Lower Risk for Tardive Dyskinesia Associated With Second-Generation Antipsychotics: A Systematic Review of 1-Year Studies

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Objective: Based on lower rates of acute extrapyramidal side effects associated with second-generation antipsychotics, compared to first-generation antipsychotics, and based on preliminary data, second-generation antipsychotics are expected to cause less tardive dyskinesia than first-generation antipsychotics. This hypothesis was examined in a systematic review of studies involving open or controlled treatment with any second-generation antipsychotic.

Method: Studies of treatment with second-generation antipsychotics lasting ≥1 year and reporting on new cases of tardive dyskinesia or dyskinesia were systematically reviewed.

Results: In 11 studies, 2,769 patients received treatment with risperidone (five studies, N=1,235), olanzapine (two studies, N=610), quetiapine (two studies, N=386), amisulpride (one study, N=331), or ziprasidone (one study, N=207) for a weighted mean and median duration of 263 and 306 days, respectively. Study designs were double blind and randomized (N=3); open-label extensions of double-blind, randomized trials (N=4); and open label (N=4). Of the four trials that had a comparator (all involving adults with schizophrenia spectrum disorders), three used haloperidol (N=408) and one used placebo (N=71). Studied populations included children (N=77), adults (N=1,419), adults and elderly persons (N=794), and exclusively patients age 54 years or older (N=479). The weighted mean annual incidence of tardive dyskinesia for second-generation antipsychotics was 0% in the children, 0.8% (range=0.0%–1.5%) in the adults, 6.8% in the mixed adult and elderly population, and 5.3% (range=0.0%–13.4%) in the patients age 54 years and older, compared to 5.4% (range=4.1%–7.4%) in adults treated with haloperidol.

Conclusions: Results from 11 long-term studies support the idea that second-generation antipsychotics have a reduced risk for tardive dyskinesia, compared to first-generation antipsychotics, although the doses of haloperidol used in the comparator studies were relatively high. More carefully designed studies, ideally lasting beyond 1 year and comparing the effects of different second-generation antipsychotics in patients who have never taken first-generation antipsychotics, are needed to estimate the true risk. It would not appear premature for clinicians to consider these findings in making long-term treatment decisions.

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Tardive dyskinesia is a socially stigmatizing and potentially irreversible long-term adverse effect of treatment with first-generation antipsychotic medications that has been linked with poor quality of life (1) and increased medical morbidity and mortality (2, 3). In long-term studies, first-generation antipsychotics have been associated with an incidence of tardive dyskinesia of approximately 5% per year in adults (4–6) and 25%–30% in elderly patients (7–10). Unfortunately, mechanisms involved in the production of tardive dyskinesia are poorly understood, and treatments have remained largely unsatisfactory (11). The frequency of tardive dyskinesia and its potential consequences are clearly distressing, especially considering that many patients require long-term antipsychotic treatment.

Mainly due to their shared feature of reduced liability for acute extrapyramidal side effects, compared to first-generation antipsychotics (12, 13), the second-generation antipsychotics, including clozapine and antipsychotics developed after the introduction of clozapine, have quickly become the preferred treatment for psychotic and various nonpsychotic disorders across age groups (14–17). Moreover, since data suggest that early extrapyramidal side effects are an important and potentially modifiable risk factor for tardive dyskinesia (10, 18, 19), it is hoped that the use of second-generation antipsychotics will also lead to less tardive dyskinesia, compared to first-generation antipsychotics (20). Furthermore, several longer-term studies (lasting from 6 months to more than 2 years) have

found stable or (nonsignificantly) lower total mean Abnormal Involuntary Movement Scale (AIMS) (21) scores after a switch from first-generation antipsychotics to a second-generation antipsychotic, including amisulpride (22), aripiprazole (23), clozapine (24), olanzapine (25, 26), quetiapine (27, 28), risperidone (26, 29–33), and ziprasidone (34). It is important to note that a limited number of longer-term trials found statistically significant reductions from baseline in mean total endpoint AIMS scores after a switch to clozapine (35) and olanzapine (36) or found lower AIMS scores, compared to patients treated with haloperidol, for patients treated with amisulpride (37), aripiprazole (38), and clozapine (39, 40), which also suggests superior safety with regard to tardive dyskinesia.

The primary aim of this study was to review the available evidence for a lower risk of tardive dyskinesia associated with second-generation antipsychotics, compared to first-generation antipsychotics, based on the results of long-term trials lasting at least 1 year. As a secondary aim, we examined the available database evaluating the association between second-generation antipsychotics and tardive dyskinesia for limitations and methodological problems that should be addressed in future research.

Method

Search Strategy

Included in this review were studies involving open or controlled treatment with any second-generation antipsychotic, i.e., amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole, sulpiride, ziprasidone, or zotepine, that involved at least 20 subjects, lasted 1 year or longer, and reported on newly identified cases of dyskinesia or tardive dyskinesia. (Amisulpride, sertindole, sulpiride, and zotepine are second-generation antipsychotics that are not available in the United States.) We conducted a computerized MEDLINE literature search in September 2002 (with an update in June 2003) using the keywords "atypical," "new," "novel," "new-generation," and "second generation antipsychotics," the generic names of the previously mentioned individual second-generation antipsychotic agents, and "tardive dyskinesia." The studies that were identified were screened for fulfillment of the inclusion criteria, and their bibliographies were searched. Furthermore, abstracts from major scientific meetings were reviewed, and pharmaceutical companies were contacted for additional information on unpublished data.

Inclusion Criteria

We restricted our analysis to studies that lasted at least 1 year in order to avoid potential underestimation of annual tardive dyskinesia rates that may be associated with studies of shorter duration and to avoid potential overrepresentation of withdrawal dyskinesia associated with discontinuation of first-generation antipsychotics. Studies that included a total of less than 20 subjects were excluded to diminish the influence of chance. This step led to the elimination of one 12-month double-blind, randomized trial comparing amisulpride (N=29) and haloperidol (N=31), as only four and nine patients in the respective treatment groups were free of tardive dyskinesia at study entry (of which one subject [25%] taking amisulpride and three subjects [33%] taking haloperidol subsequently developed tardive dyskinesia) (41). Also excluded was a report on two subgroups of 19 matched adults with first-episode schizophrenia treated for 1 year or longer with risperidone or various first-generation antipsychotics, which found no new cases of tardive dyskinesia, irrespective of treatment group (42). Furthermore, a publication by Tollefson et al. (43) that reported tardive dyskinesia rates of 1.0% (annualized: 1.5%) for olanzapine and 4.6% (annualized: 8.3%) for haloperidol was excluded from this review because these raw incidences were based on the analysis of preliminary data for a smaller group of subjects than was described in a later publication by the same group (44). Finally, investigations that merely reported on changes in AIMS scores were not included in this systematic review.

