6% ⊕ rate 1st 5 yrs

Predicting the Long-Term Risk of Tardive Dyskinesia in Outpatients Maintained on Neuroleptic Medications

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TD - rates

Background: Tardive dyskinesia (TD) has been a source of great concern to the psychiatric community because of the iatrogenic nature of the illness. Little is known about the risk of developing TD if neuroleptic medications are continued.

Method: This paper presents long-term risk estimates for TD in a prospective cohort study of 362 chronic psychiatric outpatients who were free of TD at baseline and who were maintained on neuroleptic medications.

Results: On the basis of 5 years of follow-up, we estimate the risk of persistent TD to be 32% after 5 years of neuroleptic exposure (95% confidence interval [CI] = 23%–43%), 57% after 15 years of exposure (95% CI = 47%–66%), and 68% after 25 years of exposure (95% CI = 58%–77%). For patients with 10 years of previous neuroleptic exposure, the risk is 15% after 5 more years of exposure (95% CI = 7.2%–27%) and 38% after 15 more years of exposure (95% CI = 24%–53%). Our results fall within the wide range of results found in other studies of TD incidence. Differences in incidence across studies may be explained in terms of patient characteristics and other methodological factors.

Conclusion: One implication of this finding is that patients in the first 5 years of exposure could be targeted for prevention programs if resources are limited. A potential methodological problem encountered when studying chronically exposed patients is that they may have acquired TD (persistent) prior to the study and remitted before entry.

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Tardive dyskinesia (TD) has been a source of great concern to the psychiatric community because of the iatrogenic nature of the illness.[1] In response to this concern, prescribing physicians must contend with the risks of continuing patients on neuroleptic medication or face the possible adverse consequences of dose reduction or discontinuation. Although the risk of psychotic relapse following discontinuation of neuroleptic medications is relatively well established,[2] little is known about the risk of TD if neuroleptic medications are continued. Researchers at the Long Island Jewish Hillside Hospital reported a TD rate of 0.04/year (i.e., 4 new cases per 100 person-years of follow-up) in a young, private-sector psychiatric population.[3] The risk (cumulative incidence) of developing TD after 7 years of neuroleptic exposure was 24% (95% confidence interval [CI] = 17%–31%). No one, however, has reported the occurrence of TD for neuroleptic exposure of more than 7 years. If patients do not develop TD in the first 7 years of treatment, will they eventually become cases?

The Yale TD Study, which focuses on a cohort of patients who at baseline have been exposed to neuroleptic medications for varying durations, allows an exploration of this question. In another paper,[4] we reported that the incidence rate of TD in our outpatient population is

greatest during the first 5 years of exposure and decreases steadily over the next 20 years. In this paper, we use those results to estimate the long-term risks of TD during the projected course of treatment. We also compare our results with those of other TD incidence studies.

DESIGN AND METHOD

The major outcome variable in this ongoing prospective cohort study is the new occurrence (incidence) of TD, which is diagnosed at semiannual examinations. Nearly 400 subjects at risk for TD were enrolled in the study and have been followed since the fall of 1985.

Subjects and Data Collection

The source population is the outpatient clinic of the Connecticut Mental Health Center (CMHC), which, at the time of the initiation of the study, served a population of about 450,000 people in the Greater New Haven area and provided treatment for about 1300 patients using various modalities. Most of the patients followed in this study received maintenance neuroleptic medications that were prescribed on a refillable basis over a 3- to 6-month period, then reassessed.

To be eligible for participation in the study, an individual had to meet all three of the following criteria: (1) actively enrolled as an outpatient at CMHC any time between July 1, 1985, and June 30, 1987; (2) currently maintained on neuroleptic medication as evidenced by the presence of at least one 3-month prescription in the pharmacy; and (3) free of persistent TD at intake with no history of persistent TD movements, i.e., at risk for having a first episode of persistent TD.

Data for this study came from three sources: baseline interviews of 60 to 80 minutes with all subjects; medical records; and regularly scheduled follow-up visits every 6 months, starting on the day of the baseline interview. Baseline data include a wide variety of demographic, medical, psychosocial, and behavioral variables collected from patient interviews and medical records. Medical records are used as an additional source of information on past use of all psychiatric medications and other clinical variables. Follow-up data collected by a research assistant at each visit consist of scores from two applications of the Abnormal Involuntary Movement Scale (AIMS)[5] examination (at the beginning and end of the visit) and patient-reported type and dosage of all current medications, which are confirmed with medical records.

