

Tardive Dyskinesia Rates With Atypical Antipsychotics in Adults: Prevalence and Incidence

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Both conventional and atypical antipsychotics cause an up-regulation of dopamine-2 receptors and have been associated with tardive dyskinesia. Studies of adult and elderly subjects have shown a greater incidence of tardive dyskinesia among patients who were administered conventional antipsychotic drugs than those given atypical antipsychotic drugs. This article will review studies of the prevalence and incidence of tardive dyskinesia in patients taking antipsychotic agents.

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Tardive dyskinesia is characterized by involuntary movements, typically of the mouth, lips, and tongue, but which also may involve any muscle in the body. Although antipsychotics have been implicated as causing tardive dyskinesia because of their role in the up-regulation of dopamine receptors, spontaneous dyskinesias existed among patients with schizophrenia in the pre-antipsychotic era, and high rates of abnormal involuntary movements have also been found among institutionalized geriatric patients never exposed to antipsychotics.¹ Thus, antipsychotics are not the sole cause of dyskinesias.

To evaluate whether or not an antipsychotic is associated with a risk of tardive dyskinesia, the proportion of patients exposed to the medication who develop tardive dyskinesia must be compared with the expected rate of emergence of spontaneous dyskinesia in patients with the same diagnosis.^{2,3} In a large, multisite study,⁴ 2250 subjects were examined for abnormal involuntary movements by the same team of trained raters. Spontaneous dyskinesia rates were 1.3% among 400 otherwise healthy elderly people, 4.8% among medical geriatric inpatients, and ranged from 0% to 2% among psychiatric patients never exposed to antipsychotics. Prevalence rates ranged from 13.3% among patients at a voluntary psychiatric hospital to 36.1% among state psychiatric hospital patients. With such markedly different prevalence rates across sites within the

same study, it is easy to see why prevalence is such a difficult measure to delineate or compare between different studies.

Both conventional and atypical antipsychotics have high affinity for dopamine-2 (D_2) receptors and are associated with an increase in D_2 receptor binding. This antipsychotic-induced up-regulation of D_2 receptors has been associated with the development of tardive dyskinesia. Atypical antipsychotics, however, appear to be associated with a lower risk of tardive dyskinesia than conventional antipsychotics. A study⁵ of 9 patients with DSM-IV schizophrenia who had been treated with the conventional antipsychotics haloperidol ($N = 3$) or perphenazine ($N = 1$) or with the atypical antipsychotics risperidone ($N = 3$) or olanzapine ($N = 2$) showed increases in D_2 binding potentials in both groups. Following a 14-day washout, the binding potentials of D_2 receptors in the 2 groups were measured using positron emission tomography (PET). Increases in D_2 binding were 37% in the conventional antipsychotic group and 31% in the atypical antipsychotic group. Patients who showed the highest degree of D_2 receptor up-regulation (98%) developed severe and persistent tardive dyskinesia.

Prolonged dopamine blockade, as a result of antipsychotic use, may lead to an increase in the number of receptors and the avidity with which they bind to dopamine. In addition to the up-regulation of D_2 receptor binding, PET scans in patients taking atypical antipsychotics have shown that acute motor side effects generally occur when a drug dose results in D_2 receptor occupancy of about 80% or higher.⁶

The existence of spontaneous dyskinesia among patients who have never taken antipsychotic medication complicates efforts to define the risk of antipsychotic-induced tardive dyskinesia. Also, multiple syndromes may cause abnormal movements that may collectively be mistaken for tardive dyskinesia. This article will focus on the

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prevalence and incidence of tardive dyskinesia as it relates to antipsychotic use.

PREVALENCE

Accurate estimates of the risk of tardive dyskinesia, either with antipsychotics in general or with a specific drug, are difficult to obtain and can be misleading for several reasons. First, prevalence estimates are based on the percentage of a population that is affected at a given point in time and may, therefore, vary widely. Prevalence data reported for tardive dyskinesia are generally based on a large number of individuals seen at a particular clinical facility or in an outpatient program at a given time who had abnormal involuntary movements that might be attributed to treatment with antipsychotic drugs.

Second, prevalence comparisons often fail to distinguish between risk factors (e.g., age, female sex, and diabetes mellitus) and predictive factors (e.g., early extrapyramidal symptoms [EPS], duration of exposure to antipsychotic treatment, and total dose administration over time).⁷⁻⁹ Age has been the variable most consistently related to increased prevalence of tardive dyskinesia among antipsychotic-treated patients. Some unexplained predisposing factors also contribute to the risk of developing tardive dyskinesia. Among patients receiving equivalent amounts of antipsychotic drugs, some patients develop tardive dyskinesia while others do not. Clinical differences may predispose individuals to tardive dyskinesia, e.g., nonpsychotic patients being treated with antipsychotic drugs for other conditions, particularly affective disorders. Patients who may have never received antipsychotic drugs but have abnormal movements unrelated to treatment may be considered false-positives. Many patients are examined when they are already receiving antipsychotic drugs. Some of these patients may not readily manifest evidence of tardive dyskinesia and could be considered false-negatives. These factors confound the collecting of relevant information for determining the prevalence of tardive dyskinesia.