Data Analysis

Mean values for demographic variables, medication exposure, and doses of individual second-generation antipsychotics were weighted by multiplying values by the number of subjects in each individual trial and dividing the sum by the total number of patients to reflect the population of all studies combined. Since age is a major modulating factor for the risk of tardive dyskinesia, mean tardive dyskinesia rates were separately calculated for studies involving children, adults, elderly patients, and a mixed group of adult and elderly patients in one of two studies that did not report separate rates for each subgroup (45). Annual tardive dyskinesia rates were calculated on the basis of the number of patients who were free of tardive dyskinesia at study entry, except for two studies in which the assessment of tardive dyskinesia was not a primary outcome measure and in which the exact number of patients without tardive dyskinesia at baseline was not provided (45, 46). In the four trials (45–48) that reported the number of patients with tardive dyskinesia but did not employ a Kaplan-Meier estimation (49) of 1-year probability, the reported raw incidence of "dyskinesia" (45) or tardive dyskinesia was annualized by multiplication with a factor calculated by using 365 days as the numerator and the median number of days of medication exposure as the denominator. Furthermore, mean 1-year incidences across studies were weighted according to the number of patients in each study by adding the numbers of annualized cases of tardive dyskinesia or dyskinesia in all studies and dividing that number by the total number of patients in all studies. For simplicity, we calculated mean weighted annual tardive dyskinesia rates based on Kaplan-Meier risk estimates of the 1-year probability for tardive dyskinesia as well as the annualized incidences of dyskinesia and tardive dyskinesia. This step was completed even though subthreshold dyskinesia could not be distinguished from tardive dyskinesia in one study (45) because only cases of "dyskinesia" were reported and even though the criteria used to diagnose tardive dyskinesia were not specified in two other trials (46, 50). Although this methodological difference in the definition of caseness is less than ideal, we felt that inclusion of these three trials was justified despite the reduced purity of the data because their exclusion would have reduced the number of second-generation antipsychotic-treated patients in the analysis by 17% and the number of haloperidol-treated comparison subjects by 46%. Moreover, we felt that this approach was conservative, as inclusion of cases of dyskinesia (which may or may not have fulfilled the criteria for tardive dyskinesia) would, if anything, *over*estimate the risk for tardive dyskinesia with second-generation antipsychotics.

Results

Study Characteristics

Eleven studies of second-generation antipsychotics that lasted 12 months or longer and reported on new cases of tardive dyskinesia or on dyskinesia were identified (44–48, 50–55) (Table 1). Three trials were double blind and ran-

TABLE 1. Studies of Second-Generation Antipsychotic Medications Lasting ≥1 Year and Reporting on New Cases of Tardive Dyskinesia or Dyskinesia

Study (in ascending order of subjects' mean age)	Design	Inclusion Criteria	N[a]	Male Sex (%)	White Race (%)	Mean Age (years)
Turgay et al. 2002 (50)	48-week open-label extension of a 6-week placebo-controlled, double-blind, randomized trial	Disruptive behavior disorders	77	74	73	8.7
Glazer et al. 1999 (51)[c]	≥1-year open-label extension of three 6-week double-blind, randomized trials	Schizophrenia	301	64	92	36
Rein and L'Héritier 1999 (47)[c,g]	1-year randomized, open-label trial	Schizophrenia, score of moderate or greater severity on one or more Brief Psychiatric Rating Scale items	331	67	96	36
			106	62	96	39
Beasley et al. 1999 (44)[h]	≥1-year double-blind extension of three 6-week double-blind, randomized trials	Schizophrenia, schizophreniform disorder, schizoaffective disorder	513	64	85	37
			114	65	83	36
Sanger et al. 2001 (52)	49-week open-label extension of 3-week double-blind, randomized trial	Bipolar disorder	97[i]	51	74	39
Csernansky et al. 2002 (46)	≥1-year double-blind, randomized trial	Schizophrenia, schizoaffective disorder	177[j]	72	46	40
			188[j]	68	50	40
Chouinard et al. 2002 (48)[c]	≥50-week open-label trial	Schizophrenia, schizoaffective disorder, stable condition >4 weeks	587	66	92	42
Arato et al. 2002 (45)	1-year placebo-controlled, double-blind, randomized trial	Schizophrenia, Clinical Global Impression score ≤5, inpatient status ≥2 months	207[j]	70	—	50
			71[j]	83	—	49
Davidson et al. 2000 (54)	≥1-year open-label trial	Schizophrenia, schizophreniform disorder, Positive and Negative Syndrome Scale score 60–120	139[l]	38	—	73
Jeste et al. 1999 (55)[c]	1-year open-label trial	Schizophrenia, delusional disorder, dementia, Parkinson's disease	85	49	93	76
Jeste et al. 2000 (53)	1-year open-label extension of 12-week double-blind, randomized trial	Dementia	255	31	86	82

[a] Number of patients without tardive dyskinesia at baseline.
[b] Unclear whether incidence was based on unsolicited reports or actual Extrapyramidal Symptom Rating Scale ratings.
[c] Data presented at a scientific meeting.
[d] Duration of exposure, not reported in the original study, was calculated by the authors.
[e] An increase in AIMS score over baseline of ≥3 in one body region or ≥2 in two body regions, for at least two assessments (56).
[f] Kaplan-Meier estimation of 1-year probability.

domized (N=897) (44–46); one was randomized and open label (N=331) (47); four were open-label extension studies of short-term randomized double-blind trials (N=730) in which subjects continued taking the second-generation antipsychotic, irrespective of initial randomization (50–53); and three were entirely open-label studies (N=811) (48, 54, 55) (Figure 1). Three randomized trials, two of which were double blind and one of which was open label, included a concurrent haloperidol comparison group (N=408) (44, 46, 47); one double-blind study was placebo controlled (N=71) (45).

