Tardive Dyskinesia in Older Patients

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Neuroleptic-induced tardive dyskinesia, which often appears in middle-aged and older adults early in the course of treatment with low doses of conventional antipsychotics, is 5 to 6 times more prevalent in elderly than in younger patients. In addition to age, other risk factors for tardive dyskinesia include early extrapyramidal symptoms (EPS), cumulative amounts of neuroleptics, duration of neuroleptic treatment, and history of alcohol abuse and/or dependence. The atypical antipsychotics, which have a low liability for EPS, are likely to also have low potential for tardive dyskinesia, despite the paucity of controlled studies. Starting and maintenance doses of the atypical antipsychotics should generally be lower in older than in younger adults.   *(J Clin Psychiatry 2000;61[suppl 4]:27–32)*

Tardive dyskinesia, one of the most serious adverse effects of treatment with conventional neuroleptics, is 5 to 6 times more prevalent in older than in younger adults.[1,2] Newer atypical antipsychotics are less likely to cause extrapyramidal symptoms (EPS) and may be associated with a lower risk of tardive dyskinesia. Because the risk of tardive dyskinesia increases with age in patients taking conventional neuroleptics, atypical antipsychotics should generally be tried first in older patients.

INCIDENCE

In young, healthy adults taking antipsychotics, the annual cumulative incidence of tardive dyskinesia is 4% to 5%,[3] but the risk increases with age and the duration of neuroleptic exposure. My colleagues and I have been following a group of neuroleptic-treated outpatients over the age of 45 years with diagnoses of dementia with psychotic symptoms or other severe behavioral disturbances (28%), schizophrenia (22%), mood disorder (18%), or another diagnosis (32%). We have published reports of the incidence of tardive dyskinesia in this population,[4] the risk of tardive dyskinesia in patients treated with low doses of typical neuroleptics,[5] the incidence of severe orofacial and limbtruncal dyskinesia,[6] and the effects of conventional versus newer antipsychotics.[2] At the time of study enrollment, a majority of patients had been treated with typical

antipsychotics for less than a month; the median duration of lifetime exposure was 27 days. To date, 439 relatively stable outpatients have been enrolled in the study. Until recently, the patients were generally treated with relatively low doses (usually less than 150 mg/day chlorpromazine equivalent) of conventional neuroleptics, primarily haloperidol or thioridazine. An instrumental assessment, which measures movement abnormalities by using devices such as a strain gauge and accelerometer, is performed at baseline, 1 month, 3 months, and every 3 months thereafter. The instrumental assessment is objective, reliable, and quantifiable; it also can detect subclinical abnormalities.[7,8] The diagnosis of tardive dyskinesia is based on the Schooler-Kane criteria,[9] using the Abnormal Involuntary Movement Scale (AIMS).[10] The mean cumulative annual incidence of tardive dyskinesia in this older population was 29% at 1 year, 50% at 2 years, and 63% at 3 years[2] in contrast to the incidence of 5% at 1 year, 10% at 2 years, and 15% at 3 years reported in young adults by Kane et al.[3] (Figure 1). Thus, we found the risk of tardive dyskinesia to be about 6 times higher in older patients than the incidence Kane et al. reported in younger patients.

Severe tardive dyskinesia can be especially troublesome to the elderly. Orofacial tardive dyskinesia can impair eating and swallowing as well as result in dental problems that can progress to mouth infection and/or unintelligible speech. The gait disturbances of patients with severe limbtruncal dyskinesia may lead to falls and injuries.
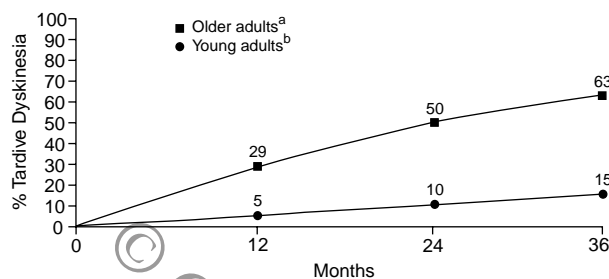
Tardive dyskinesia can appear in older patients early in the course of neuroleptic treatment. According to DSM-IV criteria, the minimum duration of neuroleptic exposure necessary to produce tardive dyskinesia is 3 months in those under 60 years and 1 month in those 60 years or over. In a group of neuroleptic-naive patients (N = 87) whose mean ± SD age was 66.2 ± 12.2 years, the incidence of tardive dyskinesia was 3.4% at 1 month and 5.9%