The percentage of patients identified as having tardive dyskinesia at baseline by Beasley et al.¹⁰ was 28.8%. My colleagues and I⁸ reported a 23.4% prevalence across 3 study sites, and other studies and reviews suggest a prevalence of about 20% among patients with schizophrenia.¹ Despite their variability depending on population, prevalence estimates have played an important role in drawing attention to antipsychotic-induced tardive dyskinesia. Prevalence studies have helped to define the scope of the problem, identify populations at risk, and suggest risk factors.

INCIDENCE

Unlike prevalence estimates, which are based on an observed population at one point in time, incidence estimates

are based on the rate of occurrence in the same set of patients observed over time. Long-term prospective studies have helped to identify specific putative risk factors for tardive dyskinesia. These potential risks include the nature of the drug being administered and treatment response, the duration of drug treatment, age, sex, race, and comorbid conditions. Also, the incidence of tardive dyskinesia among patients who have been exposed to only 1 antipsychotic appears to be lower than the incidence found in patients who have tried multiple antipsychotics (this may be related, however, to treatment responsiveness and/or vulnerability to EPS).

Patients administered conventional antipsychotic drugs have a greater incidence of tardive dyskinesia than patients administered atypical antipsychotic drugs. My colleagues and I recently conducted a systematic review¹¹ of studies that had lasted at least 1 year and involved the atypical antipsychotic medications (Table 1).^{10,12-17} The data suggest that the risk is not absent with atypical antipsychotics, but it is significantly less and may be somewhere between one fifth and one tenth of the risk seen with conventional antipsychotic drugs.

Treatment response is another indicator of the risk of tardive dyskinesia. A review of data from a prospective study of first-episode psychosis¹⁸ in 118 drug-naïve patients with schizophrenia or schizoaffective disorder who were followed for 8.5 years showed that greater illness severity at baseline and poor response to conventional antipsychotics was a significant predictor of the risk of tardive dyskinesia. Treatment responders, on the other hand, had a lower risk of presumptive tardive dyskinesia.

The risk of tardive dyskinesia may decline over time. Patients treated with conventional antipsychotics for 5 years without developing tardive dyskinesia have a lower risk during the second 5 years (J.M.K.; M. G. Woerner, Ph.D.; M. Borenstein, Ph.D.; et al., manuscript submitted, and references 19-21). Risk continues to decline with the third 5 years, and so on. Whether this pattern will hold with the atypical drugs or whether they just delay the risk is a very important question. My own experience in following patients taking clozapine for many years has shown no development of tardive dyskinesia, which also bodes well for some of the other atypical drugs.

Age is the most consistently replicated risk factor in incidence studies. Annual cumulative incidence rates of tardive dyskinesia have been reported to be 4% to 5% in young adults.⁸ In studies that focused specifically on the elderly, as discussed by Jeste²² elsewhere in this supplement, the incidence estimates tended to be 5 or 6 times higher than those in young adult populations.

Early-occurring EPS, including early parkinsonism or akathisia, may be associated with a subsequent risk for developing tardive dyskinesia.^{23,24} As a class, atypical antipsychotics have shown a reduced risk of acute EPS compared with conventional antipsychotic drugs, and this may

Table 1. Atypical Antipsychotics in New Cases of Tardive Dyskinesia or Dyskinesia in Adults^a

