

## Incidence and risk factors for severe tardive dyskinesia in older patients\*

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**Background** Severe tardive dyskinesia (TD) represents a serious and potentially disabling movement disorder, yet relatively little is known about the incidence of and risk factors for severe TD.

**Method** We report the results of a longitudinal prospective incidence study of severe TD in 378 middle-aged and elderly neuropsychiatric patients. Psychiatric, neuropsychological, pharmacological and motor variables were obtained at intake and at regular intervals for 36 months.

**Results** The cumulative incidence of severe TD was 2.5% after one year, 12.1% after two years, and 22.9% after three years. Individual univariable Cox regression analyses were conducted to identify demographic, psychiatric, motor and pharmacological predictors of severe TD. Results indicated that higher daily doses of neuroleptics at study entry, greater cumulative amounts of prescribed neuroleptic, and greater severity of worsening negative symptoms were predictive of severe TD.

**Conclusions** These findings suggest that conventional neuroleptics may be prescribed to older patients only when necessary and at the lowest effective dosage. Additional caution is recommended in patients exhibiting negative symptoms.

Severe tardive dyskinesia (TD) represents a serious and potentially disabling movement disorder (Yassa, 1989; Kane *et al*, 1992). Severe oral dyskinesia may result in dental and denture problems that can progress to ulceration and infection of the mouth, as well as muffled or unintelligible speech. Severe orofacial TD can impair eating and swallowing, which in turn could produce significant health problems. Gait disturbances due to limb dyskinesia may leave patients vulnerable to falls and injuries. Severe TD may impair mobility and often impacts on an individual's likelihood of returning to work. Psychosocially, ambulatory patients with obvious TD may experience shame, guilt, anxiety and depression. Prevalence studies suggest that 5-10% of patients undergoing chronic neuroleptic treatment develop TD that is severe enough to impair functioning (Yassa, 1989). The progression of TD from its insidious onset to a more severe form may be gradual over a period of years, although some findings suggest that severe disabling TD is more likely to develop rapidly within the first six months of neuroleptic treatment rather than gradually (Gardos *et al*, 1987b).

Understanding the risk and course of severe TD is limited by the lack of a consensus definition of severe TD. The prevalence of severe TD varies in part according to the criteria being used (Table 1). For example, the mean prevalence of severe TD in the three studies using either an item or global Abnormal Involuntary Movements (AIMS) score of '4 or severe' as the criterion was 3.7% (range 1.0-6.8%), whereas the mean prevalence of severe TD in three studies using either an item or global AIMS score '≥ 3 or moderate' as the criterion was 5.2% (range 1.9-30.0%). Using a time-domain criterion, such as continuous movements, the weighted mean prevalence in two studies was 2.4%. While the cross-sectional studies reported in Table 1 suggest several clinical and demographic correlates of severe TD such as advanced age, female gender, and

continuous neuroleptic exposure, they do not necessarily address, in a prospective manner, factors that are predictive for the development of severe TD. While severe and disabling cases of TD represent a minority of patients seen with TD, identifying cases likely to reach this stage has remained elusive.

We previously reported that the cumulative one-year incidence of TD was 26.1% and the three-year incidence was 59.8% among neuropsychiatric patients over the age of 45 years (Jeste *et al*, 1995). Greater duration of neuroleptic treatment at study entry, greater cumulative exposure to conventional neuroleptics (especially high-potency), history of alcohol misuse and dependence, and subtle movement disorder at baseline were all found to be significant risk factors for TD. The aim of the present study was to identify the incidence of, and risk factors for, severe TD in older psychiatric out-patients. We hypothesised that the incidence of severe TD would be greater with advanced age, increasing severity of extrapyramidal symptoms (EPS) and neuroleptic exposure.

## METHOD

### Patients

The 378 patients included in the present study represent an extension of previously reported TD studies involving a smaller number of patients (Jeste *et al*, 1995; Paulsen *et al*, 1996). All patients met the following criteria for study inclusion: (a) any psychiatric diagnosis based on DSM-III-R criteria (American Psychiatric Association, 1987) and confirmed by at least two board-certified psychiatrists, with neuroleptics being indicated; (b) availability of reliable past medical and psychiatric history (including past neuroleptic use) from the patient, medical records and/or significant others; (c) ambulatory and community-dwelling; (d) age over 45 years; (e) not meeting Schooler & Kane (1982) criteria for TD at intake; and (f) signed informed consent by the patient. Patients were recruited from a variety of sources, the majority coming from the San Diego Veterans Affairs Medical Center.

