Tardive Dyskinesia Rates With Atypical Antipsychotics in Older Adults

Dilip V. Jeste, M.D.

Tardive dyskinesia is a chronic drug-induced movement disorder that tends to be persistent in older adults who are treated with antipsychotics. Tardive dyskinesia can affect older patients both physically and psychologically, leading to frequent falls, difficulty eating, and depression. While atypical antipsychotics may cause tardive dyskinesia, the percentage is usually significantly lower than with conventional antipsychotics. Using atypical antipsychotics, particularly at lower doses, may aid in preventing symptoms of tardive dyskinesia in older adults.

(J Clin Psychiatry 2004;65[suppl 9]:21–24)

Older patients are often at risk for developing serious side effects as a result of antipsychotic treatment. Drug-induced movement disorders, such as tardive dyskinesia, are more persistent in older than in younger patients. The risk of tardive dyskinesia from conventional antipsychotic treatment is 5 to 6 times higher in older than in younger adults.[1,2] In the majority of patients who develop tardive dyskinesia, symptoms persist for months or even years. Tardive dyskinesia can lead to a number of physical and psychological complications such as difficulty eating and swallowing, weight loss, falls and difficulty keeping balance, feelings of depression, and potentially suicide. Research indicates that atypical antipsychotics may have a lower risk of tardive dyskinesia than conventional antipsychotics and may therefore be a safer treatment for the elderly.

INCIDENCE OF TARDIVE DYSKINESIA IN ELDERLY PATIENTS TREATED WITH CONVENTIONAL ANTIPSYCHOTICS

While tardive dyskinesia affects antipsychotic-treated patients across all age spectrums, the incidence of tardive dyskinesia has been found to be higher among older patients treated with conventional antipsychotics than younger patients. In one study,[1] my colleagues and I found a cumulative 1-year incidence of tardive dyskinesia to be 29% among older patients (mean age of 65 years), whereas Kane et al.[3] found a 1-year cumulative incidence of tardive dyskinesia of 5% in younger patients.[3] After 2 years, the cumulative incidence was 50% for older patients and 10% for younger adults, and after 3 years, the rates were 63% and 15%, respectively (Figure 1). Older patients in our study[1] were treated with much lower dosages of these drugs compared with the younger adults.[3] Despite these low dosages, the conventional antipsychotics have a high risk of producing tardive dyskinesia in older adults.

We also examined the incidence of severe tardive dyskinesia in older adults; 378 patients were monitored for the development of tardive dyskinesia.[4] All participants were over the age of 45 years, did not meet the Schooler and Kane criteria for tardive dyskinesia at entrance, and suffered from a DSM-III-R–defined psychiatric disorder such as schizophrenia. Patients were prescribed low doses of conventional antipsychotics and were followed for up to 36 months. Severe tardive dyskinesia was defined according to the DSM-III-R criteria and a score of at least 3 on the Abnormal Involuntary Movement Scale (AIMS). The cumulative proportion of all patients who developed severe tardive dyskinesia was 2.5% after 1 year and 22% after 3 years. Moderate-to-severe tardive dyskinesia was found to be significantly associated with a greater cumulative antipsychotic dosage in these older patients.

INCIDENCE OF TARDIVE DYSKINESIA IN ELDERLY PATIENTS TREATED WITH ATYPICAL ANTIPSYCHOTICS

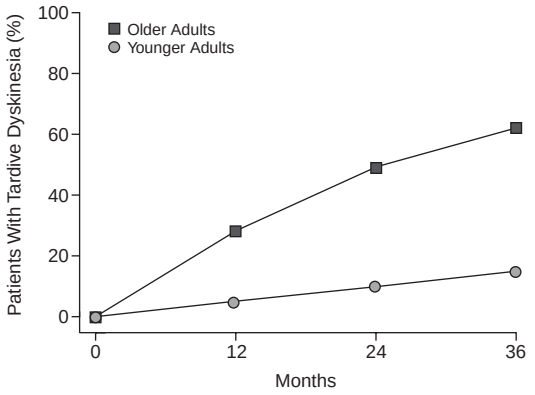
While atypical antipsychotics can also cause tardive dyskinesia, the rate is usually significantly lower than with conventional agents, even in older patients. In a recent

From the Division of Geriatric Psychiatry, University of California, San Diego, and Veterans Affairs San Diego Health Care System, San Diego, Calif.