Figure 1. Cumulative Incidence of Neuroleptic-Induced Tardive Dyskinesia

aData from Jeste et al.[2]
bData from Kane et al.[3]

Figure 2. Cumulative Incidence of Tardive Dyskinesia in Early Stages of Treatment With Typical Neuroleptics[a]
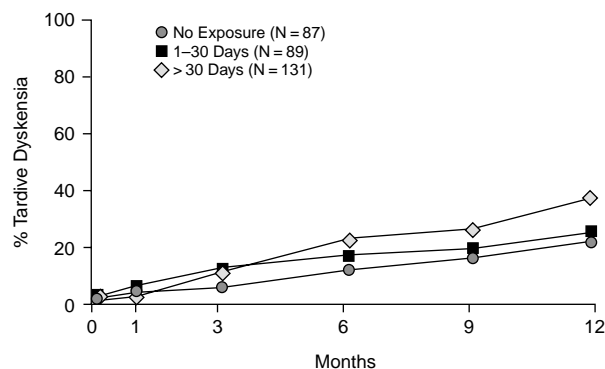

aFrom Jeste et al.,[5] with permission.

at 3 months.[4] At the end of 1 year of treatment with less than 100 mg/day chlorpromazine equivalent, the incidence of tardive dyskinesia was 23% in patients who had been neuroleptic naive at baseline (Figure 2). The risk increases with the duration of neuroleptic exposure. The incidence at 1 year was somewhat greater (p = .08) for those with more than 30 days of previous neuroleptic exposure at baseline (N = 131) than those with 30 days or less (N = 176).

RISK FACTORS

Despite numerous studies over the past 35 years, our understanding of the risk factors for tardive dyskinesia remains incomplete. Old age appears to be the predominant patient-related risk factor.[11,12] Previous researchers have also associated tardive dyskinesia with early EPS,[13–15] alcohol abuse or dependence,[16,17] and ethnicity.[18,19]

As described earlier, my colleagues and I have studied risk factors for tardive dyskinesia in older patients.[4] The patients, who were over 45 years old, were treated with either a high-potency or low-potency neuroleptic, but were maintained on relatively low doses. Principal risk factors for the occurrence of tardive dyskinesia were a baseline duration of neuroleptic use totaling more than 90 days, the cumulative amount of neuroleptics (especially high-potency ones) used, a history of alcohol abuse or dependence at baseline, and the presence of subtle movement disorder at baseline. The cumulative amount of neuroleptic used is a product of daily dose and length of treatment, and high amounts of high-potency conventional neuroleptics were more likely to cause tardive dyskinesia than similar amounts of low-potency agents. One reason why earlier studies may have failed to find a difference in tardive dyskinesia risk between low-potency and high-potency neuroleptics is due to the intimate relationship between potency and dose used. When measured in chlorpromazine equivalents, low-potency neuroleptics, unlike high-potency neuroleptics, are rarely used at high dosages.

Previous reports of early EPS as a risk factor for tardive dyskinesia could conceivably be related to the likelihood that patients with early EPS generally received high-potency antipsychotics.

Development of EPS early in the course of treatment with conventional neuroleptics has been suggested as a risk factor for tardive dyskinesia.[8,13–15] In recent years, instrumental procedures have been developed to provide a sensitive and quantitative battery for the assessment of neuroleptic-induced movement disorders. These instrumental assessments can measure abnormalities such as instability, tremor, movement speed, and rigidity that are below the threshold of human detection. My colleagues and I have found that the presence of subtle, subclinical movement disorder or tremor at the beginning of neuroleptic treatment increases the risk for development of tardive dyskinesia.[5]

Several factors, including baseline movement abnormalities and movement abnormalities that develop early in the course of neuroleptic treatment, have a role in the relationship between EPS and tardive dyskinesia. These early movement abnormalities may predict the type of movement disorder (e.g., tremor vs. bradykinesia, rigidity vs. dyskinesia) or the subtype of tardive dyskinesia. Orofacial tardive dyskinesia is twice as common in middle-aged and elderly patients as limbtruncal tardive dyskinesia. Paulsen et al.[20] found the cumulative incidence of orofacial tardive dyskinesia was 38.5% after 1 year and 65.7% after 2 years of neuroleptic exposure, while the incidence of limbtruncal tardive dyskinesia was 18.6% after 1 year and 32.6% after 2 years. The presence of preclinical dyskinesia was predictive of both subtypes of tardive dyskinesia, while the presence of tremor was predictive of limbtruncal tardive dyskinesia only, and a history of alcohol abuse or dependence was predictive for orofacial tardive dyskinesia only.