Our definition of TD, derived from our previous research,[6–8] is based on a liberal modification of the Research Diagnoses for Tardive Dyskinesia (RD-TD).[9] To be diagnosed with probable TD at a given visit, a patient must have a total AIMS score of 3 or more on each AIMS examination and at least one anatomical score of 2 (mild) or more on each examination. A *new persistent case of TD* is defined as any patient, who, after a negative baseline evaluation, meets the above criteria for two consecutive visits. Thus, on the second visit, if these criteria are met, the patient is diagnosed with *persistent TD*, dropped from the incidence study, and followed in the Yale TD Clinic. For purposes of analysis, the first visit during which probable TD was noted is treated as the time of occurrence. To ensure reliability of ratings, weekly interrater meetings were held for a year; since then, monthly sessions have been held on an ongoing basis. In these sessions, ratings of patients are completed independently, then discussed. The intraclass correlation coefficients[10] for agreement on total AIMS scores in groups of two to four raters are above 0.80.

Neuroleptic exposure history was determined at the time of the baseline interview by patient self-reports and chart review, including records sent from other facilities. In questioning patients about their use of neuroleptics, the interviewer would mention the brand name of a neuroleptic medication and show the actual tablets or capsules in their different dosages. For each positive response, patients were asked to identify the dosage and time period during which they had taken that medication. Another reviewer would examine the patient's medical chart and record medications and dosages prescribed by CMHC physicians and summarized for other institutions. If the reviewer learned from the patient or from the chart review that there were undocumented neuroleptic treatment episodes, this fact was recorded. To measure the total duration of neuroleptic use, we relied on chart information exclusively if there were no missing periods of exposure. When there were missing periods, we supplemented chart information with patient reports that coincided with the missing periods. We also checked patients' self-reports against medical records for periods of overlap and found very good agreement.

Statistical Methods

By combining data from patients with different durations of neuroleptic exposure at baseline, we can estimate the *risk* of (i.e., the probability of developing) TD for exposure periods that greatly exceed the observed duration of follow-up (about 5 years). Thus, for example, if the baseline histories of previous neuroleptic exposure for patients with no history of TD range from nearly 0 years to more than 20 years, we can estimate TD risks for periods as long as 20 + 5 = 25 years of neuroleptic treatment. The major assumption required for these long-term risk estimates is that the TD incidence *rate* (i.e., new cases per person-year of follow-up experience at risk) for a given duration of previous neuroleptic exposure remains approximately constant over (calendar) time in the source population of neuroleptic users.

We used the "density method" of risk estimation in which average incidence rates (incidence densities) are

Table 1. Estimated Risk of TD (and 95% Confidence Intervals),* by Net Years of Previous Neuroleptic Use (Without TD) and Additional Years on Neuroleptics: Results of the Yale TD Study, 1985–1990

Years of Previous Neuroleptic Use	Additional Years on Neuroleptics				
	5	10	15	20	25
0	0.318 (0.225, 0.429)	0.494 (0.396, 0.592)	0.567 (0.468, 0.662)	0.647 (0.546, 0.736)	0.684 (0.579, 0.774)
5	0.258 (0.177, 0.360)	0.366 (0.266, 0.478)	0.482 (0.369, 0.598)	0.537 (0.411, 0.658)	
10	0.145 (0.072, 0.270)	0.302 (0.189, 0.445)	0.376 (0.241, 0.533)		
15	0.184 (0.092, 0.333)	0.270 (0.145, 0.446)			
20	0.106 (0.030, 0.315)				

*Risk estimates are based on the density method, conditional on the number of net years of previous neuroleptic use[11]; confidence-limit estimates are based on a modification of Rothman's method.[12]

first computed for 5-year intervals of previous neuroleptic exposure at baseline.[11] For example, an at-risk patient with 3 years of previous neuroleptic exposure at baseline could contribute as much as 2 person-years of follow-up to the first exposure interval (0 to 5 years) and about 3 more person-years to the second exposure interval (5 to 10 years). These rate estimates (expressed per year) are converted to 5-year risk estimates (cumulative incidences) and combined across exposure intervals. To assess the expected change in risk during the full course of neuroleptic treatment, the method was repeated for patients with 0, 5, 10, 15, and 20 years of previous neuroleptic exposure during which they had remained free of TD. Ninety-five percent confidence intervals were computed for all risk estimates, using a modification of Rothman's method for life-table analysis.[12]

