Incidence of Tardive Dyskinesia With Atypical Versus Conventional Antipsychotic Medications: A Prospective Cohort Study

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Objective: Most previous studies of the incidence of tardive dyskinesia with atypical antipsychotics compared with conventional antipsychotics have not had tardive dyskinesia as their primary focus. The current study aimed to compare the incidence of tardive dyskinesia with atypical vs conventional antipsychotics using methods similar to those from a previous prospective cohort study at our site in the 1980s.

Method: Three hundred fifty-two initially tardive dyskinesia–free psychiatric outpatients (diagnosed at baseline using the Structured Clinical Interview for *DSM-IV*) were examined for a new diagnosis of tardive dyskinesia (using the Abnormal Involuntary Movement Scale and Glazer-Morgenstern criteria) every 6 months for up to 4 years at a community mental health center. At baseline, subjects were receiving conventional antipsychotics *only* (23%), atypicals *only* (64%), or both (14%). Only 26 subjects had never received conventional antipsychotics. Baseline evaluations were conducted from November 2000 through May 2003. Follow-ups were conducted through February 2005.

Results: Compared with subjects treated with conventional antipsychotics alone since the previous visit, the adjusted tardive dyskinesia incidence rate-ratio for subjects treated with atypical antipsychotics alone was 0.68 (95% CI, 0.29–1.64). The incidence and prevalence of tardive dyskinesia was similar to previous findings at this site in the 1980s.

Conclusions: The incidence of tardive dyskinesia with recent exposure to atypical antipsychotics alone was more similar to that for conventional antipsychotics than in most previous studies. Despite high penetration of atypical antipsychotics into clinical practice, the incidence and prevalence of tardive dyskinesia appeared relatively unchanged since the 1980s. Clinicians should continue to monitor for tardive dyskinesia, and researchers should continue to pursue efforts to treat or prevent it.

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When atypical antipsychotics became available, it was hoped that they would be associated with a lower risk of tardive dyskinesia (TD) than were the older conventional antipsychotics. A 2004 systematic review of early conventional-controlled and other studies indicated that the evidence seemed to support the idea that this hope had been realized.[1] As noted in the review, however, few of the existing studies were designed to focus on TD and its accurate identification. It is possible that a limited focus on TD diagnosis could have introduced bias in favor of atypicals.[2] The primary aim of the current study was to compare the incidence of TD among users of atypical and conventional antipsychotics. Methods were similar to those from a previous TD incidence study conducted at our site during the conventional antipsychotic era.[3,4]

METHOD

Study Design

We conducted a cohort study of TD incidence in a population of outpatients maintained on antipsychotics at the Connecticut Mental Health Center in the United States. Baseline evaluations were conducted from November 2000 through May 2003. Following baseline evaluation, subjects at risk for TD were followed prospectively with examinations every 6 months through February 2005.

Subjects

The source population was the outpatient division at the Connecticut Mental Health Center. When the study began, the Connecticut Mental Health Center served a mostly urban catchment of 250,000 people and maintained an average daily census of roughly 2000 patients, of whom about 60% were maintained on antipsychotic medications. The racial/ethnic breakdown was 57% non-Latino white, 25% non-Latino African American, and 18% Latino.

Inclusion criteria required subjects to have been maintained on antipsychotic medication for ≥ 3 months. The sole exclusion criterion was inability to examine subjects for TD due to primary neurologic disease (such as Huntington's). With institutional review board approval, we asked clinicians

for permission to approach eligible patients for consent. Subjects who provided informed consent underwent baseline evaluation.