Patient Characteristics

In 11 trials, a total of 2,769 patients received second-generation antipsychotics. The weighted mean age of the patients was 45.4 years, 60.8% were male, and 85.8% were white (based on nine studies with information on race). One study included children (N=77; mean age=8.7 years, range=5–12) (50), five studies (44, 46, 47, 51, 52) included predominantly young and middle-aged adults (N=1,419; mean age=37.1 years, range=18–69), two trials (45, 48) included both adult and elderly patients (N=794; mean age=44.1 years, range=18–84), and three investigations (53–55) included exclusively older patients (N=479; mean age=78.3, range=54–96) (Figure 2). Eight studies included patients with schizophrenia spectrum disorders (N=2,276, 82.2%) (i.e., schizophrenia [N=2,072], schizophreniform disorder [N=24], schizoaffective disorder [N=177], or delusional disorder [N=3]), one of which had additional subjects with psychosis due to dementia (N=56) and Parkinson's disease (N=8) (55). The remaining three trials included either exclusively patients with dementia (N=255) (53), resulting in a total of 311 patients with dementia; patients with bipolar disorder (N=97) (52); or children with disruptive behavior disorders and subaverage intelligence (N=77) (50) (Figure 3). One of the studies in schizophrenia included more severely ill subjects, i.e., patients with Positive and Negative Syndrome Scale (57) scores of 60–120 (54), while the only placebo-controlled study included patients who were more stable, i.e., patients who had been hospitalized for at least 2 months and who had Clinical Global Impression ratings of no more than "moderately ill" (45). In the three trials that had an active haloperidol arm, the 408 patients had a weighted mean age of 38.6 years

Drug	Mean Dose (mg/day)	Exposure (days) Mean	Exposure (days) Median	Tardive Dyskinesia Rating Scale and Assessment Schedule	Case Definition	Annualized Tardive Dyskinesia Incidence (%)
Risperidone	1.4	322	—	Extrapyramidal Symptom Rating Scale at 1, 2, 3, 4, 5, 6, 9, and 12 months	"Tardive dyskinesia"	0.0[b]
Quetiapine	475	272[d]	—	Abnormal Involuntary Movement Scale (AIMS) at 1.5, 3, 6, 9, and 12 months	Schooler-Kane criteria[e]	0.7[f]
Amisulpride	624	261	359	AIMS at 1, 3, 6, 9, and 12 months	Schooler-Kane criteria[e]	1.5
Haloperidol	14.6	240	352			5.9
Olanzapine	13.5	—	260	AIMS every 1 or 2 months	Schooler-Kane criteria[e]	0.5[f]
Haloperidol	13.9	—	259			7.4[f]
Olanzapine	13.9	198	—	AIMS monthly	Schooler-Kane criteria[e]	0.0
Risperidone	4.9	—	364	Extrapyramidal Symptom Rating Scale monthly	"Tardive dyskinesia"	0.6
Haloperidol	11.7	—	238			4.1
Long-acting injectable risperidone	55.2[k]	276	350	Extrapyramidal Symptom Rating Scale at 1, 2, 3, 6, 9, and 12 months	Schooler-Kane criteria[e]	0.7
Ziprasidone	92.0	—	206	AIMS at 0, 7, and 13 months	"Dyskinesia"	6.8
Placebo	—	—	72			35.7
Risperidone	3.7	—	—	Extrapyramidal Symptom Rating Scale at 1, 2, 3, 6, 9, and 12 months	Schooler-Kane criteria[e]	13.4[f]
Quetiapine	172	—	—	AIMS at 1.5, 3, 6, 9, and 12 months	Schooler-Kane criteria[e]	2.7[f]
Risperidone	0.96	230	273	Extrapyramidal Symptom Rating Scale every 2 months	Schooler-Kane criteria[e]	2.6[f]

[g] Significant difference between treatment groups ($p<0.03$).
[h] Significant difference between treatment groups ($p=0.002$).
[i] Twelve of 113 patients did not have AIMS evaluations, and four of 113 had tardive dyskinesia at baseline.
[j] Number of patients free of tardive dyskinesia at baseline not specified.
[k] Mean dose in milligrams given every 2 weeks.
[l] A total of 125 subjects remained in the study at 6 months; 97 subjects completed the study.

(range=18–65), 65.9% were male, 71.1% were white, 89.0% had a diagnosis of schizophrenia, 0.2% had a diagnosis of schizophreniform disorder, and 10.8% had a diagnosis of schizoaffective disorder. In the only placebo group, the 71 patients had a mean age of 48.7 years (range=20–76), 100% had a diagnosis of schizophrenia, and 83% were male; ethnicity was not reported in that study.

Treatment Characteristics

Five studies involved risperidone (N=1,235; mean dose: 2.7 mg/day, range=0.5–8.0, for oral risperidone and 55.2 mg/14 days for long-acting injectable risperidone), two each involved olanzapine (N=610; mean dose=13.6 mg/day, range=2.5–20) or quetiapine (N=386; mean dose=408.3 mg/day, range: not reported to 800 mg), and one each involved amisulpride (N=331; mean dose=624 mg/day, range=400–800) and ziprasidone (N=207; mean dose=92 mg/day, range=40–160) (Figure 4). Three trials, none involving exclusively elderly patients, had an active haloperidol arm (N=408; mean dose=13.1 mg/day, range=5.0–20.0), and one study was placebo controlled (N=71) (45). In six trials for which sufficient information was available, previous antipsychotic medications (and anticholinergic drugs) were discontinued abruptly (within 0–1 day) (47, 54, 55), over short periods ranging between 2 and 4 days (45, 52), ranging between 2 and 9 days (44), and during the course of 1 week (46). In the study by Jeste et al. (53), 3 months of stable risperidone treatment preceded the extension phase, during which tardive dyskinesia data were collected. The weighted mean and median duration of exposure in the six trials each with sufficient information were 263 and 306 days, respectively. Six studies extended beyond 1 year (44, 46, 48, 50, 51, 54), up to a maximum of 799 days in one study (46) and 949 days in another study (44). In one trial, information on the mean or median treatment duration was not provided, but 69.8% of the subjects were reported to have completed the 1-year trial (54).