Study	Design	Inclusion Criteria	Drug	N ^b	Sex: Male (%)	Race: White (%)	Mean Age (y)	Mean Dose (mg/d)	Mean Exposure (d)	Tardive Dyskinesia Rating Scale (Frequency)	Case Definition	Annualized Tardive Dyskinesia Incidence (%)
Glazer et al, 1999 ¹²	≥ 1 y open-label extension of 3 6-wk double-blind, randomized trials	Schizophrenia	Quetiapine	301	64	92	36	475	NR (calculated: 272 [mean])	AIMS (1.5, 3, 6, 9, 12 mo)	Schooler-Kane criteria	0.7 ^c
Rein and L'Heritier, 1999 ¹³	1 y randomized, open-label trial	Schizophrenia, ≥ 1 BPRS item ≥ moderate	Amisulpride Haloperidol	331 106	67 62	96 96	36 39	624 14.6	359 (median) 352 (median)	AIMS (1, 3, 6, 9, 12 mo)	Schooler-Kane criteria	1.5 5.9 (p = .028) ^d
Beasley et al, 1999 ¹⁰	≥ 1 y double-blind extension of 3 6-wk double-blind, randomized trials	Schizophrenia, schizoaffective disorder	Olanzapine Haloperidol	513 114	64 65	85 83	37 36	13.5 13.9	260 (median) 259 (median)	AIMS (every 1 or 2 mo)	Schooler-Kane criteria	0.5 ^e 7.4 ^c (p = .002) ^d
Sanger et al, 2001 ¹⁴	49-wk open-label extension of 3-wk double-blind, randomized trial	Bipolar disorder	Olanzapine	97 ^e	51	74	39	13.9	198 (mean)	AIMS (monthly)	Schooler-Kane criteria	0.0
Csernansky et al, 2002 ¹⁵	≥ 1 y double-blind, randomized trial	Schizophrenia, schizoaffective disorder	Risperidone Haloperidol	177 ^f 188 ^g	72 68	46 50	40 40	4.9 11.7	364 (median) 238 (median)	ESRS (monthly)	Tardive dyskinesia	0.6 4.1
Chouinard et al, 2002 ¹⁶	≥ 50-wk open-label trial	Schizophrenia, schizoaffective disorder stable > 4 wk	Risperidone (long-acting injectable)	587	66	92	42	55.2 ^h	350 (median)	ESRS (1, 2, 3, 6, 9, 12 mo)	Schooler-Kane criteria	0.7
Arato et al, 2002 ¹⁷	1 y placebo-controlled, double-blind, randomized trial	Schizophrenia (CGI ≤ 5, inpatient ≥ 2 mo)	Ziprasidone Placebo	207 ^f 71 ⁱ	70 83	NR NR	50 49	92.0 ...	206 (median) 72 (median)	AIMS (0, 7, 13 mo)	Dyskinesia	6.8 35.7

^aAdapted with permission from Correll et al.¹¹
^bStudy sample based on patients without tardive dyskinesia at baseline.
^cKaplan-Meier estimation of 1-year probability.
^dCompared with haloperidol, amisulpride had a significantly lower incidence of tardive dyskinesia.
^e113 patients began the study; 12 were excluded because they did not have AIMS evaluations and 4 were excluded because they had tardive dyskinesia at baseline.
^fNumber of patients free of tardive dyskinesia at baseline not specified.
^gMean dose in milligrams given every 2 weeks.
^hAbbreviations: AIMS = Abnormal Involuntary Movement Scale, BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions scale score, ESRS = Extrapyramidal Symptom Rating Scale, NR = not reported, PANSS = Positive and Negative Syndrome Scale.

be why long-term data show that the incidence of tardive dyskinesia is lower with atypical drugs. Several incidence studies^{21,25-27} have supported the hypothesis that tardive dyskinesia is more likely to occur in patients who experience early extrapyramidal symptoms.

In general practice, clinicians have been hesitant to prescribe continuous drug treatment with conventional antipsychotics in first-episode patients with psychosis, patients with affective disorders who have psychotic signs and symptoms, or psychotic patients whose diagnosis is uncertain. Because continuous conventional antipsychotic treatment is associated with a risk of tardive dyskinesia, reducing total cumulative antipsychotic drug exposure through intermittent or targeted treatment would seem a logical course of action. Unfortunately, studies^{28,29} that have examined that issue consistently found that intermittent or targeted treatment was associated with significantly higher rates of relapse and rehospitalizations than continuous treatment. Thus, from a clinical efficacy standpoint, intermittent or targeted treatment was not as efficacious as continuous treatment and did not reduce the incidence of tardive dyskinesia.

CONCLUSION

Accurate estimates of the risk of tardive dyskinesia are difficult to obtain and can be misleading. Antipsychotic-induced up-regulation of D₂ receptor binding is associated with the development of tardive dyskinesia, but conventional antipsychotics carry a greater risk than atypical antipsychotics. PET scans have provided some evidence of the relationship between the up-regulation of D₂ receptor binding and the development of tardive dyskinesia. Spontaneous dyskinesia and other syndromes that include abnormal movements further complicate the investigation into the prevalence and incidence of tardive dyskinesia.

Prevalence estimates may be misleading because they cannot adequately evaluate many risk factors or predictive factors, nor can they take into account clinical differences or the fact that some patients are drug naïve while others are already receiving antipsychotic drugs. Incidence estimates, on the other hand, are helpful in determining risk factors because they include the same set of patients over a period of time. The challenge with incidence studies, however, is that patients are often treated with a variety of different medications over time and are frequently lost to follow-up.

Regardless of the methods used to determine the rate of tardive dyskinesia in adults taking antipsychotic drugs, atypical antipsychotics are associated with a reduced risk of tardive dyskinesia compared with conventional antipsychotics. Further longitudinal studies with atypical agents are needed to determine if tardive dyskinesia is being delayed or is actually prevented.

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

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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