Procedures

At each visit, we examined subjects for dyskinesia using the Abnormal Involuntary Movement Scale (AIMS).[5] We gave the AIMS examination twice at each visit, at visit beginning and end, employing the Glazer-Morgenstern criteria[6] for dyskinesia. These criteria require the total AIMS score to be ≥ 3, with at least 1 body area rated ≥ 2 (mild), on both AIMS examinations at that visit. The Glazer-Morgenstern criteria[6] are slightly more inclusive than the Schooler-Kane criteria,[7] which require at least 2 body areas to be ≥ 2 or 1 body area to be rated ≥ 3 (moderate). The AIMS raters were blind to medication status. In subjects meeting Glazer-Morgenstern criteria, an investigator conducted a verification examination, when possible, on the same day.

At study outset, the previous Yale Tardive Dyskinesia Study principal investigator (W.M.G.) and project coordinator conducted a full-day training session on the use of the AIMS and the Glazer-Morgenstern criteria. Particular attention was paid to distinguishing dyskinesia from akathisia, tremor, dystonia, mannerisms, and tics. After initial training, reliability assessment exercises using videotaped examinations were conducted approximately quarterly. In 17 taped examinations with a median of 5 raters per examination, the intraclass correlation for agreement among raters[8] on the AIMS total scores was 0.93.

We considered subjects to be *prevalent cases* of persistent TD when Glazer-Morgenstern criteria were met at the first visit if there was a history of TD from medical record review. Subjects with no clinical history of TD were considered prevalent cases when Glazer-Morgenstern criteria were met at the first 2 consecutive visits.

At-risk cases were defined on the basis of history and baseline examination. Prevalent cases and patients who previously received a Glazer-Morgenstern research diagnosis of persistent TD in the first Yale TD study (1985–1993)[3,4,6] or in the Connecticut Mental Health Center TD Clinic (1978–1993)[9] were defined as *not at risk*. Otherwise, subjects were considered at risk to develop TD. At-risk subjects included those with a positive clinical history when the baseline research examination was negative. The at-risk status of these subjects was considered an empirical question because the clinical diagnosis had been established by a means whose reliability had not been evaluated. Lastly, at-risk subjects also included those with a negative clinical history who met Glazer-Morgenstern criteria at the initial but not at the second examination. These cases were considered instances of transient dyskinesia, and, therefore, these subjects were still at risk for developing persistent TD. All at-risk cases were scheduled for follow-up evaluation every 6 months.

Incident cases of persistent TD were those who, having first met at-risk criteria at baseline, subsequently met Glazer-Morgenstern criteria at 2 consecutive follow-up visits for both examinations at each visit and on verification examination when available.

Antipsychotic exposure history was determined for at-risk subjects primarily by review of available medical records, including records sent from other facilities. Prescribed dose and duration were recorded for each lifetime episode of treatment with each antipsychotic and antiparkinsonian agent. We utilized chart information exclusively if there were no missing periods of exposure. When periods were missing, we supplemented chart information for duration of exposure using subject reports that coincided with gaps in the medical record. Subjects generally could not remember specific doses, so subject reports were not used to supplement missing dose information. Staff conducting medical record reviews and interviews of subjects about medications were blind to results of AIMS examinations. We converted all antipsychotic doses to chlorpromazine equivalents, using published equivalencies for oral conventional[10] and atypical[11] antipsychotics. We converted depot doses to oral doses using the manufacturers' recommended equivalents: haloperidol (15 mg/4 weeks per 1 mg/d), fluphenazine (12.5 mg/3 weeks per 10 mg/d), and risperidone (25 mg/2 weeks per 2 mg/d); these equivalencies are supported by empirical studies.[12–14] Drug exposure variables derived from these data included antipsychotic type and years of exposure to, and mean dose of, antipsychotic by type before and since the prior visit.

Antipsychotic exposure during follow-up intervals was characterized as *conventional only* since the prior visit, *atypical only* since the prior visit, or *both conventional and atypical* at some point since the prior visit. We explored heterogeneity in the pattern of overlap and nonoverlap within this last group. In approximately half of these intervals (78.7 patient-years of exposure), atypical and conventional medications were prescribed simultaneously for all but ≤ 30 days since the prior visit. In the remaining half of these intervals (87.3 patient-years), patients were prescribed atypical and conventional medications during the intervals in a wide variety of simultaneous, sequential, and cross-tapering patterns. Crude TD incidence rates were similar for these 2 groups (0.102 per year and 0.092 per year, respectively), so these exposure intervals were considered together for purposes of analysis.