Methods of Rating Tardive Dyskinesia

In all 11 studies, the presence or absence of dyskinesia was assessed prospectively at baseline and at regular time intervals. In most studies, assessments took place every 3 months. In four studies, assessments occurred more frequently, i.e., monthly ratings beyond 5 weeks (52) or for

FIGURE 1. Distribution of Methods in 11 Studies of Second-Generation Antipsychotic Medications Lasting ≥1 Year and Reporting on New Cases of Tardive Dyskinesia or Dyskinesia

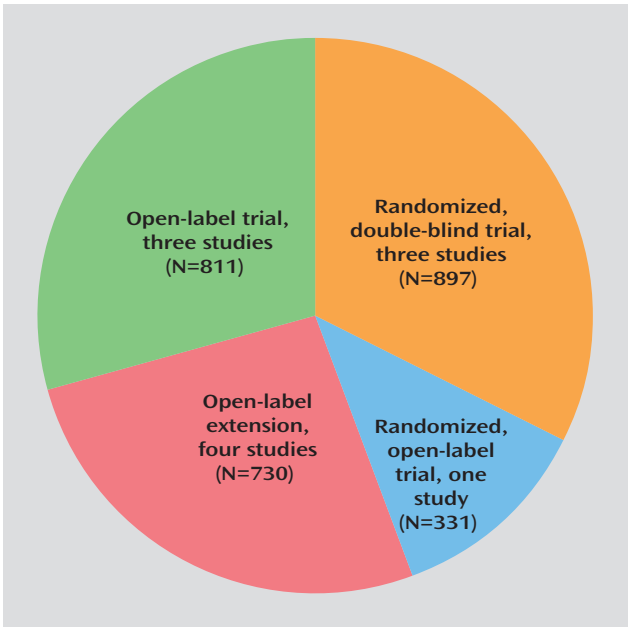
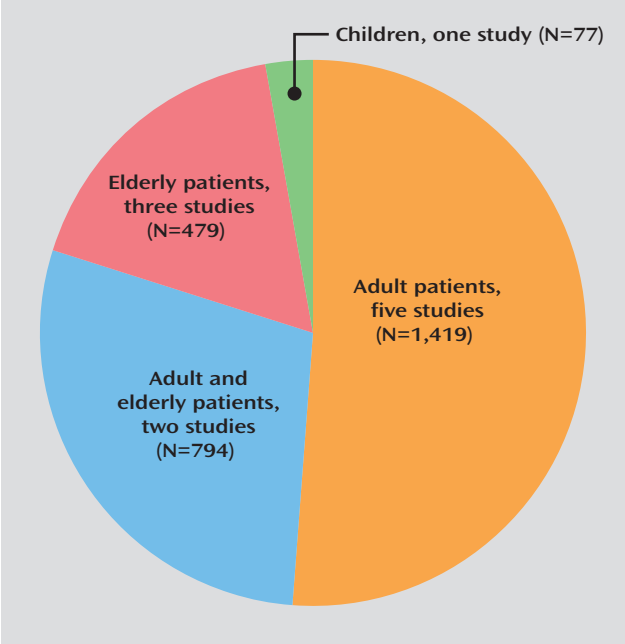


FIGURE 2. Distribution of Age Groups Among Subjects (N=2,769) Treated With Second-Generation Antipsychotic Medications in 11 Studies Lasting ≥1 Year and Reporting on New Cases of Tardive Dyskinesia or Dyskinesia



the first 6 months (50), monthly or bimonthly ratings beyond the first 6 weeks (44), or bimonthly assessments throughout (53). Only one study had less frequent examinations, i.e., at baseline and at 7 and 13 months (45). Tardive dyskinesia rating scales were used in all 11 studies; the AIMS was used in six, and the Extrapyramidal Symptom Rating Scale (58) was used in five. Subjects with tardive dyskinesia at baseline were excluded in all but three studies, and those three studies did not have tardive dyskinesia as a primary outcome measure (45, 46, 52). Only one trial (50) did not specify the definition used for the exclusion of patients with tardive dyskinesia at study entry. Definitions were the Glazer-Morgenstern criteria (59) (i.e., a total AIMS score ≥3 and at least one AIMS item score ≥2) (44, 51, 55) or the Schooler-Kane criteria (56) with a higher threshold (i.e., any AIMS item score ≥3 or at least two AIMS item scores ≥2) (47, 48, 53, 54). Tardive dyskinesia as an outcome was defined by using the Schooler-Kane criteria (i.e., an increase in AIMS scores over baseline of ≥3 for one body region or ≥2 for two body regions, for at least two assessments) in eight studies. The remaining three trials reported rates of "dyskinesia" (45) or "tardive dyskinesia" (46, 50) without specification of the criteria used. Kaplan-Meier survival rates were calculated as a risk estimation for tardive dyskinesia in all three studies involving older patients (53–55) and in two trials involving adults (44, 51). Four of the other six studies reported only raw incidences (i.e., irrespective of the duration of patients' exposure) either of tardive dyskinesia (46–48) or dyskinesia (45), and in the remaining two studies, which lacked any new cases, no specific risk estimation method was needed (50, 52).

Findings

The weighted mean annual incidence risk of tardive dyskinesia associated with second-generation antipsychotics across all different second-generation antipsychotics and age groups was 2.1%. Stratified by age group, the weighted mean annual tardive dyskinesia risk was 0% in the one trial involving children; 0.8% (range=0%–1.5%) across the five studies involving adults, including also 545 adult subjects from a mixed-population trial (48); 6.8% in the one investigation that included adults as well as elderly patients (and did not report separate rates for the two age groups); and 5.3% (range=0%–13.4%) across the three studies involving older subjects, including also 42 subjects from a mixed-population study (48) (Figure 5). By contrast, the weighted mean annual tardive dyskinesia risk for haloperidol in the three randomized, double-blind studies involving adults (N=408) was 5.4% (range=4.1%–7.4%). Finally, in the study by Arato et al. (45), the annualized dyskinesia rate in patients who received placebo was 35.7%. Tardive dyskinesia risk estimates among individual second-generation antipsychotics varied in the reviewed trials. In the five studies involving adults, rates ranged closely from 0% to 0.5% with olanzapine and from 0.6% to 0.7% with risperidone and with quetiapine; while in the study of amisulpride by Rein et al. (47), the annualized tardive dyskinesia rate was 1.5%. In the only long-term study with ziprasidone, the annualized rate for dyskinesia was 6.8% (45); while in the only study with the long-acting injectable formulation of risperidone (48), the annualized tardive dyskinesia rate was 0.7%. Although both of these

