*f*	0.52	2.1	1.7	.03
Stage 2					
AIMS global score	*t*	0.84	4.5	2.3	<.001
ADRS total score	*t*	0.13	2.7	1.1	.01
Stage 4§					
Tremor (amplitude, dB)	*t*	0.02	1.8	1.0	.07
Movement speed (velocity, degrees/s)	*t*	0.14	1.7	1.2	.06

**CPZE indicates chlorpromazine equivalent; MMSE, Mini-Mental State Examination; AIMS, Abnormal Involuntary Movement Scale; and ADRS, Simpson Abbreviated Dyskinesia Rating Scale.*

†See the section on "Fixed [f] and Time-Dependent [t] Covariates" under "Statistical Methods" for a detailed description of the individual stages and f and t variables.

‡Risk ratio is e^{β}, where e is the base of the natural logarithm, 2.72. See the text for a definition of risk ratio.

§None of the t clinical rating scale scores (set 3: Brief Psychiatric Rating Scale subscale scores or Hamilton Depression Rating Scale total score) was significant at stage 4.

Table 3. Cumulative Multivariable Analysis for Several Cox Proportional Hazards Models for Onset of Tardive Dyskinesia for All Cases With Relevant Data*

Variable	Type of Variable†	$\hat{\beta}$ Coefficient	$\hat{\beta}$/SE ($\hat{\beta}$)	Risk Ratio‡	P
Stage 1§					
Alcohol (abuse/dependence)	*f*	0.68	2.7	2.0	.008
Neuroleptic duration (logarithmic days)	*f*	0.34	3.4	1.4	<.001
Cumulative high-potency neuroleptic amount (logarithmic mg of CPZE)	*t*	0.15	2.2	1.2	.02
Stage 2‖					
AIMS global score	*t*	0.92	4.9	2.5	<.001
Neuroleptic duration (logarithmic days)	*f*	0.31	2.9	1.4	.004
Cumulative high-potency neuroleptic amount (logarithmic mg of CPZE)	*t*	0.12	1.8	1.1	.07
Alcohol (abuse/dependence)	*f*	0.65	2.6	1.9	.01
Stage 4‖¶					
Tremor (amplitude, dB)	*t*	0.02	2.6	1.0	.01
Neuroleptic duration (logarithmic days)	*f*	0.26	2.3	1.3	.02
Cumulative high-potency neuroleptic amount (logarithmic mg of CPZE)	*t*	0.22	2.2	1.2	.02
Alcohol (abuse/dependence)	*f*	0.54	1.8	1.7	.08
AIMS global score	*t*	0.89	4.0	2.4	<.001

**CPZE indicates chlorpromazine equivalent; AIMS, Abnormal Involuntary Movement Scale.*

†See the section on "Fixed [f] and Time-Dependent [t] Covariates" under "Statistical Methods" for a detailed description of the individual stages and f and t variables.

‡Risk ratio is e^{β}, where e is the base of the natural logarithm, 2.72. See the text for a definition of risk ratio.

§N=216 for the entire basic data set. Since logarithmic neuroleptic duration, t logarithmic cumulative high-potency neuroleptic amount, and alcohol (abuse/dependence) were the only significant variables in the multivariable analysis, these three variables were rerun in a backward stepwise Cox regression at their full N=262 to better estimate the three regression coefficients.

‖Considerations similar to those described for stage 1 also applied here.

¶None of the t clinical rating scale scores (set 3: Brief Psychiatric Rating Scale subscale scores or Hamilton Depression Rating Scale total score) was significant at stage 4, individually or in combination with logarithmic neuroleptic duration, t logarithmic cumulative high-potency neuroleptic amount, alcohol (abuse/dependence), or t AIMS global score.

dropouts was similar, but the haloperidol group had a higher 1-year cumulative incidence of TD than the thioridazine group (30.3% vs 9.3%; P=.05 and P=.02 using Breslow and Mantel-Cox statistics, respectively).