The mean (s.d.) age of the 378 patients was 65 (13) years. The majority of the subjects were male (79%) and Caucasian (82%). All patients had psychotic or severe behavioural symptoms requiring neuroleptic intervention. Psychiatric diagnoses included

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**Table 1** Published studies of prevalence and associations of severe TD<sup>1</sup>

Authors	n	% severe TD <sup>2</sup>	Severe TD criterion	Risk factors <sup>3</sup>
<i>Criterion for defining severe TD: AIMS global score or any item <math>\geq 3</math></i>				
Asnis <i>et al</i> (1977)	69	4.3	AIMS global score $\geq 3$	Edentulous state
Guy <i>et al</i> (1986)	739	1.9	AIMS global score $\geq 3$	Not specified
Bergen <i>et al</i> (1989)	101	30.0	Any AIMS item score $\geq 3$	Not specified
Total	909	5.2		
<i>Criterion for defining severe TD: AIMS global score or any item =4</i>				
Smith <i>et al</i> (1979)	293	6.8	Any AIMS item score =4	Advanced age, female gender
Wojcik <i>et al</i> (1980)	210	1.0	AIMS global score =4	Advanced age
McCreadie <i>et al</i> (1982)	117	1.0	AIMS global score =4	Advanced age, in-patient status, negative symptoms
Total	620	3.7		
<i>Criterion for defining severe TD: continuous movements</i>				
Brandon <i>et al</i> (1971)	910	1.5	Continuous movements	Advanced age, female gender
Barnes <i>et al</i> (1983)	88	11.4	Continuous movements	Advanced age, akathisia
Total	998	2.4		
<i>Other miscellaneous criteria</i>				
Gimenez-Roldan <i>et al</i> (1985)	13	All	Any AIMS item score =4	Advanced age, female gender
Gardos <i>et al</i> (1987a,b)	19	All	Patients with subjective distress or impaired functioning	Rapid onset, continuous neuroleptic exposure, affective disorder
Edwards (1970)	184	8.7	Unspecified	'Organic' diagnosis

1. Literature review obtained from a computerised literature search with severe TD as the key search word.

2. Percentage of study patients with severe TD is indicated only if patients with severe TD were differentiated from patients without TD as well as those with milder forms of TD.

3. It was difficult, in some instances, to differentiate risk factors pertaining to TD in general, compared with those pertaining specifically to severe TD.

dementia (mostly Alzheimer's disease, 26%), other organic mental syndromes (11%), schizophrenia (26%), mood disorder (18%), psychosis not otherwise specified (3%) and other mixed diagnoses including anxiety disorders, adjustment disorder, delusional disorder and substance misuse (16%) for which neuroleptics were prescribed. Subjects had received a mean 39 (33) days of cumulative lifetime neuroleptic treatment before enrolment into the study.

### Neuroleptic treatment

Patients were mostly treated with relatively low doses of conventional neuroleptics (commonly haloperidol 1–3 mg, or thioridazine 10–100 mg per day). Moderate to severe acute and sub-acute neuroleptic-induced EPS were treated with appropriate antiparkinsonism regimens (usually benzotropine mesylate at doses of 2 mg/day or less). Only 16% of patients, however, required concomitant anticholinergic medication at some time during the study.

### Assessments

Comprehensive details of specific research assessments performed have been described elsewhere (Jeste *et al*, 1995) but will be briefly reviewed here. At study entry, each patient underwent an initial assessment consisting of:

- A comprehensive neuropsychiatric and medical examination.
- Collection of pertinent demographic information such as age, duration of neuropsychiatric illness, gender and ethnicity.
- Review of pharmacological history, including current and cumulative lifetime exposure to neuroleptic medication defined as the estimated cumulative previous neuroleptic exposure scaled in mg chlorpromazine equivalent. This was computed by multiplying the average daily neuroleptic dose by duration of treatment at that dose. We recognise that partial non-compliance on the part of some patients may have compromised our estimate of lifetime neuroleptic exposure. However, since most of our

patients had relatively short periods (mean 39 days) of prior treatment with neuroleptics, we could compute the total amount with some confidence.