FIGURE 3. Distribution of Diagnoses Among Subjects (N=2,769) Treated With Second-Generation Antipsychotic Medications in 11 Studies Lasting ≥1 Year and Reporting on New Cases of Tardive Dyskinesia or Dyskinesia

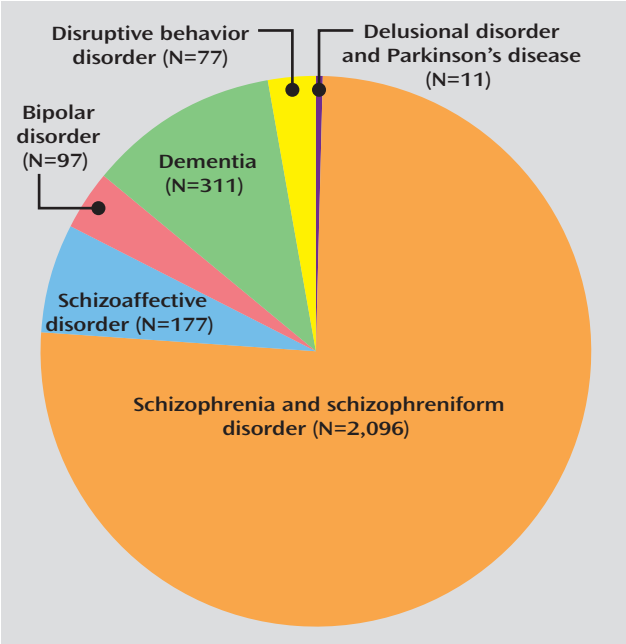
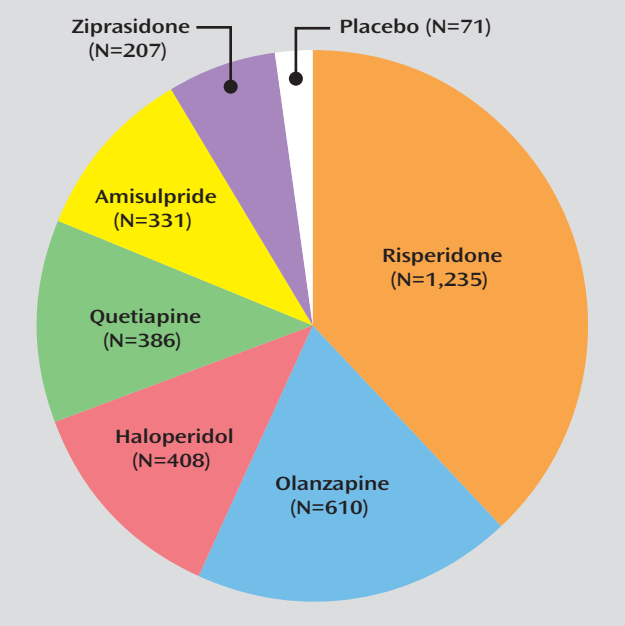


FIGURE 4. Distribution of Subjects Treated With First- and Second-Generation Antispychotic Medications or Placebo (N=3,248) in 11 Studies Lasting ≥1 Year and Reporting on New Cases of Tardive Dyskinesia or Dyskinesia



trials involved a mixed population of adult and elderly patients, the tardive dyskinesia rate in the study by Chouinard et al. (48) was based entirely on results for the 545 subjects younger than age 65 years. Finally, the risk estimate for elderly patients was 2.7% with quetiapine, ranged from 2.6% to 13.4% with risperidone (Table 1), and was 0% in the subgroup of 42 elderly subjects treated with risperidone microspheres (48).

In addition to reporting on the incidence of tardive dyskinesia, four studies analyzed baseline-to-endpoint changes in AIMS scores with risperidone (46), long-acting risperidone (48), amisulpride (47), and olanzapine (43) (in an earlier analysis of the data published by Beasley et al. [44]). These studies found statistically significant improvements in each of the groups treated with second-generation antipsychotics, compared to haloperidol. Furthermore, three studies with oral or long-acting injectable risperidone found statistically significant improvements in all five Extrapyramidal Symptom Rating Scale dyskinesia subscores, compared to baseline, in additional patients with preexisting dyskinesia (48, 53, 54). Finally, in one study, a significant relationship between dose of risperidone and the risk for tardive dyskinesia (p=0.02) was observed (53).

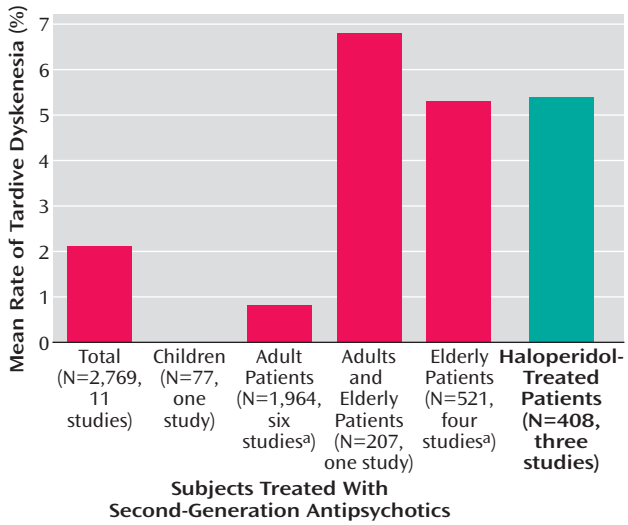
Discussion

Major Findings

The major finding of this systematic review is that the available data from 11 long-term studies involving 2,769 patients seem to support the expectation that second-generation antipsychotic agents have a reduced risk for tardive dyskinesia, compared with conventional antipsychotics (12, 20). It is important to note that this finding was true for children, adults, and the particularly vulnerable elderly population.