3. Total high-potency only (n=126) vs low-potency only (n=64) neuroleptic-treated patients. The high-potency group had a nonsignificantly higher risk of TD (P=.10, Breslow test; P=.11, Mantel-Cox test). Although the two groups were similar in terms of the rate

of dropouts, the high-potency group received higher time-dependent cumulative amounts of neuroleptics ($P<.001$, Mann-Whitney U test). To sort out the relative contribution of potency vs amount, we dichotomized the high-potency group at its median amount and split it into two subgroups: high-potency/low amount (n=63) and high-potency/high amount (n=63). The former subgroup had a mean daily neuroleptic dose (50.9 mg of chlorpromazine equivalent) comparable to that of the low-potency group (62.5 mg of chlorpromazine equivalent). The high-potency/high-amount group obviously had a much greater daily dose (535.8 mg of chlorpromazine equivalent) ($P<.001$, Kruskal-Wallis analysis of variance) than the other two groups. The three groups were similar in dropout rates. Using life-table analysis, the 1-year cumulative incidence of TD was as follows: low-potency group, 24.4% (95% CI, 8.9% to 39.80%); high-potency/low-amount group, 31.4% (95% CI, 14.8% to 48.0%); and high-potency/high-amount group, 35.8% (95% CI, 22.7% to 49.0%). However, with such small samples, the curves were not significantly different.

COMMENT

We found a distressingly high (26.1%) cumulative annual incidence of TD among psychiatric outpatients with a mean age of 65.5 years who were being treated with relatively low daily doses (average, 150 mg of chlorpromazine equivalent) of neuroleptics. This rate is five to six times that reported in younger adults.[3] Although a number of risk factors were significant in univariable analysis, the final stage of the cumulative multivariable analysis yielded only five significant predictors of TD: fixed baseline duration of prior neuroleptic use, time-dependent cumulative high-potency neuroleptic amount, fixed history of alcohol abuse/dependence, time-dependent AIMS global score, and time-dependent tremor on instrumental assessment.

Two highly significant predictors of TD risk were duration of neuroleptic use at baseline and cumulative neuroleptic amount. Some of the surprising findings can also be explained on the basis of the primacy of neuroleptic use as the most important risk factor for TD. For example, age was negatively and MMSE total score was positively related to the risk of TD—ie, younger (middle-aged) and cognitively less impaired patients had a higher risk of TD than elderly and cognitively more impaired patients. The former group (with higher risk of TD) mainly comprised subjects with schizophrenia and mood disorders, who received greater amounts of neuroleptics than the latter group, which comprised elderly patients with "organic" disorders. With a cumulative multivariable model, neither age nor diagnosis contributed significantly to TD risk, suggesting that these patient-related variables were less important than neuroleptic-related ones as risk factors for TD.

This study had several limitations. Despite our best efforts to obtain as complete information as was possible, we cannot be absolutely certain about the accuracy of neuroleptic history prior to study entry. Similarly, there might have been errors in our calculations of subsequent neuroleptic amounts because of unsuspected noncompliance. Also, there was an approximately 20% annual dropout rate, although the dropouts were similar to the study completers on all the significant predictors of TD risk except for a history of alcohol abuse/dependence. Finally, our findings may not be generalizable to a population under the age of 45 years or to one including predominantly nonveteran or female subjects.

THE FINDING of cumulative high-potency neuroleptic amount as a significant risk factor for TD must be viewed in the context of other limitations of the study. We could not randomize a majority of the patients to haloperidol or thioridazine, as originally planned, for clinical and ethical reasons. More patients were treated with high-potency neuroleptics than with low-potency ones. This might have been partly an artifact of uneven randomization. Also, among the patients not treated with haloperidol or thioridazine, a greater number were receiving high-potency antipsychotics prior to study entry and refused randomization, opting instead to continue receiving the same medications. Furthermore, our patients who were treated only with high-potency antipsychotics received a significantly greater amount of neuroleptics (in milligram chlorpromazine equivalents) than patients treated with low-potency neuroleptics only. The two groups, however, had a similar level of psychopathologic conditions (BPRS and HAM-D scores) at baseline as well as at follow-up visits, suggesting that the doses of medications used were clinically equivalent in reducing psychopathologic conditions to comparable levels. The dosages of medications had been adjusted for individual patients by their respective clinicians. It was not clear why the milligram chlorpromazine equivalent amounts of clinically (therapeutically) equivalent doses were significantly different for high-potency vs low-potency neuroleptics. Several investigators have noted a growing clinical practice in recent years (without clear justification) of using higher dosages of high-potency neuroleptics compared with low-potency agents.[55-57]

Our data suggest that high amounts of high-potency neuroleptics constitute a risk factor for TD. We could not separate out the effects of potency from neuroleptic amount statistically because of inadequate sample sizes in individual subgroups. Nevertheless, these results indicate that high-poteney antipsychotics may be more likely to cause TD in at least some older subjects. Our findings may serve to explain some early reports from cross-sectional studies suggesting that drugs such as fluphenazine (a high-potency agent) were associated with a higher prevalence of TD.[26,58,59] A number of researchers have reported early EPS as a risk factor for TD.[3,25,26] This finding could conceivably be related to the patients with early EPS receiving high-potency neuroleptics, which are much more likely than low-potency neuroleptics to produce EPS.