- Administration of standardised psychiatric rating scales such as the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962), the Hamilton Depression Rating Scale (HAM-D; Hamilton, 1967) and the Mini-Mental State Examination (MMSE; Folstein *et al*, 1975).
- Standardised clinical and instrumental motor assessments consisting of the Simpson–Angus' Scale for early EPS (SAEPS; Simpson & Angus, 1970) and a battery of instrumental assessments for measuring postural tremor, bradykinesia and rigidity (Caligiuri *et al*, 1991). Postural tremor of the upper extremity and hand was quantified using measures of force instability. Bradykinesia was evaluated by measuring the peak instantaneous velocity associated with simple ballistic movements of the wrists. Rigidity was assessed by quantifying

abnormality in wrist muscle tone (i.e. stiffness).

Patients were followed for up to 36 months at regular intervals beginning at one and three months post-intake and continuing every three months thereafter. The follow-up assessments were similar to those conducted at study entry. All the rating scales and standardised assessments were completed by non-treatment team personnel who were kept 'blind' to other clinical information.

### Operational criteria for severe TD

Diagnosis of neuroleptic-induced TD was based on DSM-III-R criteria. Additionally a patient had to score at least 3 on the AIMS global severity item to meet our operational criteria for severe TD. No standard definition of severe TD exists at this time. We chose this criterion because inspection of the distribution of total AIMS scores revealed a distinct subgroup of 31 patients with a score of at least 3 on the global severity item (item 8) of the AIMS. The mean total AIMS score for the 31 patients who met criteria for moderate to severe TD was 11.35 (2.56). These criteria for severe TD are consistent with those in several of the studies reviewed in Table 1. High interrater reliability (intra-class correlation coefficient >0.84) was maintained for the AIMS using standardised video-tapes with expert consultation.

### Statistical analyses

Our analysis strategy involved several simple and complex variable types with the hazard condition being onset of severe TD, while using two main methods of analysis. Actuarial life table survival analysis was employed to determine the cumulative incidence of severe TD (Cutler & Ederer, 1958). Cox regression analysis was used to investigate risk factors individually for the occurrence of severe TD. Three separate Cox regression analyses were performed by varying the dichotomous dependent variable: (a) *v.* all other outcomes; (b) severe TD *v.* no TD; and (c) severe TD *v.* non-severe TD. All the statistical analyses were performed using BMDP software (Dixon, 1992).

### Predictor variables

Data collected through the research assessments described above were considered potential predictor variables (risk factors). Potential predictor variables for severe TD

were considered to be either fixed (*f*) or time-dependent (*t*) covariates. The values of fixed covariates were those variables that did not change from those observed at baseline. Fixed covariates included: age at study entry, duration of neuropsychiatric illness, gender, education, ethnicity (Caucasian *v.* non-Caucasian), history of alcohol misuse or dependence, history of diabetes mellitus and history of smoking. Additionally, the duration of prior neuroleptic use and the daily neuroleptic dose at study entry were also treated as (*f*) covariates.

Time-dependent covariates were the variables that were reassessed at subsequent research visits and could change as a function of the follow-up time (e.g. MMSE total). With the exception of the cumulative neuroleptic amount, (*t*) variables were evaluated repeatedly from baseline to one visit prior to the most recent visit for cases without severe TD (i.e. drop-outs and censored cases), or to one visit prior to the visit when severe TD was diagnosed. These 'one-visit-back' variables included: MMSE total, BPRS subscale scores for depression, disorganisation, hostility and negative symptoms, HAM-D total, SAEPS total and instrumental assessments of postural tremor, bradykinesia and rigidity. For example, to estimate the risk of severe TD at the nine-month visit, we used a patient's MMSE total at the six-month visit as the one-visit-back (*t*) MMSE covariate.

Cumulative neuroleptic exposure was treated as a changing contemporary (*t*) covariate. The cumulative neuroleptic amount was evaluated repeatedly from study entry to the month of the hazard condition being predicted or to the last visit (in cases that did not develop severe TD). Thus, to estimate the risk of severe TD at the nine-month visit, we used a patient's total lifetime amount of neuroleptics received until the nine-month visit as the contemporary (*t*) covariate.

The neuroleptic variables had extremely large ranges and highly skewed distributions, and were transformed via base 10 logarithmic function in order to obtain useful beta coefficients.