Across the six studies including 1,964 adults, the weighted mean annual tardive dyskinesia incidence for second-generation antipsychotics was only 0.8%. Except for one trial without any new cases of tardive dyskinesia during olanzapine treatment of 97 patients with bipolar disorder (in which 12 patients were excluded from the tardive dyskinesia analysis for unclear reasons), the rates from two studies with risperidone and one study each with amisulpride, olanzapine, and quetiapine were relatively similar (0.5%–1.5%). Furthermore, the mean annual tardive dyskinesia risk of less than 1% per year is considerably lower than the mean annualized tardive dyskinesia incidence of 5.4% for haloperidol in the three studies that included haloperidol as an active comparator. Moreover, the tardive dyskinesia rates for haloperidol were significantly higher, compared to those for olanzapine and amisulpride, in the studies that reported comparative statistical analyses (44, 47), and the rates for haloperidol were consistent with 1-year incidences of about 5% for first-generation antipsychotics described in the literature (12, 60). As the mean haloperidol doses were above 10 mg/day in all three trials, a dose effect in the haloperidol group cannot be excluded. However, the rates of tardive dyskinesia in subjects taking haloperidol were very similar to the rates in subjects taking conventional antipsychotics in the Hillside longitudinal study of tardive dyskinesia development, a naturalistic study that involved multiple neuro-

FIGURE 5. Mean Weighted 1-Year Rate of Tardive Dyskinesia Among Subjects Treated With Second-Generation Antipsychotic Medications (N=2,769) or Haloperidol (N=408) in 11 Studies Lasting ≥1 Year and Reporting on New Cases of Tardive Dyskinesia or Dyskinesia



[a] One study reported separate rates of tardive dyskinesia in adult patients and in elderly patients.

leptics and doses (unpublished paper of J.M. Kane et al.). On the other hand, a recently published study found a 12-month incidence of probable or persistent tardive dyskinesia of 12.3% in 57 subjects with a first episode of a nonaffective psychotic disorder treated with low-dose haloperidol at a mean dose of 1.7 mg/day (61). Although in this study a higher haloperidol dose was a significant predictor of tardive dyskinesia, these results suggest that, at least, the high-potency first-generation antipsychotic haloperidol carries a significant risk for the development of tardive dyskinesia, even if given at low doses (61). Similarly, an earlier study in an elderly population also demonstrated a high risk of tardive dyskinesia after 1 year of treatment with low median doses of conventional antipsychotics (68 mg/day of chlorpromazine equivalents) (7). In addition to the results from the long-term studies included in this analysis, lower rates of tardive dyskinesia with second-generation antipsychotics have been reported in several shorter-term studies involving adults with similar mean ages (i.e., 35–40 years). Based on pooled data from a mix of 12 open-label and 15 double-blind studies with risperidone (nine lasting ≥3 months, and seven lasting ≥1 year), the incidence of tardive dyskinesia was observed to be 0.2% in 878 adults (median age=35 years, range=17–85) who completed at least 3 months of treatment (62) and was only slightly higher (0.3%) when the analysis was restricted to the seven 1-year studies (63). However, these data were derived from heterogeneous studies and did not take individual exposure times into consideration, and most important, both of these incidences were extrapolated only from spontaneous reports of adverse effects. Although common for many industry databases, the use of unsolicited reports of tardive dyskinesia as an adverse event is problematic since it may markedly underestimate the true risk for tardive dyskinesia. In the study by Davidson et al. (54), for example, no "spontaneous reports" of tardive dyskinesia as an adverse event were recorded; yet, six new cases of tardive dyskinesia could be detected among 139 patients who were free of tardive dyskinesia at baseline when the patients underwent formal assessment with the Extrapyramidal Symptom Rating Scale. Similarly, neither the rating scale nor the case definition of tardive dyskinesia was specified in another 6-month, open-label, adjunctive trial with risperidone involving 541 adults (430 completers) with bipolar disorder and schizoaffective disorder (30). In that study, no new case of tardive dyskinesia was detected during three follow-up visits (at 1, 3, and 6 months). On the other hand, in an 18-week double-blind, placebo-controlled trial (subjects' mean age=39 years, range=18–70) that compared olanzapine and clozapine and included 90 patients with treatment-resistant schizophrenia in each treatment group, the tardive dyskinesia incidence of 2.2% in the olanzapine group was comparatively high and significantly higher ($p<0.03$) than in the clozapine group, which had no new cases (64). This finding, however, may have been related to the fact that the subjects were patients with treatment-resistant schizophrenia who had, by definition, been exposed to relatively long periods and high doses of antipsychotic treatment before study entry.

In the five trials that also included elderly patients or that were restricted to elderly patients (mean age ≥50 years), the weighted annual rates for dyskinesia and tardive dyskinesia associated with second-generation antipsychotics were 6.8% and 5.3%, respectively (including the unusual finding of no case with tardive dyskinesia among 42 elderly subjects treated for an unreported duration with long-acting injectable risperidone [48]). These results are consistent with the findings of a 9-month open-label study involving 61 adults with schizophrenia, mood disorders, dementia, and organic mental disorders who were older than age 45 years (mean age=66 years) (65). That study found a cumulative incidence of tardive dyskinesia of 5% with risperidone (median dose=1.0 mg/day), compared to 32% in haloperidol-treated comparison subjects (median dose=1.0 mg/day), matched for age, sex, and duration of treatment with neuroleptics ($p<0.05$). However, the individual 1-year tardive dyskinesia rates in the reviewed studies involving elderly patients were more dissimilar than those for adults, ranging from 0% to 13.4%. Nevertheless, this disparity appears to be largely due to methodological differences. For example, the relatively high annualized rate of 6.8% with ziprasidone in the study by Arato et al. (45) was based on cases with dyskinesia, not tardive dyskinesia. Moreover, this comparatively high rate may be at least partly attributable to early withdrawal dyskinesias, since previous antipsychotic medications were discontinued rapidly over 1–3 days. This rate is also consistent with the otherwise counterintuitive finding that in