Several possible explanations may be considered regarding why a difference between high-potency and low-potency neuroleptics in their ability to produce TD has not been reported in the past. Cross-sectional studies,

which account for most of the literature on TD, cannot determine risk factors for TD. The few published prospective longitudinal studies could not compare different types of neuroleptics because the average duration of neuroleptic use prior to study entry ranged from 9 months to several years. This made it difficult to compute the exact amounts of different medications received in the past. In our investigation the median duration of total lifetime neuroleptic use at study entry was 21 days.

A history of alcohol abuse/dependence was a strong predictor of the risk of TD. Olivera et al[10] and Dixon et al[11] previously reported a higher-than-expected prevalence of TD in subjects with a history of alcohol abuse. The mechanisms underlying possible alcohol-induced susceptibility to TD are presently unknown.

Our finding of tremor (detected using instrumental assessment) prior to development of TD as a predictor of TD risk is consistent with reports linking early EPS to increased incidence of TD.[3,25,26] The clinical ratings of EPS[39] were, however, not significant predictors, possibly suggesting that subclinical motor abnormalities may define the TD risk better. The presence of borderline or minimal abnormal involuntary movements at baseline (AIMS global score >0) as a risk factor for TD indicates that spontaneous or acute neuroleptic-induced dyskinesia could be made worse by continued use of neuroleptics. The finding of time-dependent AIMS global score as a predictor of TD indicates that whenever a patient receiving neuroleptics has an AIMS global score greater than 0, he or she is at a high risk of having TD diagnosed within a few months.

Anticholinergic use is a potentially important risk factor for TD. Because of our policy of avoiding unnecessary medications, 89% of the patients did not receive anticholinergic agents. Nonetheless, the increased incidence of TD in our patients who received anticholinergic agents suggests that caution should be used in prescribing these drugs to older subjects.

Although nonsignificant, two interesting predictors, being nonwhite and having diabetes mellitus, had risk ratios of 1.5 and 1.4, respectively. The role of ethnicity as a risk factor for TD needs further evaluation.[60]

CLINICAL IMPLICATIONS

The observation that a small but significant number of our patients developed TD after less than 3 months of neuroleptic treatment suggests that in older subjects, the research criterion of the minimum length of treatment prior to a diagnosis of TD should be changed from 3 months[34] to 1 month. (This has been done for the clinical diagnosis of TD in *DSM-IV*.[61]) Occurrence of TD with comparable frequency in schizophrenic and nonschizophrenic patients should help put to rest the notion that TD is merely a symptom of schizophrenia. In older patients, neuroleptics are prescribed more frequently for indications other than schizophrenia, mainly by nonpsychiatrist physicians. There is a need for a greater awareness of TD among all clinicians treating older patients. In nonschizophrenic patients, long-term use of neuroleptics should not be undertaken without strong justification. In patients with chronic schizophrenia, neuroleptic discontinuation is associated with a significantly elevated risk of psychotic relapse.[62] Individualized treatment usually aimed at gradually reducing the neuroleptic dose to the lowest effective level is therefore indicated in most patients with schizophrenia.[63]

The frequent assertion that all "typical" neuroleptics are similar in their risk of TD is not based on any large-scale prospective comparison of different types of neuroleptics. We found a higher risk of TD with greater amounts of high-potency neuroleptics. At the same time, there is a well-known risk of anticholinergic toxic effects with low-potency neuroleptics, resulting in confusion, delirium, urinary retention, etc. It is therefore recommended that the use of any type of neuroleptic be restricted to the lowest effective doses. Finally, if the newer serotonin-dopamine antagonists, such as risperidone,[64] olanzapine, sertindole, seroquel, and others, are found to have lower risk of TD, they could significantly change the risk-benefit ratio for neuroleptic treatment.

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