This article is derived from the teleconference "Drug-Induced Movement Disorders," which was held October 27, 2003, and supported by an unrestricted educational grant from Janssen Medical Affairs, L.L.C.

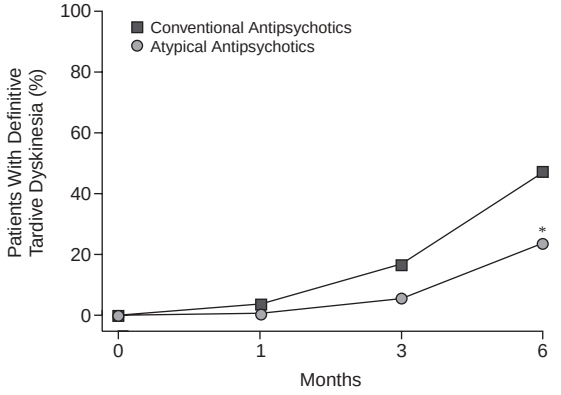
Corresponding author and reprints: Dilip V. Jeste, M.D., Division of Geriatric Psychiatry, VA San Diego Health Care System (116-A-1), 3350 La Jolla Village Drive, San Diego, CA 92161 (e-mail: djeste@ucsd.edu).

Figure 1. Cumulative Incidence of Tardive Dyskinesia With Conventional Neuroleptics[a]



[a]Data from Jeste et al.[1] and Kane et al.[3]

Figure 2. Cumulative Incidence of Definitive Tardive Dyskinesia in Older Patients With Borderline Dyskinesia[a]



[a]Reprinted from Dolder and Jeste[5] with permission.
*p < .001.

study,[5] the risk of developing definitive tardive dyskinesia after treatment with either a conventional antipsychotic or an atypical antipsychotic was measured in middle-aged and older adults. Selection criteria included a diagnosis of borderline tardive dyskinesia and that the participants had to be currently receiving an atypical or conventional antipsychotic. Definitive tardive dyskinesia was defined as at least two ratings of 2 or one rating of 3 on the AIMS. A total of 240 patients (130 treated with conventional agents and 110 treated with atypical agents including risperidone, olanzapine, and quetiapine) met the selection criteria. Patients treated with conventional antipsychotics were about twice as likely to develop tardive dyskinesia as patients treated with atypical antipsychotics ($p < .001$). The 6-month mean cumulative incidence of definitive tardive dyskinesia in this very high-risk patient population was 44.9% for conventional antipsychotics and 24.1% for atypical antipsychotics (Figure 2).

Clozapine

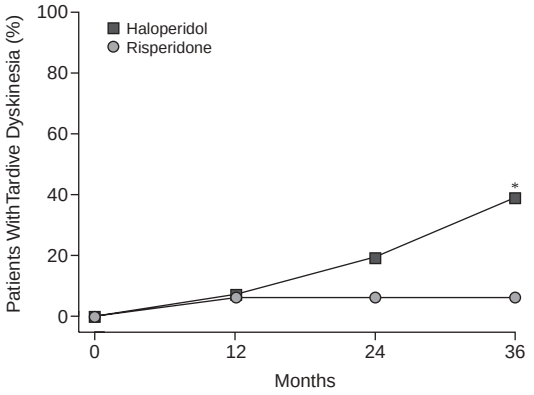
Clozapine is the oldest of the atypical antipsychotics. While studies do not exist on the rate of tardive dyskinesia in elderly patients treated with clozapine, other side effects such as leukopenia and agranulocytosis often limit the use of clozapine in the elderly. However, clozapine has been reported to benefit psychotic patients with Parkinson's disease,[6,7] and it has been suggested that clozapine may improve disabling tremor common to patients with Parkinson's disease.[8]

The rate of tardive dyskinesia has been found to be low among patients treated with clozapine. Kane and collegues[9] conducted a 1-year study of the rate of tardive dyskinesia associated with clozapine in 28 patients with a diagnosis of either schizophrenia or schizoaffective disorder. Participants had no known history of tardive dyskinesia or the presence of tardive dyskinesia at baseline. A diagnosis of tardive dyskinesia was based on a modified Simpson Dyskinesia Scale, and patients were considered to have a diagnosis of tardive dyskinesia if they received a rating of at least "mild" on 2 consecutive visits during a 3-month period. The data from the clozapine-treated group were compared with those from participants in an ongoing prospective study of tardive dyskinesia development in patients with schizophrenia or schizoaffective disorder treated with conventional antipsychotics (N = 409). In the clozapine-treated group, only 2 patients received global ratings of mild tardive dyskinesia on 2 consecutive examinations. However, both of these patients had received a global rating of "questionable" at baseline, which may suggest that the condition of tardive dyskinesia was preexisting. It appears that the risk of tardive dyskinesia is lower with clozapine than with conventional antipsychotics.