the placebo group the annualized risk for dyskinesia was as high as 35.8%. Conversely, in a 28-week randomized, double-blind study involving adults age 18–65 years (mean age=39 years) that compared ziprasidone (N=148, mean dose=116.5 mg) and haloperidol (N=153, mean dose=8.6 mg) and included a 3–14-day washout phase, not one case of tardive dyskinesia was observed in the ziprasidone group, compared to an annualized tardive dyskinesia rate of 3.4% with haloperidol (34). Although this trial did not include subjects older than age 65 years and the AIMS ratings took place only at baseline and week 28, these data suggest that the annualized dyskinesia rate of 6.8% for ziprasidone in a mixed population may be an overestimate of the true risk for tardive dyskinesia. On the other hand, the marked difference between the annual tardive dyskinesia risks in the two studies with oral risperidone in elderly patients, i.e., 2.6% (53) versus 13.4% (54), seems to be due to higher doses in the latter trial (mean daily dose of 3.7 mg, compared with 0.96 mg), which included markedly ill patients with chronic schizophrenia. In addition, these individuals probably had a higher lifetime exposure to antipsychotic agents than the subjects with dementia in the study by Jeste et al. (53). Furthermore, the tardive dyskinesia incidence could also have been increased by early withdrawal dyskinesia, as previous antipsychotic and anticholinergic medications were stopped abruptly and "gradual" discontinuation was used only "when medically appropriate" (54). In contrast, in the trial by Jeste et al. (53), the patients had undergone a 3-month lead-in with risperidone or placebo. Notwithstanding these differences in annual tardive dyskinesia rates in elderly patients, however, the reviewed data still support a fivefold reduction in risk for the development of tardive dyskinesia with second-generation antipsychotics in this particularly vulnerable population, compared to reported rates of new-onset tardive dyskinesia in 25%–30% of patients per year with first-generation antipsychotics (7–10). It is interesting to note that in the reviewed long-term studies with second-generation antipsychotics, the ratio between annual tardive dyskinesia rates in adults and in elderly patients was quite similar to the ratio for first-generation antipsychotics in those two age groups reported in the literature (i.e., about 1:5), adding face validity to the rates observed in the long-term studies with second-generation antipsychotics.

However, the reviewed data also seem to indicate that the benefits of lower tardive dyskinesia risk with second-generation antipsychotics may be reduced at higher doses. This effect for higher doses is suggested for risperidone by the significant dose effect in one trial (53) and by the more than fivefold higher tardive dyskinesia rate in the study by Davidson et al. (54), in which patients received a 3.8 times higher risperidone dose, compared to the dose in the study by Jeste et al. (53), irrespective of having a lower mean age (73 years versus 82 years). The effect of higher doses is also consistent with the finding that at higher doses second-generation antipsychotics are associated with more extrapyramidal side effects (12, 13) and that the presence of acute extrapyramidal side effects (10, 18, 19), as well as utilization of anticholinergic medications (66, 67), has been associated with an increased risk for tardive dyskinesia. However, the question of whether a similar dose relationship exists for second-generation antipsychotics other than risperidone awaits further study. Finally, as discussed for acute extrapyramidal side effects (68), similar tardive dyskinesia rates for amisulpride (which does not block serotonin receptors), compared to other second-generation antipsychotics, suggest that serotonin blockade may not be a necessary factor in the reduced risk of tardive dyskinesia associated with second-generation antipsychotics, in contrast to first-generation antipsychotics.

Limitations of the Database

Although the results of the reviewed long-term trials strongly support the assumption that second-generation antipsychotics induce less tardive dyskinesia than first-generation antipsychotics, the available database is still small in light of the wide utilization of these agents, particularly in the United States (69–71). Although the subjects in eight studies were randomly assigned to study groups at study entry, only three studies maintained randomization throughout the trial, and only three trials had a blinded design. Furthermore, the comparison with first-generation antipsychotics was based mostly on historical data, as only three of the studies involving adults and none of the studies involving elderly patients included a first-generation antipsychotic (i.e., haloperidol) as an active comparator. However, in the geriatric population the confirmed high risk for tardive dyskinesia in association with first-generation antipsychotics may render a direct comparison in this population unethical. Moreover, in the three active-comparator studies, haloperidol doses were 14.7, 14.6, and 11.7 mg/day, respectively, which is higher than generally considered necessary (12). Thus, studies using lower doses of first-generation antipsychotics (e.g., 5 mg/day of haloperidol) are necessary to exclude a dose-dependent phenomenon and to confirm the superior safety of second-generation antipsychotics regarding the development of tardive dyskinesia. Furthermore, to our knowledge, there are no studies in which second-generation antipsychotics are compared with low-potency first-generation antipsychotics, even though preliminary data suggest a reduced risk for tardive dyskinesia with phenothiazines compared to haloperidol (adjusted odds ratio=1.56) (59) and despite the fact that chlorpromazine, which is relatively inexpensive, is still the most widely used antipsychotic in most of the developing world (72). Finally, none of the long-term studies evaluated the potential confound of an increased tardive dyskinesia risk with haloperidol due to intermittent or interrupted treatment that could lead to withdrawal dyskinesia, given the fact that noncompliance and early

medication discontinuation have been found to occur more frequently with first-generation antipsychotics, compared to second-generation antipsychotics (73, 74), even in controlled settings (75).

Another complication in interpreting the available data stems from the fact that patients in the reviewed studies had only a weighted mean median exposure of 306 days or 10 months (with mean exposures being considerably lower, whenever reported). This finding implies that the majority of patients did not complete 12 months of treatment, even in the trials that extended beyond 1 year (44, 46, 50, 51, 54). To account for a potential underestimation of the true 1-year tardive dyskinesia incidence with second-generation antipsychotics, five studies calculated annualized tardive dyskinesia risk estimates using Kaplan-Meier survival analysis, yet five reported only raw incidences of tardive dyskinesia and one reported the raw incidence of dyskinesia. Even though the annualized raw incidences and Kaplan-Meier risk estimates for tardive dyskinesia were not too disparate, at least in the studies involving adult patients, the importance of calculating survival rates is highlighted by the difference between the population-based incidence of 4.3% and the annualized Kaplan-Meier survival probability of 13.6% in the study with risperidone by Davidson et al. (54). In addition, the lack of explicit exclusion of patients with baseline tardive dyskinesia (45, 46, 52) could lead to either an underestimation of true tardive dyskinesia rates, as incidences were based on the entire study population, or an overestimation, if patients with tardive dyskinesia at baseline were included. Finally, in the study by Arato et al. (45), the potential for an underestimation of the true risk was further increased by the rather infrequent follow-up AIMS examinations (at 7 and 13 months), as was the potential for an overestimation because of high rates of withdrawal dyskinesia in the placebo group and a low threshold for caseness.