## RESULTS

### Incidence of severe TD

The cumulative proportion (with 95% confidence interval) of all enrolled patients developing severe TD was 2.5% (0.5–4.5%) after one year, 12.1% (6.7–17.5%) after

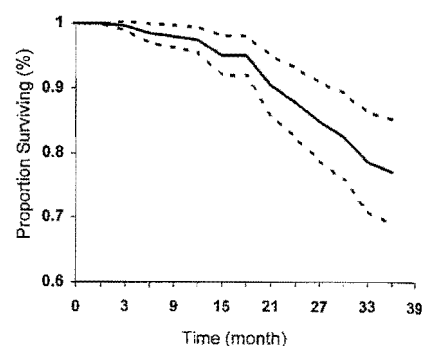


Fig. 1 Cumulative incidence curve for severe tardive dyskinesia onset, with 95% confidence intervals (total  $n=378$ ).

two years, and 22.9% (14.7–31.1%) after three years. Figure 1 shows the cumulative incidence curve for severe TD for the first three years.

### Risk factors

Significant results of the Cox regression analyses on demographic, psychiatric, motor and pharmacological predictor variables are listed in Table 2. Greater cumulative lifetime neuroleptic amount was found to be a significant predictor of moderate-severe TD for analyses including only non-TD patients, only patients with mild-moderate TD, or patients with either condition (i.e. all three regression analyses). A higher amount of daily neuroleptic dose in mg chlorpromazine equivalent at study entry was a significant predictor of moderate-severe TD for the largest regression model only, in which 378 cases were included. Increased severity of negative symptoms from baseline to the last visit was a significant factor predicting moderate-severe TD for analyses involving patients without TD. Lastly, an increase in instrumentally derived movement velocity (bradykinesia) from baseline to the last visit was a significant predictor of moderate-severe TD for analyses involving patients without TD.

None of the demographic or clinical variables, or neuropsychological variables, including those we previously found to be predictive of at least mild TD (e.g. history of alcohol misuse or dependence), was found to predict the development of severe TD.

Statistical examinations of risk factors associated with the topography of severe TD (orofacial *v.* limb-truncal) were deemed not feasible because of the relatively small total number of cases meeting criteria for severe TD ( $n=31$ ). Inspection of the 31 individual

**Table 2** Significant univariable predictors of severe TD

Variable name	n	b	s.e.	Relative risk <sup>1</sup>	P
<i>Severe TD v. all other outcomes</i>					
(f) Daily neuroleptic dose at study entry (log mg CPZE)	378	0.3581	0.1719	1.4306	0.034
(t) Cumulative neuroleptic exposure (log mg CPZE)	378	0.3165	0.1460	1.3723	0.031
(t) BPRS negative symptom subscale score	319	0.1265	0.0537	1.1349	0.018
<i>Severe TD v. no TD</i>					
(t) Cumulative neuroleptic exposure (mg CPZE)	173	0.3668	0.1724	1.4432	0.035
(t) Duration of neuroleptic exposure (days)	170	0.4366	0.1516	1.5474	0.003
(t) Instrumental movement velocity (degrees per second)	173	0.0015	0.0005	1.0001	0.001
<i>Severe TD v. non-severe TD</i>					
(t) Cumulative neuroleptic exposure (mg CPZE)	137	0.2982	0.1407	1.3475	0.035
(t) BPRS negative symptoms subscale score	137	0.1156	0.0595	1.1225	0.049

CPZE, chlorpromazine equivalent; b, regression coefficient; s.e., standard error of regression coefficient; (f), fixed covariate; (t), time-dependent covariate.  
<sup>1</sup>Relative risk=natural antilog of b (e<sup>b</sup>). This is the estimated multiplicative change in the risk of severe TD when the value of the predictor is increased by 1 unit.

cases revealed that 23 (74.2%) had orofacial TD, one (3.2%) had limb-truncal TD, and seven (22.6%) had both orofacial and limb-truncal TD that met criteria for moderate-severe.

## DISCUSSION

### Incidence

We found a cumulative three-year incidence of severe TD of 22.9% among older out-patients treated with relatively low dosages of conventional neuroleptics. To our knowledge, this study represents the first longitudinal prospective study of severe TD among older neuropsychiatric out-patients. The average prevalence of severe TD extracted from the literature shown in Table 1, for studies employing TD criteria consistent with the present study, was 5.2%. This prevalence value is intermediate between the present cumulative incidence values after one year (2.5%) and two years (12.1%) of treatment. The prevalence rate is determined by both incidence and remission of TD. Overall, TD tends to fluctuate (Bergen *et al*, 1989; Lacro *et al*, 1994), although the course of severe TD remains to be studied.