RESULTS

A total of 398 eligible patients were enrolled in the study between July 1, 1985, and December 31, 1986. As of July 1, 1990, a total of 2612 examinations had been performed. Of the 398 patients examined at baseline, 362 were reexamined at least once; thus, the maximum sample size for analyses of TD incidence is 362. The mean baseline age of the total cohort was 42 years (range, 19–73); 53% were women and 25% were nonwhite (23% Afro-American). Eighty-two percent of the sample was single, separated, divorced, or widowed. Thirty-four percent had received less than 12 years of education, 39% had 12 years, and 27% had more than 12 years. Seventy percent of the sample was unemployed at baseline.

At the baseline interview, the mean duration of previous neuroleptic use was 8 years (range, 3 months–33 years); the distribution of this variable was 18% with less than 2 years of exposure, 17% with 2 to 4 years, 25% with 4 to 8 years, 15% with 8 to 12 years, and 25% with more than 10 years. The mean age at first neuroleptic exposure was 29 years (range, 4–72). The mean age of first outpatient treatment was 24 years (range, 1–72), and the mean age at first hospitalization was 26 years (range, 8–65). Seven percent of the sample had never been hospitalized, 53% had been hospitalized fewer than five times, and 40% had been hospitalized five or more times. All 398 patients were categorized into five mutually exclusive Research Diagnostic Criteria diagnostic groups, called "primary diagnosis." Equal weight was given to definite and probable diagnoses and to present, past, and lifetime designations. The five categories and number of subjects in each group were 167 (42%) schizophrenia; 67 (17%) schizoaffective disorder; 60 (15%) affective disorders (i.e., bipolar and major depressive disorder); 40 (10%) "mixed" diagnoses (i.e., combinations of the first three categories); and 64 (16%) other diagnoses (i.e., minor depressive disorder, alcoholism, drug use disorder, other psychotic disorder, and schizotypal features). In addition, 90 (23%) subjects in the total cohort were diagnosed with alcohol- or drug-abuse disorders—42 (25%) of the schizophrenics, 22 (33%) of the schizoaffectives, 8 (13%) of the affectives, 10 (25%) of the mixed diagnoses, and 8 (13%) of the others diagnoses.

Risk of TD

There were 62 new persistent cases of TD detected during 1167 person-years of follow-up, giving an average incidence rate of 0.053/year and a 5-year risk (cumulative incidence) of about 20%. Table 1 shows the estimated risk of TD by net years of previous neuroleptic exposure (without TD) and additional years of neuroleptic use. Thus, the table gives TD risk estimates for various intervals (5 to 25 years) (columns) for patients who have remained free of TD and have been maintained on neuroleptics for 0, 5, 10, 15, and 20 years (rows). For example, the estimate of 0.318 or 31.8% in

Table 2. Estimated Risk of Persistent TD (and 95% Confidence Intervals),* by Net Years of Previous Neuroleptic Use at Baseline and Additional Years on Neuroleptics, Excluding 22 Patients With Probable TD at Baseline: Results of the Yale TD Study, 1985–1990†

Years of Previous Neuroleptic Use	Additional Years on Neuroleptics				
	5	10	15	20	25
0	0.327 (0.229, 0.442)	0.458 (0.356, 0.563)	0.538 (0.433, 0.639)	0.602 (0.495, 0.700)	0.647 (0.532, 0.747)
5	0.194 (0.121, 0.295)	0.313 (0.215, 0.431)	0.409 (0.295, 0.534)	0.476 (0.343, 0.612)	
10	0.147 (0.073, 0.274)	0.267 (0.159, 0.411)	0.350 (0.214, 0.515)		
15	0.140 (0.061, 0.288)	0.237 (0.115, 0.426)			
20	0.113 (0.032, 0.333)				

*Risk estimates are based on the density method, conditional on the number of net years of previous neuroleptic use[11]; confidence-limit estimates are based on a modification of Rothman's method.[12]
†Number at risk = 340; number of new cases observed = 52.

the upper left-hand cell is the risk of developing TD within the first 5 years of exposure to neuroleptics. Moving horizontally in that row, we see that the 10-year risk of TD after first exposure is 49.4%; the 95% CI is 0.396, 0.592, which means we are 95% confident that this interval covers the true risk during that exposure period. The second row of the table pertains to patients who have already had 5 years of neuroleptic exposure. The risk of TD developing in these patients over the next 5 years is 25.8% (95% CI = 17.7%–36.0%). Note that the 5-year risk of TD is less for patients with 5 years of previous TD-free exposure than for new neuroleptic users. Returning to the first row, we see that for new neuroleptic users the risk of developing TD after 25 years of continuous exposure is 68.4% (95% CI = 57.9%–77.4%).