Risperidone

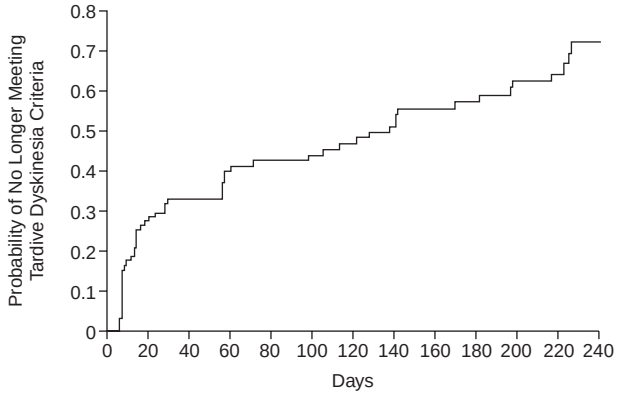
Risperidone has been cited as having a low incidence of tardive dyskinesia. My colleagues and I[10] studied the risk of persistent tardive dyskinesia in elderly patients with dementia who had successfully completed a 12-week double-blind study with placebo and risperidone. Persistent tardive dyskinesia was defined by symptoms of tardive dyskinesia present on 2 successive visits that were 2 months apart. The trial was a 1-year open-label study in which 330 patients received 0.5 to 2 mg/day of risperidone. The Extrapyramidal Symptom Rating Scale was used to assess extrapyramidal symptoms (EPS) and persistent tardive dyskinesia. The cumulative annual incidence of persistent tardive dyskinesia was found to be 2.6% among the 133 patients who completed the trial. The cumulative incidence of persistent tardive dyskinesia, with a dose of 0.75 to 1.5 milligrams of risperidone, was only about 1%.

Figure 3. Tardive Dyskinesia Incidence in Older Patients: Haloperidol Versus Risperidone[a]



[a]Reprinted from Jeste et al.[11] with permission.
*p < .05.

Figure 4. Olanzapine and Remission of Tardive Dyskinesia[a]



[a]From Kinon et al.[13] with permission.

Several studies report the risk of tardive dyskinesia with risperidone in comparison with other drugs in older patients. In one study,[11] the risk of tardive dyskinesia with haloperidol was compared with that of risperidone in patients aged 45 years and older. Sixty-one patients treated with risperidone were matched by age, diagnosis, and length of antipsychotic treatment with 61 patients treated with haloperidol. A majority of these patients had either schizophrenia or dementia with psychosis or agitation. Assessments for tardive dyskinesia were conducted at baseline and at 1, 3, 6, and 8 months with the AIMS, Simpson-Angus sale for EPS, Brief Psychiatric Rating Scale, and Mini-Mental State Examination. Both risperidone- and haloperidol-treated patients received a median daily dose of 1 mg/day; however, the cumulative incidence of tardive dyskinesia was significantly higher with the haloperidol group than the risperidone group ($p = .045$) (Figure 3).

Olanzapine

Olanzapine has been found to have significantly lower rates of tardive dyskinesia when compared with haloperidol. Beasley and colleagues[12] conducted a double-blind comparison between patients treated with haloperidol and patients treated with olanzapine. All patients were participants in 1 of 3 multicenter trials that had been conducted at an earlier date by Beasley and colleagues. The 3 trials had observed either olanzapine versus placebo; olanzapine, haloperidol, or placebo; or olanzapine versus haloperidol. All placebo-treated patients were excluded from the current trial, and 1192 olanzapine-treated and 522 haloperidol-treated patients were included. Patients had been treated for up to 2.6 years and met the Schooler and Kane criteria for a diagnosis of tardive dyskinesia at 2 consecutive AIMS assessments. The Kaplan-Meier survival analysis was used to estimate the risk of developing tardive dyskinesia. The relative risk for the overall follow-up period was significantly lower for olanzapine-treated patients than haloperidol-treated patients ($p < .001$); 2.5% of olanzapine-treated patients developed tardive dyskinesia, while 8.02% of haloperidol-treated patients developed tardive dyskinesia.