### Risk factors

A comparison of the commonly reported risk factors from Table 1 with those found

in the present study revealed one similarity and several important differences. Our finding of an increased risk associated with higher cumulative amounts of neuroleptics is consistent with the identification of 'continuous neuroleptic exposure' as a risk factor for severe TD in one of the studies listed in Table 1 (Gardos *et al*, 1987a), as well as our previous paper on the overall risk of TD (Jeste *et al*, 1995). Length of neuroleptic exposure has been found to be a consistent factor related to increased prevalence of TD in general (Toenniessen *et al*, 1985). Improvement on our instrumental measure of bradykinesia was a significant predictor of moderate-severe TD only when studied against non-TD patients (see Table 2). Our results suggest that patients without TD exhibit either persistent bradykinesia or show no change in movement speed, whereas patients with severe TD improve on this measure over time. This suggests that extrapyramidal motor signs, such as bradykinesia, which relate to reduced dopaminergic state, may suppress or delay the emergence of significant TD.

While a number of the studies from Table 1 reported that advanced age was a risk factor for the prevalence of severe TD, we did not confirm this finding. This discrepancy may be explained on the basis of study design. Prevalence studies give values for the proportion of existing cases

from a cross-sectional patient sample, whereas the present incidence study yielded the proportion of new-onset cases of severe TD. Also, in the present study, patients under the age of 45 were excluded, causing both a shift upward in the average age and a reduced age range relative to other studies. An alternative explanation may be that the older patients in this study, that is, those over the age of 70 years, could tolerate only low-dose neuroleptic treatments which, according to our regression model, lowered the risk of developing severe TD.

The second discrepancy between the previous literature on severe TD and the present results pertained to gender. In three studies (Table 1), female gender was reported to be a risk factor for severe TD. In the present study consisting of mostly (79%) male patients, we found that gender was not a risk factor for severe TD. In all of the above-mentioned three studies listed in Table 1, advanced age was also reported to be a risk factor. A greater number of women in the present study sample could possibly have revealed an interaction between older age and female gender in predisposing to severe TD.

The finding of the severity of negative symptoms as a risk factor for TD is consistent with a number of reports (McCreadie *et al*, 1982; Waddington *et al*, 1985; Yuen *et al*, 1996; Waddington & Youssef, 1996). It differs from the literature, however, in associating the development of severe TD with worsening of negative symptoms from baseline to the last visit. It is not known whether the increase in the negative symptoms over time was directly related to a greater cumulative amount of neuroleptic treatment, and if so, what the nature of this relationship was.

### Limitations

The present study has several limitations. Firstly, despite rigorous attempts to obtain complete and accurate historical data from patients and family members, we cannot be certain that the medication histories reported to us were completely accurate. The possibility of at least partial non-compliance both before and during the study period cannot be eliminated. Secondly, we did not have a control group of non-neuroleptic-treated patients. Hence the possibility of spontaneous dyskinesia in some patients cannot be excluded. Thirdly, the observation that some postulated risk factors (e.g. diabetes mellitus) were not significant predictors of severe TD

could be due to the relatively small number of cases of severe TD. Our operational definition of severe TD differs from some of those reported in Table 1. It is possible that, to a certain extent, the risk factors for severe TD vary according to the defining criteria used. Finally, the (*f*) and (*t*) covariates we chose to study were recorded prior to the development of moderate-severe TD. We found that a significant change in negative symptoms preceded the development of moderate-severe TD; however, we do not know the time course of change in negative symptoms. It is possible that gradual worsening of negative symptoms could indicate a more 'progressive' nature of the relationship between negative symptoms and severe TD, as has been suggested for the relationship between cognitive dysfunction and TD (Waddington & Youssef, 1996).

In view of the possibility of a lower risk of TD with the newer atypical antipsychotics, these drugs may be preferred to the conventional neuroleptics, especially when worsening of negative symptoms is observed. At the present time, however, data are unavailable in the published literature on the incidence of TD with atypical antipsychotic medications in older patients.

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## CLINICAL IMPLICATIONS

- A 22.9% three-year cumulative incidence of severe TD among older neuropsychiatric out-patients represents a clinically significant problem.
- Severe TD has a serious impact on the patient's psychosocial and cognitive functioning.
- Clinicians providing treatment to elderly neuropsychiatric patients should restrict the prescription of conventional neuroleptics to only when necessary and at the lowest effective dose.

## LIMITATIONS

- Despite attempts to obtain complete and accurate historical data from patients and family members, we cannot be certain that the medication histories reported to us were completely accurate.
- Our results may not generalise to patient populations under the age of 45 years, or to those consisting predominantly of women or of non-Caucasian patients.
- We did not have a control group of non-neuroleptic-treated patients, and so the possibility of spontaneous dyskinesia in some patients cannot be excluded.

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