The risk of EPS is also high in the elderly. My colleagues and I[21] recently found a high incidence of EPS in

24 outpatients with Alzheimer's disease who were treated with extremely low doses of conventional neuroleptics for psychosis or severe agitation. Their mean age was 75 years, and their mean score on the Mini-Mental State Examination was 20. All patients were neuroleptic naive at study entry. After 9 months of treatment with a mean ± SD dose of 26 ± 18 mg/day of chlorpromazine equivalent (two thirds of the patients received haloperidol and one third, thioridazine), 67% of the patients had developed clinically significant parkinsonism. One important risk factor for EPS in this population was the presence of pretreatment subclinical bradykinesia, which was measured instrumentally.

Ethnicity is another predictive factor for the occurrence of tardive dyskinesia. Previous studies have found a higher incidence of tardive dyskinesia in African Americans as opposed to Caucasians.[18,19] In the Jeste et al. study,[2] the cumulative annual incidence of tardive dyskinesia was 46.5% in African Americans and 27.2% in Caucasians. The 2 ethnic groups were similar in terms of diagnostic breakdown, age, percentage of men and women, length of neuroleptic exposure at baseline, and amount of cumulative neuroleptic use.

ATYPICAL ANTIPSYCHOTICS AND TARDIVE DYSKINESIA

Unlike conventional antipsychotics, atypical agents are potent central serotonin antagonists in addition to being central dopamine receptor antagonists. Four of these atypical agents—clozapine, olanzapine, quetiapine, and risperidone—are available in the United States, although clozapine is indicated only for treatment-refractory schizophrenic patients because of the risk of agranulocytosis. All 4 atypical agents are associated with a lower incidence of EPS than conventional neuroleptics. The low risk of tardive dyskinesia in clozapine-treated adults is well established.[22] Since EPS have been reported to be a risk factor for tardive dyskinesia in the elderly,[5,13] the incidence of tardive dyskinesia with the other atypical agents is also likely to be lower than the incidence with conventional neuroleptics. However, long-term studies are needed to determine the exact risk of tardive dyskinesia in older patients treated with the atypical antipsychotics.

Clozapine

Well-controlled published studies of the use of clozapine in the elderly are rare, but a number of open reports indicate the usefulness of clozapine for psychotic patients with Parkinson's disease,[23,24] and some researchers have reported improvements in disabling tremor in patients with Parkinson's disease.[25] Although clozapine has a low risk of tardive dyskinesia, other side effects limit its use in the elderly. Patients who take clozapine are at risk for leukopenia and even agranulocytosis. This risk necessitates

Figure 3. Tardive Dyskinesia (TD) Incidence in Haloperidol- vs. Risperidone-Treated Patients[a]
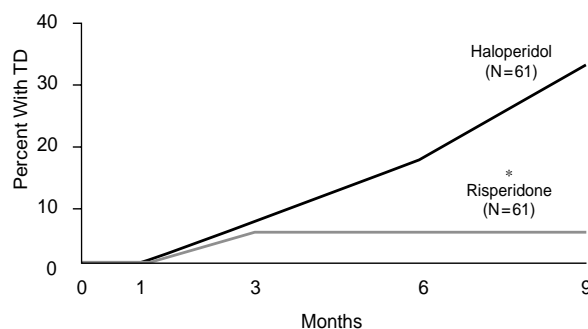
[a]Data from Jeste et al.[26]
*Peto-Prentice p < .05 risperidone vs. haloperidol.

weekly blood monitoring during the first 6 months of treatment and semimonthly monitoring thereafter. Elderly patients, particularly those who are frail, may have trouble complying with these requirements. Despite its side effects, clozapine may be indicated for some Parkinson's disease patients with psychotic symptoms, treatment-refractory psychotic patients, or those who have severe tardive dyskinesia.