At baseline, psychiatric diagnoses were established using the Structured Clinical Interview for *DSM-IV*.[15] We also assessed other reported risk factors for incident TD (parkinsonian and akathisia symptoms, psychosis positive and negative symptom severity, premorbid adjustment, educational attainment, handedness, cognitive impairment, obstetrical complications, smoking, diabetes, and alcohol and substance use)[4,16–31] to treat as potential confounders or modifiers of the atypical/conventional drug effect.

Statistical Methods

Analyses focused on the relative incidence rate of TD, comparing recent users of atypical antipsychotics only (in

the past 6 months) or recent users of both antipsychotic types with recent users of conventional antipsychotics only, controlling for potential confounders (ie, TD risk factors associated with type of antipsychotic exposure). Proportional hazards analysis was used to estimate drug-type effects (rate-ratios [RRs] and their 95% CIs), control for confounders, and assess possible interactions between antipsychotic drug type and other TD predictors by adding product terms to the model. Certain predictors, including type of antipsychotic exposure since the prior visit, were treated as time-dependent variables. Following estimation of crude (unadjusted) recent drug effects, we adjusted for core model variables from our prior report: age at baseline, race, years of conventional antipsychotic exposure, and recent antipsychotic chlorpromazine-equivalent dose.[4] The other reported risk factors were then added to the core model 1 at a time to determine if they had confounded or modified the estimated effect of antipsychotic drug type. Schoenfeld residuals analysis indicated that the proportionality assumption held satisfactorily. In addition to these primary analyses of recent antipsychotic use, we also estimated the effects of lifetime use (available on request from S.W.W.).

Literature Review Methods

We searched PubMed for studies with the words *tardive*, *clozapine*, *risperidone*, *olanzapine*, *quetiapine*, *aripiprazole*, or *ziprasidone* in the title, as well as bibliographies and subsequent citations (in ISI Web of Science) of the identified articles. Studies selected for inclusion were those that reported incidence of new-onset cases of TD prospectively over time among adult subjects who were free of TD at baseline and that compared incidence during treatment with atypical antipsychotics to incidence during treatment with conventional antipsychotics. Geriatric and adolescent/child studies were not included. When multiple definitions of incident TD cases were reported, we selected the definition that corresponded most closely to incident persistent TD, eg, present on 2 consecutive occasions. From each study and from each identified medication group, we abstracted the number of subjects at risk for TD, the number of incident cases, and the follow-up time, or we calculated these quantities from published data. Atypical/conventional RRs and their 95% CIs were then calculated, and the RRs were synthesized across study using a random-effects Mantel-Haenszel model in Review Manager 5.[32] In studies in which several atypical arms were compared to a single conventional arm, the atypical arms were first weighted by person-years of follow-up and were pooled.

RESULTS

Sample Description

Baseline evaluation was completed on 619 subjects. Of these, 195 met criteria for persistent TD at baseline (estimated prevalence, 31.5%; 95% CI, 27.9%–35.3%) and were ineligible for the incidence analysis. In addition, 23 subjects with negative baseline TD examinations were also not eligible for the incidence sample because of previous Glazer-Morgenstern TD diagnoses. The remaining 401 subjects were free of TD at baseline; of these, 352 were reexamined at least once during follow-up (the study population). Demographic, diagnostic, and treatment characteristics of the study population are shown in Table 1. Female sex and longer histories of conventional exposure were more common among subjects receiving conventional antipsychotics at baseline, and histories of atypical exposure were less common in this group. Most of the 352 subjects (81%) qualified as at-risk by virtue of both negative clinical histories and negative initial research examinations. The remainder had no clinical history but a positive research examination that was negative on repeat (3%)—or had a positive clinical history but a negative baseline research examination (17%). The distribution of conventional medications at baseline is shown in Table 1.

