Tardive Dyskinesia in the Elderly: Data From a Prospective Study

John M. Kane, MD

Tardive dyskinesia has been a major concern in the long-term use of antipsychotic medications. Prospective studies have been a valuable tool in helping to advance knowledge regarding incidence, risk factors, and course. Numerous prevalence surveys have suggested advancing age as an important risk factor; however, cross-sectional surveys do not enable an accurate determination of the duration of drug exposure given uncertainty as to how long the condition was present at the time of identification. Because age may be a risk factor for severity and persistence, these also could contribute to higher apparent prevalence rates.

PREVALENCE SURVEY

Prior to initiating a prospective study, we conducted a large-scale prevalence survey. A total of 2,250 individuals from psychiatric and geriatric settings were examined for the presence for abnormal involuntary movements. All examinations were done by the same team of trained raters using a standard examination technique and rating instrument. “Spontaneous” dyskinesia rates were 1.3% among 400 healthy elderly people surveyed at senior citizen centers and 4.8% among medical geriatric inpatients, and ranged from 0 to 2% among psychiatric patients who had never been exposed to neuroleptic medications. For patients who had received treatment with antipsychotic drugs, prevalence rates ranged from 13.3% among patients at a voluntary psychiatric hospital (mean age: 33; 47% male) to 36.1% among a sample of patients residing in state hospitals (mean age: 45; 56% male).

Logistic regression analyses revealed a large effect of age on tardive dyskinesia prevalence and an interaction of age with sex. Among younger individuals, men had higher rates; among those older than age 40, rates were higher for women. Edentulousness, which removes normal proprioceptive feedback and can contribute to abnormal tongue movements, and the presence of other neurological disorders were possible contributors to high rates for the elderly. Even with attempts to control for age, sex, and duration of neuroleptic exposure, prevalence differed markedly from one treatment setting to another. These results confirm age is a significant risk factor for tardive dyskinesia and baseline rates of so-called spontaneous dyskinesia do not account for the higher risk found in the elderly.

The extent to which abnormal involuntary movements may be present spontaneously in individuals without any history of exposure to neuroleptics has long been a source of debate. The prevalence rates in those populations exposed to medications is significantly higher than in patients without such exposure.

PROSPECTIVE STUDIES

Young Patients

We also conducted a long-term prospective study in young patients who were fairly early in their treatment course (mean age: <30 years; median duration of lifetime exposure to antipsychotic medication: <14 months). This population included a range of diagnostic conditions,
including schizophrenia as well as psychotic and nonpsychotic affective illness. In addition, some patients with no history of exposure to antipsychotics also were included to assess the incidence of spontaneous dyskinesias and to help keep the raters blind to treatment history. Patients were treated with a variety of conventional antipsychotics, including long-acting depot preparations in some cases. The incidence of new cases of tardive dyskinesia averaged 5.3% per year of antipsychotic drug exposure. This estimate of risk is consistent with other longitudinal data available in the literature.7,8

**Elderly Patients**

In a separate study,9 we examined the risk of tardive dyskinesia development in a sample of 261 elderly patients.

**Study Protocol**. Patients ≥55 years who were just beginning a course of antipsychotic drug treatment were recruited from the geriatric services of two medical centers and one geriatric center in the New York metropolitan area. The physicians who were treating these patients gave permission for us to approach the patients and family members. Oral agreement was obtained for participation and written informed consent was obtained for special procedures (e.g., videotaping). Written releases were obtained for records of any prior treatment.

Any patient who manifested abnormal involuntary movements prior to receiving antipsychotic medication was excluded from the analysis. Patients with a prior history of antipsychotic drug treatment and patients with a neurological disorder associated with abnormal movements (e.g., Huntington's or Parkinson's disease) also were excluded.

The Tardive Dyskinesia Rating Scale10 was completed 4 weeks following entry to the study and then every 12 weeks thereafter. No attempt was made to influence treatment decisions in terms of specific medication, dosage, or duration of treatment. The research team did suggest antipsychotic drug discontinuation if tardive dyskinesia emerged, and most patients with and without tardive dyskinesia were withdrawn from medication at various times by their treating physician.

The incidence of tardive dyskinesia was estimated using survival analysis procedures. Cox proportional hazards regression was used to examine the impact of putative risk factors. Because it is possible for some patients to develop dyskinesias that appear to be drug-related after the discontinuation of antipsychotic drugs, we allowed a 3-month interval following complete drug discontinuation before considering a patient to be no longer at risk for developing tardive dyskinesia. Thus, any possible dyskinesia that developed after this interval would not have contributed to the incidence estimates.

To be included in our reported analysis, patients had to have had at least 7 days of treatment with antipsychotic medication and undergo follow-up in the study for at least 4 weeks. Mean follow-up was 115 weeks. The research team played no role in the initial decision to prescribe an antipsychotic medication. As would be expected in routine clinical practice, most patients received antipsychotic medication because of psychotic symptoms either with or without agitation.