Risperidone

A lower incidence of tardive dyskinesia was reported for risperidone compared with haloperidol after 9 months of treatment in a recent study (Figure 3).[26] The subjects, who were 45 years or older (mean age = 66 years) had diagnoses of schizophrenia, dementia, mood disorders, or other conditions with psychotic symptoms or severe behavioral disturbances and had never been previously treated with an atypical antipsychotic. Sixty-one risperidone-treated patients were matched by age, diagnosis, and length of pre-enrollment neuroleptic exposure with 61 haloperidol-treated patients. Twenty-one percent of the haloperidol-treated patients and 31% of the risperidone-treated patients were neuroleptic-naive at study entry. In the patients who had previously received treatment with conventional neuroleptics, the median number of days of neuroleptic use was 72 in the haloperidol group and 89 in the risperidone group; 20% of the patients in each group were taking anticholinergic medication. The median dose of each medication was 1 mg/day, quite low for this heterogeneous population. Life-table analysis revealed that tardive dyskinesia was significantly more likely to develop in haloperidol-treated than in risperidone-treated patients (p < .05).

Brecher[27] also reported a very low incidence of tardive dyskinesia in 216 risperidone-treated patients who had been exposed to the agent for a mean ± SD of 184 ± 128 days. The patients, who were being treated for dementia, received 0.5, 1, or 2 mg/day of risperidone. Both the

Figure 4. Study in Alzheimer's Patients: Acute Extrapyramidal Symptoms[a]
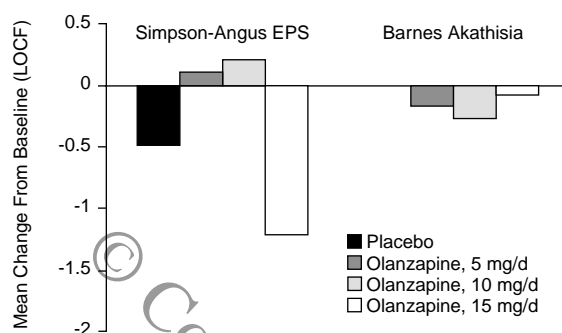
[a]Data from Street et al.[29] Abbreviations: EPS = extrapyramidal symptoms, LOCF = last observation carried forward.

Table 1. Usual Recommended Doses for Atypical Antipsychotics in Elderly Patients[a]

Drug	Initial Dose (mg/d)	Typical Range (mg/d)
Clozapine	6.25–12.5	50–100
Risperidone	0.25–0.5	1–2.5
Olanzapine	1–5	5–15
Quetiapine	12.5–25	75–125

[a]Patients with dementia should be administered doses at the lower end of the range and those with schizophrenia should be administered doses at the upper end of the range.

1-mg/day and 2-mg/day risperidone doses were equally effective, but the 2-mg/day dose was associated with more EPS.

Olanzapine

Although data on the incidence of tardive dyskinesia in elderly patients treated with olanzapine have not yet been reported, preliminary evidence indicates a low risk for EPS in this population, and the risk of tardive dyskinesia in young olanzapine-treated adults appears to be low.[28] In a randomized, double-blind, placebo-controlled study[29] of 3 doses of olanzapine in 206 elderly nursing-home patients with Alzheimer's disease, there was no significant difference in EPS between any of the doses of olanzapine and placebo (Figure 4). Patients who had psychiatric symptoms and behavioral disturbances associated with Alzheimer's disease were randomly assigned to 5, 10, or 15 mg/day of olanzapine or placebo for up to 6 weeks. The Simpson-Angus scale and Barnes Akathisia Scale were used to assess the patients weekly.

In a randomized, double-blind, 6-week study of schizophrenic patients over the age of 65 years,[30] the incidence of EPS was significantly (p < .05) greater with haloperidol than olanzapine when patients were assessed with the Simpson-Angus and Barnes Akathisia scales. The patients were withdrawn from their previous neuroleptic and randomly assigned to treatment with olanzapine or haloperidol. At the end of 6 weeks of treatment, the Simpson-Angus scale scores had decreased 2.5 in the olanzapine-treated patients and increased 0.5 in the haloperidol-treated patients, while the Barnes Akathisia Scale scores had decreased 0.4 in the olanzapine-treated patients and increased 0.5 in the haloperidol-treated patients. These data suggest that the risk of tardive dyskinesia in older patients should be lower for olanzapine than for haloperidol.