Although we attempted to exclude subjects with a history of persistent TD at baseline, it is possible that some subjects had a transient form of TD that reappeared early in the follow-up period. To address this possibility, we redid selected analyses as displayed in Table 2, excluding those 22 subjects who met the AIMS criteria for probable TD at baseline, but who did not meet these criteria at the second visit and, therefore, were still at risk for developing persistent TD. Since 10 of these subjects became cases, their exclusion reduced the 25-year risk of TD after first exposure from 0.684 (Table 1) to 0.647 (Table 2). Visual inspection of the two tables finds little difference in estimated risks by the various exposure durations.

Comparison With Other Studies

We are aware of six prospective studies of TD incidence[3,13–17] in addition to our own.[4] For the purposes of comparison, we have selected the Kane et al.[3] report from 1982 rather than 1986[18] because the former paper included only those patients at risk, while the latter included in the analysis patients who had been identified as having TD at baseline (prevalent cases). A comparison of patient characteristics across studies reveals several differences (see Table 3). Relative to the study by Kane et al.,[3] the populations of other studies were older (mean age > 40 years) and exposed to neuroleptic medication for a longer duration. The populations of Yassa and Nair[13] and Waddington et al.[17] were exposed to neuroleptics the longest—almost twice the duration of the others and 20 times that of Kane et al.[3] In all but the study of Waddington et al.,[17] the patients were ambulatory and the majority were schizophrenic or schizoaffective. Chouinard and colleagues'[14] population appears to be more severely ill as evidenced by the descriptor "poor prognosis." Risk factors identified by these groups include increased age,[3,4] Afro-American race,[4] affective diagnosis,[3] family psychiatric history,[17] extrapyramidal symptoms,[3,14] poor schizophrenic prognosis,[14] deteriorating cognitive status,[16] neuroleptic treatment duration,[4,14] and dosage.[17]

The studies by Kane et al.[3] and Morgenstern and Glazer[4] are the most extensive in that they followed more patients with periodic examinations over an extended duration of follow-up time (Table 4). All studies except Gibson's[16] used the AIMS to diagnose TD. To compare the new occurrence of TD across studies (Table 4), we calculated average yearly incidence rates from reported results, and we estimated the 5-year risk of TD, assuming that the rate remained constant during the exposure period.[11] We found a range in 5-year risk from 17.5%[3] to 42.1%[17]; the 5-year risk in our study was 19.8%.[4] (Note: This latter estimate was obtained for the observed follow-up period of 5.2 years.)

DISCUSSION

In this paper we report the estimated long-term risk of patients' developing TD as a function of previous neuro-

Table 3. Comparison of TD Incidence Studies: Description of Study Populations*

Study	Mean Age[a] (y)	% Male	Mean Neuroleptic Exposure[a] (y)	Neuroleptic Dose[a] (CPZE)	Psychiatric Diagnosis	Risk Factor
Gibson[16]	50	29	10	Fluphenazine decanoate 25 mg q 3 wk Flupenthixol 40 mg q 3 wk	NR	Older (not quantified)
Kane et al[3]	28	46	1.6	NR	52% schizophrenic 11% schizoaffective 21% affective	Older Affective diagnosis History of ECT Longer psychiatric history Longer exposure to neuroleptic and antiparkinsonian agents
Yassa and Nair[13]	50	51	19.5	Mean > 1000	65% schizophrenic 12% bipolar 9% mentally retarded 5% organic brain syndrome	None
Chouinard et al[14]	40	47	9.5	Median = 300	72% poor prognosis schizophrenic 24% brain damage	Parkinsonian side effects Poor prognosis Rx duration > 5 y
Gardos et al[15]	45	48	NR	Mean = 559	NR	High neuroleptic dose at baseline
Waddington et al[17]	56	58	16	Mean = 988	NR	Decreased cognitive function Positive family psychiatric history Increase in daily dosage of neuroleptics
Morgenstern and Glazer[4]	42	47	8	Mean = 311	41% schizophrenic 16% schizoaffective 15% affective 26% other	Older Neuroleptic exposure duration and dose Afro-American

*Abbreviations: CPZE = chlorpromazine equivalent milligrams per day, Rx = treatment, NR = not reported.
[a]At baseline.