**Study Findings**. Average age of patients was 77. Twenty-six percent of the patients were men and 74% were women. Eighty-five percent of the subjects were white, 9% were black, and 5% were Hispanic. Primary (DSM-III-R) diagnosis was organic mental syndrome in 63% and other axis I disorders in 37% (predominantly major mood disorder). Ninety-four percent had at least one chronic medical condition, most frequently cardiovascular disorder.

The most frequently (68%) prescribed antipsychotic in this population was haloperidol (this study was conducted prior to the introduction of risperidone, olanzapine, and quetiapine). Seventy-six percent of patients were treated continuously for the first month. For the average patient, the dosage of medication would be considered to be low. The average daily dose in chlorpromazine equivalents was 80 mg (or 1.6 mg haloperidol equivalents) at the start and ≤50 mg for half of the patients who were still taking medication after 1 year.

Sixty patients developed dyskinesias during the prospective evaluation. Seventy-seven percent were rated as mild at the initial diagnosis. At some point during follow-up, 40% received at least one rating of moderate and 13% moderately severe. Movements persisted for at least 3 months in 77% of cases and at least 6 months in 67%.
The incidence of tardive dyskinesia after 1 year was 20% (95% confidence interval [CI]: 14% to 26%), 30% (CI: 22% to 38%) after 2 years, and 42% (CI: 32% to 53%) after 3 years (calendar) of follow-up. If the incidence of tardive dyskinesia is estimated per year of antipsychotic drug exposure (in contrast to calendar year since some individuals receive medication intermittently), then rates increased to 25%, 34%, and 53% after 1, 2, and 3 years, respectively.

In terms of risk factors, patients were more likely to exhibit tardive dyskinesia when examined while not taking antipsychotic medication compared to periods on medication. In this older population, gender and age were not significant risk factors. No relationship was found between risk and race, educational level, smoking history, substance abuse history, or use of anticholinergics. Those with diabetes (defined as receiving oral hypoglycemics or insulin medication) were not significantly more likely to develop tardive dyskinesia.

Patients with multi-infarct dementia were significantly more likely to develop dyskinesias than those with other organic mental syndrome diagnoses. Those with mood disorders were more at risk than those with other axis I psychiatric disorders. Higher mean daily dose and cumulative antipsychotic dosage early in treatment was associated with greater risk; however, this effect diminished later. History of electroconvulsive therapy as well as early extrapyramidal signs were also risk factors.

The incidence rates found in this sample were similar to those in two other studies that followed older patients from the beginning of their exposure to antipsychotic medication. The results regarding risk factors confirm our finding from the study with younger adults that extrapyramidal side effects occurring early in antipsychotic drug treatment are a risk factor for tardive dyskinesia. In this study, we were able to examine the impact of different diagnoses on the risk of tardive dyskinesia controlling for dosage of medication received.

Even though electroconvulsive therapy was not a common treatment, a relationship was found between this variable and risk of dyskinesias. This may be confounded with a diagnosis of severe mood disorder, and it was not possible in this data set to tease apart these factors. It is also possible that the physiological effects of electroconvulsive therapy are relevant above and beyond the role of an affective diagnosis.

Our inability to find a relationship between diabetes and tardive dyskinesia could be related to our reliance on chart diagnosis and treatment rather than direct laboratory examination for disturbances in glucose regulation. Because both diabetes and cerebrovascular insult are age-related factors, they could both contribute in some degree to the increased vulnerability of older individuals to tardive dyskinesia. As diabetes is a risk factor for cerebrovascular disease, including multi-infarct dementia, this also could contribute to the association.

Collectively, these data are compelling in suggesting that among elderly individuals treated with conventional antipsychotics, the risk of developing tardive dyskinesia is four to five times higher than observed in younger patients. This occurs despite the fact that older patients tend to be treated with much lower doses and for shorter periods of time than younger patients. In addition, the mean level of severity of abnormal involuntary movements tends to be higher in older patients as well as does the degree of persistence. The fact that age and gender are not risk factors in this sample may be due to the truncated age range and the relatively small proportion of men in the study.

**CONCLUSION**

The significantly higher risk of drug-induced movement disorders in the elderly highlights the importance of further studies in this population to identify treatments with less inherent risk. Data with the new-generation antipsychotic drugs have been highly consistent in showing lower rates of extrapyramidal symptoms than observed with conventional antipsychotics. Given our findings that early extrapyramidal symptoms are associated with a subsequent risk of developing tardive dyskinesia, one might predict a lower risk with these compounds. Certainly, clozapine has demonstrated a low propensity to produce tardive dyskinesia in large populations of younger adult patients, particularly treatment-resistant patients who tend to have high exposure to conventional antipsychotic...
medications before receiving clozapine. Emerging data with other new-generation antipsychotics such as olanzapine,14 risperidone,15 and quetiapine16 also are encouraging in suggesting lower rates of tardive dyskinesia.

REFERENCES