Another study[13] found that symptoms of tardive dyskinesia were significantly less severe in patients treated with olanzapine. Ninety-five patients who had been diagnosed with tardive dyskinesia by the restricted Schooler and Kane criteria were treated with olanzapine in a double-blind study. Participants received between 5 and 20 mg/day of olanzapine for 8 months, and tardive dyskinesia symptoms were assessed with the AIMS and Positive and Negative Syndrome Scale. After 8 months, almost 70% of participants no longer met the restricted Schooler and Kane criteria (Figure 4).

In one recent multisite international study of elderly patients with schizophrenia conducted by my colleagues and me,[14] we found that there was no significant difference between risperidone and olanzapine (mean daily doses of 2 and 10 mg, respectively) in the changes in the Extrapyramidal Symptom Rating Scale over an 8-week period.

Quetiapine

Few studies exist on the incidence of tardive dyskinesia with quetiapine. However, evidence does seem to indicate that the incidence of tardive dyskinesia is quite low with quetiapine treatment. Quetiapine was associated with a substantial reduction in the AIMS score in one patient previously treated with a mean dose of 6 mg/day of haloperidol for 3 months.[15] Sacchetti and Valsecchi[15] observed the effects of haloperidol, quetiapine, olanzapine, and clozapine in a 124-week case report. During the haloperidol treatment period, the patient's mean AIMS score was 19. The patient was then switched to olanzapine (maximum

dose of 500 mg/day) and after 28 days her score on the AIMS had been reduced to 3.

In an uncontrolled trial,[16] the effect of quetiapine in the elderly was observed. Patients with psychotic disorders meeting the DSM-IV criteria who were 65 years or older participated in this multicenter, open-label, 52-week trial. Participants were treated with quetiapine at a mean daily dose of 100 mg/day. Abnormal involuntary movements were assessed using the Simpson-Angus Neurologic scale and the AIMS. A total of 115 patients completed the trial. The change from baseline on the AIMS score was not statistically significant. Patients appeared to have a small but statistically significant improvement on the Simpson-Angus scores from baseline.

My colleagues and I[17] examined the cumulative annual incidence of persistent tardive dyskinesia with quetiapine in 85 patients from the above mentioned study. Participants were 65 years of age and older with a DSM-IV diagnosis of schizophrenia, delusional disorder, psychosis of dementia, or psychotic disorder in Parkinson's disease. Of the original 184 participants, 85 participants had no signs of tardive dyskinesia at baseline. These patients were assessed for the presence of persistent tardive dyskinesia using the Schooler and Kane criteria. Among these patients, the median daily dose of quetiapine was 172 mg. At the 12-month study endpoint, the incidence of persistent tardive dyskinesia in patients without a history of persistent tardive dyskinesia was less than 3%.

DOSAGE

Although atypical antipsychotics appear to have a lower risk of tardive dyskinesia than do conventional antipsychotics, physicians should still prescribe atypical antipsychotics at appropriately low doses in older patients. Elderly patients will more often respond to lower doses of atypical antipsychotics than younger patients do. It is generally advised that clinicians start at low doses of antipsychotics for older adults and then slowly titrate upward. Older patients with dementia more often respond to lower antipsychotic doses than do younger patients with schizophrenia. While the risk of tardive dyskinesia is low, older patients are still at risk for other serious side effects associated with atypical antipsychotics. Keeping maintenance doses low with atypical antipsychotics, as well as avoiding polypharmacy with other antipsychotics, may enable physicians to avoid serious medical conditions in older patients.

CONCLUSION

Tardive dyskinesia is a serious medical condition that affects a significant proportion of older patients who are treated with antipsychotics. Research indicates that atypical antipsychotics may reduce the risk of tardive dyskinesia in older patients as compared with conventional agents. Treating older adults with atypical antipsychotics in doses lower than those for younger patients may enable physicians to adequately reduce the risk of tardive dyskinesia.

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

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, clozapine, haloperidol, olanzapine, quetiapine, and risperidone are not approved by the U.S. Food and Drug Administration for the treatment of psychosis and agitation in dementia.

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