Table 4. Comparison of TD Incidence Studies: Study Methods and Results

Study	No. At Risk	Follow-Up Time (y)	Frequency of Exams	Method of TD Diagnosis	Average Rate (/y)[a]	5-Year Risk (%)[b]
Gibson[16]	343	3	1/y	Author's exam mild-moderate-severe	≥ 0.0559[c]	≥ 24.4[c]
Kane et al[3]	554	7	4/y	RD-TD (all types)	0.0392	17.8
Yassa and Nair[13]	108	2	3/y	2 consecutive "mild" on AIMS	0.0385	17.5
Chouinard et al[14]	131	5	2 exams	RD-TD "probable"	0.0865	35.1
Gardos et al[15]	15	7	2 exams	RD-TD "probable"	0.0666	28.3
Waddington et al[17]	38	5	2 exams	Global "mild"	0.1093	42.1
Morgenstern and Glazer[4]	362	5	2/y	Modified RD-TD "persistent"	0.0531	19.8

[a]Computed from the published results of each study, assuming that the rate remains constant during the follow-up period.
[b]The risk of getting TD after 5 years of continuous neuroleptic exposure. These estimates were computed from the average rate, assuming that the rate remains constant during the entire period of exposure.
[c]Rate and risk estimates are lower limits in this study, since we had to assume that all prevalent cases at baseline were counted as cases again at follow-up examination. To the extent that this assumption is not true, we have underestimated the number of incident cases.

leptic treatment. The results are disconcerting: About vo out of every three patients maintained on neuroleptic treatment can be expected to develop persistent TD within 25 years of continued exposure. Furthermore, the risk of TD is not uniform over the course of treatment; it is substantially greater in the first 5 years of exposure (see Table 1 and reference 4). One implication of this finding is that patients in the first 5 years of exposure could be targeted for prevention programs if resources are limited. For example, if an institution decides to

commit personnel for quality assurance screening of patients at risk for TD but is unable to involve all patients because of high volume, one could justify a focus on the subgroup of "early exposed" patients.

The reader may question the appropriateness of studying TD incidence in patients chronically exposed to neuroleptic medications as opposed to patients who have just started neuroleptic treatment. The method employed in this paper has generated results that could not otherwise be obtained without 25 years of follow-up of a newly exposed sample. Because our subjects were initially free of dyskinetic movements and had no history of persistent dyskinesia, they were still *at risk* of developing TD. It is therefore appropriate and, we believe, informative to study the occurrence of TD in this population. Indeed, there is considerable variability in the distribution of previous neuroleptic use at baseline, ranging from 3 months to 33 years. Thus, we were able to compare the TD rate for different periods of neuroleptic treatment.[4]

On the other hand, a potential methodological problem encountered when studying chronically exposed patients is that they may have acquired TD (persistent) prior to the study and remitted before entry; thus, some subjects may not have been at risk for having a first episode of persistent TD. The patients in this study were selected from a source population that had an active TD clinic in operation for 5 years prior to entry. In a prevalence study reported elsewhere[19] we found that 80% of the identified cases had been previously diagnosed with TD by the psychiatrists working in that TD clinic. Therefore, it is likely that this TD clinic had diagnosed most of the cases that were in the source population, and in so doing, prevented them from entering the incidence study.

We also addressed the concern about intermittent cases by excluding from the analyses those 22 subjects with probable TD at baseline. The results shown in Table 2 indicate that eliminating such patients who are most likely to be intermittent cases does not alter the risk estimates appreciably.

Our risk estimates are not standardized for other TD risk factors because there are too few TD cases to stratify on such TD predictors as age, race, and neuroleptic dose when applying our extended method of risk estimation. Nevertheless, in our other paper,[4] we found that the effect of previous neuroleptic exposure did not diminish when adjusting for other TD risk factors. It is also important to point out that our risk estimates are based on a retrospectively obtained history of neuroleptic exposure at baseline. Since we relied heavily on data from the patients' medical records, it is likely that we underestimated exposure duration in some patients because these records would not necessarily contain information from treatments in other facilities. Although it is difficult to predict how such a misclassification would distort our results, the most likely effect would be to reduce slightly the inverse association between years of previous neuroleptic use and TD. This bias, however, is not likely to have distorted appreciably the long-term risk estimates reported here.