There is also a case report[31] of improvement in haloperidol-induced tardive dyskinesia in an elderly patient who was switched from haloperidol to olanzapine. After 12 months of haloperidol treatment, the 76-year-old woman had AIMS scores ranging from minimal (face, tongue, and lower limbs) to moderate (lips, jaw, and upper limbs). The EPS often interfered with eating. Haloperidol was stopped and a week later 10 mg/day of olanzapine introduced. After 5 weeks of olanzapine treatment, there was substantial improvement of all abnormal movements—AIMS scores ranged from not present (face, jaw, tongue, lower limbs) to minimal (lips and upper limbs).

Quetiapine

Data are lacking for the tardive dyskinesia liability of older patients who are treated with quetiapine. However, preliminary reports indicate few EPS in this population. In an open-label study of 151 elderly patients who were treated with quetiapine for psychosis,[32] after 1 year of treatment there was a significant decrease from baseline on the Simpson-Angus EPS scale but no change in the AIMS. The mean score on the Simpson-Angus EPS scale decreased a mean ± SD of 2.1 ± 4.1 over 1 year of treatment (p < .001). Parsa and Bastani[33] reported on 2 patients in whom treatment with quetiapine controlled psychotic symptoms without worsening motor disability.

These uncontrolled, open studies provide additional evidence that movement disorders are reduced in older patients treated with atypical antipsychotics. Since the risk of tardive dyskinesia is high in patients over the age of 45 years who are treated with even low doses of typical neuroleptics, atypical agents should generally be the preferred first-line treatment in elderly patients.

Dosing

Elderly patients will often respond to lower doses of atypical antipsychotics than younger patients. When older patients are treated with novel antipsychotics, the clinician should generally start at a low dose and titrate upward slowly (Table 1). Patients with dementia will usually respond to a lower dose than patients with schizophrenia or other primary psychotic disorders.

Since quetiapine was not introduced into clinical practice until 1997, more clinical evidence exists for olanzapine and risperidone dosages. I recommend that the starting dose of olanzapine in elderly patients should be 1 to

5 mg/day, and the maintenance dose should be 5 to 15 mg/day. In the study of olanzapine in Alzheimer's patients,[29] 5 and 10 mg/day were superior to 15 mg/day, while in the schizophrenia study,[30] the optimal olanzapine dose was between 10 and 15 mg/day.

Starting and maintenance dosages of risperidone should be much lower than those recommended for younger patients since EPS are more likely to occur with risperidone than with the other atypical antipsychotics.[34] While 1 mg/day and 2 mg/day doses of risperidone were equally effective in a group of patients with dementia,[27] 1 mg/day was associated with fewer adverse effects, including EPS, than 2 mg/day. Risperidone should be started at a dose of 0.25 to 0.5 mg/day and increased by that amount once or twice a week up to a maximum of 1.0 to 2.5 mg/day. Patients with dementia, Parkinson's disease, or significant hypotension should generally not receive more than 1 to 1.5 mg/day of risperidone.

The maintenance dose of an atypical antipsychotic should be as low as possible since some atypical antipsychotics have been associated with EPS at higher doses, and there is evidence that EPS early in treatment are a risk factor for tardive dyskinesia. Polypharmacy with combinations of psychotropic agents should be avoided in older patients who are often also receiving medications for a variety of other medical problems. To achieve the full benefits of a medication, a longer trial may be needed in the elderly than would be necessary in younger patients.

CONCLUSION

Since tardive dyskinesia is 5 to 6 times more prevalent in older than in younger patients who are treated with conventional antipsychotics and since there is evidence that early EPS are a risk factor for tardive dyskinesia in this population, the atypical antipsychotics, which have a low liability for EPS, should be the preferred first-line treatment for the elderly. Clinicians should start treatment in elderly patients with a low dose and increase the dose slowly until the lowest effective dose is reached.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), thioridazine (Mellaril and others).

Disclosure of off-label use: The author of this article has determined that, to the best of his knowledge, the following agents are not approved by the U.S. Food and Drug Administration for the treatment of agitation or aggression in patients with dementia: chlorpromazine, clozapine, haloperidol, olanzapine, quetiapine, risperidone, and thioridazine.

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