On the other hand, the true risk for tardive dyskinesia with second-generation antipsychotics may turn out to be even lower than currently assumed, as studies involving patients who have never been exposed to first-generation antipsychotics are still missing. In this regard, the inclusion of patients with subthreshold dyskinetic movements in all available studies introduces a considerable confound for the etiological evaluation of "new-onset" tardive dyskinesia, as tardive dyskinesia may already have been incipient due to previous antipsychotic treatment before the switch to a second-generation antipsychotic. That baseline AIMS scores may turn out to be a relevant factor for the understanding of the true long-term risk for tardive dyskinesia with second-generation antipsychotics is suggested by an important finding in the study by Beasley et al. (44). When the Kaplan-Meier annualized risk analysis was stratified by using baseline AIMS scores of zero versus scores greater than zero, the risk for development of tardive dyskinesia with olanzapine was substantially lower for patients without dyskinetic movements at study entry than for patients with subthreshold dyskinesia (1.1% versus 6.0% for the overall period and 0% versus 2.0% for the period after week 6, respectively). Conversely, such a stratification by AIMS scores did not significantly alter the risk for tardive dyskinesia in patients treated with haloperidol for the overall trial period (7.1% versus 10.0%) and after week 6 (7.5% versus 6.4%). This finding indicates that for patients treated with haloperidol the tardive dyskinesia risk was independent of whether a pathophysiological process involved in the development of dyskinesia had already begun, whereas it mattered for patients treated with olanzapine. It is interesting to note that, at least in the data set analyzed by Beasley et al. (44), treatment with olanzapine for a median of 260 days seemed not to have produced any new cases of tardive dyskinesia among 375 patients without preexistent dyskinetic movements, a compelling finding that clearly needs replication.

Another limitation of the currently available database is that it does not provide information about the comparative risk for tardive dyskinesia among different second-generation antipsychotics, that sex differences have not been examined, that nonwhite patients are markedly underrepresented (14.2% of subjects in the nine studies with information on ethnicity were nonwhite), and that patients with bipolar disorder or schizoaffective disorder represented only 9.9% of the subjects in the reviewed studies. The latter is in stark contrast to the wide utilization of second-generation antipsychotics as adjunctive or even primary treatment for manic symptoms (15) and to data suggesting that patients suffering from mood disorders may be at higher risk for developing tardive dyskinesia, compared to patients with schizophrenia (76). In addition, more and larger-scale long-term studies are needed to examine risk in children and adolescents, who despite the favorable findings in the one available study (50) may represent a particularly vulnerable patient group (77, 78) but for whom second-generation antipsychotics are used widely in treatment of psychotic, mood, and disruptive behavior disorders (17). In addition, the quality of the tardive dyskinesia assessments may also vary between the few studies that were conducted in a limited number of sites and with well-trained raters (e.g., the study by Jeste et al. [53]) and the overwhelming majority of studies that had multiple sites and inevitable difficulties regarding interrater reliability. Finally, we cannot exclude the possibility that studies showing no reduced risk for tardive dyskinesia with second-generation antipsychotics, compared to first-generation antipsychotics, may have been withheld from publication. However, few studies have been conducted with tardive dyskinesia as the primary outcome measure, and, therefore, the available data are usually from clinical trials where tardive dyskinesia was a secondary focus.

Conclusions

Despite methodological problems in some of the studies, the results of 11 trials that lasted 1 year or longer support the expectation that second-generation antipsychotics have a reduced risk for tardive dyskinesia, compared with first-generation antipsychotics. In adult patients and elderly patients, the incidence of tardive dyskinesia with second-generation antipsychotics appears to be about one-fifth of the risk observed with first-generation antipsychotics. However, the available evidence is based on a mix of controlled and uncontrolled studies and blinded and open-label studies, as well as historical and limited direct comparisons with first-generation antipsychotics (the latter unfortunately exclusively with medium to high doses of haloperidol). Furthermore, potential sex differences have not been examined, and 1-year data are scant for nonwhite subjects, as well as for children and adolescents. In addition, the lower risk for acute and chronic extrapyramidal side effects associated with second-generation antipsychotics has to be weighed against other potential side effects, particularly weight gain, hyperglycemia, and dyslipidemia, which may occur more frequently with certain second-generation antipsychotics (79–81). More carefully designed long-term studies across the entire age range and including more women and minorities are required to confirm these findings and to estimate the true risk of tardive dyskinesia associated with second-generation antipsychotics. Ideally, studies should be randomized and double-blind, last longer than 1 year, formally assess the presence of tardive dyskinesia at least every 3 months using the AIMS or Extrapyramidal Symptom Rating Scale, and add one additional assessment of patients who fulfill the criteria for tardive dyskinesia for the first time at study endpoint. In addition, it would be particularly valuable to compare different second-generation antipsychotics head-to-head (preferentially in patients naive to first-generation antipsychotics). If a first-generation antipsychotic is used as a comparator, doses should be low to medium (e.g., ≤10 mg/day of haloperidol or ≤600 mg/day of chlorpromazine equivalents for other first-generation antipsychotics) and low-potency first-generation antipsychotics should also be studied, given that rates of extrapyramidal side effects for those agents at doses below 600 mg/day of chlorpromazine equivalents may be comparable to those for second-generation antipsychotics (82). Other important issues include the need for a slow discontinuation of previous antipsychotic medications and restriction of the analysis to the time beyond the first 4–6 weeks, as well as a careful assessment of compliance in order to minimize the confound of withdrawal dyskinesia or the potential effect on risk of intermittent treatment. Finally, subjects with tardive dyskinesia at baseline or a history of tardive dyskinesia should be excluded from the analysis, and tardive dyskinesia rates should be annualized or, even better, reported as relative risk estimates, taking individual exposure times into consideration.

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