As noted in the Statistical Methods section, the validity of long-term risk estimates obtained by combining information across 5-year intervals of neuroleptic exposure depends on the approximate uniformity of interval-specific rates over time (calendar). Although this condition is assumed in most life-table analyses, it may not be correct in our study if treatment practices change. Thus, for example, if patients in the future are treated at lower doses[4] or with safer drugs, our estimates of TD risk may exaggerate the actual TD risks experienced by patients.

We estimated that more than 50% of all patients treated with neuroleptics for at least 15 years will develop persistent TD (see top row of Table 1). Yet TD *prevalences* of 50% or more are seldom observed in cross-sectional studies.[19] Nevertheless, there are several alternative, but compelling, explanations for this apparent inconsistency: (1) diagnostic criteria in cross-sectional studies are often set to classify mild cases as noncases; (2) many persistent cases of TD may eventually remit permanently or temporarily even without medication changes, as we found in a follow-up study of 192 cases diagnosed in the Yale TD Clinic[20]; (3) TD cases may be less likely than noncases to be selected for prevalence studies (i.e., selection bias); and (4) the proportion of patients in most cross-sectional studies with more than 10 years of exposure is small, possibly because patients with more exposure may be less likely than patients with less exposure to be selected for these studies. Thus, prevalence findings may indicate very little about the occurrence (risk) of TD in specific populations at risk.

Our TD risk estimates fall within the range of those reported by other investigators (Table 4), although that range is relatively wide, i.e., 5-year risks of 17.5% to 42.1%. A comparison of these studies (Tables 3 and 4) indicates that several factors related to study methods and population characteristics might explain this variation: (1) differences in TD diagnostic criteria; (2) differences in the number of patients lost to follow-up; and (3) differences in the distribution of TD risk factors such as age, exposure duration, psychiatric diagnosis, diagnostic criteria for TD, and cognitive impairment.

Differences in TD diagnostic criteria have resulted in considerable variability in prevalence estimates[21,22] and prompted the development of the RD-TD criteria,[9] which were employed as the method of diagnosis in our study[4] along with five[3,13–15,17] of the other six incidence studies reviewed here. Nevertheless, the RD-TD criteria were applied differently across these six studies; although the

differences appear subtle, they might explain much of the variation in risk estimates. Three studies[14,15,17] involved a diagnosis of TD that was based on one examination, i.e., "probable TD." Two studies[4,13] required two AIMS examinations 4 to 6 months apart with positive findings, i.e., "persistent TD." One study[3] included *all* RD-TD types as cases.

Another explanation for the variation in risk estimates across the seven studies is possible bias from loss to follow-up. The amount of attrition is influenced by several factors including the intensity of surveillance and the frequency of reexamination; e.g., only three[3,4,13] of the seven studies employed more than two examinations over the follow-up period. Patient location is another factor that can influence patient participation in a longitudinal study, e.g., only one study[17] included long-term inpatients who are easier to locate on follow-up examination. Chronicity of illness is another factor that can affect the number of patients lost to follow-up because third-party coverage and location of care change as patients become chronically disabled. For example, in the study by Kane et al.,[3] which focused on a young population, more than half of the at-risk patients were lost after 7 years of follow-up. In our study, 26% of the chronic outpatients were lost after 5 years of follow-up.

Finally, some of the variability in reported incidence across studies may be explained by differences in the distributions of measured and unmeasured risk factors. As summarized in Table 3, there was considerable variation across studies in the frequencies of several possible risk factors, such as age, sex, psychiatric diagnoses, and neuroleptic prescribing practice. An example of an unmeasured risk factor may be race, since we found that Afro-American patients were twice as likely to develop TD as Caucasian patients.[4] Since race was not measured in most of the other six studies, there is no way of knowing to what extent this factor influenced the reported rates.

As we await the development of an antipsychotic medication that will not cause TD and other serious side effects, we must accept that long-term treatment of patients with most neuroleptic medications carries a high risk of TD. This disturbing reality must be counterbalanced by the sensible and judicious prescription of neuroleptic medication. Studies of risk factors underlying TD will aid in the prevention of the disorder and may increase our knowledge of the actions of neuroleptic agents as well as the disorders these agents are used to treat.

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