At-risk individuals underwent 1,344 follow-up examinations. There were 52 new persistent cases of TD detected during 783 person-years of follow-up, yielding an average incidence rate of 0.066 per year. The TD risk (cumulative incidence) after 3.9 years of follow-up was 19.7% (95% CI, 15.2%–25.1%). The mean of the 4 total AIMS scores leading to a TD diagnosis in the 52 incident cases was 4.8 (range, 3.0 to 8.2).

Estimated Effects of Recent Antipsychotic Type on New Occurrence of Tardive Dyskinesia

Crude analyses revealed that patients receiving conventional antipsychotics alone since the prior visit developed new-onset TD at a rate of 5.6 per 100 patient-years of exposure (8 cases per 141.8 patient-years, or 0.056 per year), patients receiving atypical antipsychotics alone developed TD at a rate of 0.059 per year (28 cases per 475.2 patient-years), and patients receiving both types of antipsychotics since the prior visit developed TD at a rate of 0.096 per year (16 cases per 166.0 patient-years). Based on crude (unadjusted) analyses, subjects treated with atypical antipsychotics alone since the prior visit developed TD at a similar rate as subjects treated with conventional antipsychotics alone (crude RR = 1.04; 95% CI, 0.50–2.22). Subjects treated with both types of antipsychotic since the prior visit developed TD at a somewhat higher rate than subjects treated with conventionals alone (crude RR = 1.71; 95% CI, 0.77–3.82).

On the basis of adjusted results from our core model, subjects treated with atypical antipsychotics alone since the prior visit developed TD at approximately two-thirds the rate as subjects treated with conventionals alone (adjusted RR = 0.68; 95% CI, 0.29–1.64). Subjects treated with both types of antipsychotic since the prior visit developed TD at nearly double the rate of subjects treated with conventionals alone (adjusted RR = 1.85; 95% CI, 0.72–4.75).

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Table 1. Demographic, Diagnostic, and Treatment Findings by Antipsychotic Type at Baseline

Variable	Antipsychotic Type at Baseline			
	Conventional Only,[a] n = 80 (23%)	Atypical Only, n = 224 (64%)	Combined Atypical and Conventional, n = 48 (14%)	Total, N = 352
Age, median (range), y	43 (18–78)	41 (20–75)	38 (22–66)	42 (18–78)
Sex, female, n (%)	48 (60)	87 (39)	20 (42)	155 (44)
Race, n (%)				
White	47 (59)	122 (54)	19 (40)	155 (53)
African American	26 (32)	74 (33)	26 (54)	126 (36)
Hispanic	5 (6)	19 (8)	3 (6)	27 (8)
Mixed or Asian	1 (1)	8 (4)	0	9 (3)
Native American	1 (1)	1 (< 1)	0	2 (1)
Principal diagnosis, n (%)				
Schizophrenia	35 (44)	79 (35)	21 (44)	135 (38)
Schizoaffective disorder	20 (25)	63 (28)	18 (38)	101 (29)
Affective disorder	19 (24)	72 (32)	8 (17)	99 (28)
Other disorder	6 (8)	10 (4)	1 (2)	17 (5)
Lifetime hospital days, median (range)[b]	32 (0–1,664)	46 (0–6,067)	67 (0–3,115)	47 (0–6,067)
Antipsychotic dose at baseline, median (range), mg/d[c]	275 (25–3,500)	300 (12–2,000)	700 (200–5,157)	300 (12–5,157)
Years of conventional use before baseline, median (range)	12.9 (0.3–41.4)	3.6 (0.0–39.2)	7.5 (0.2–37.8)	6.0 (0.0–41.4)
Years of atypical use before baseline, median (range)	0.1 (0.0–4.3)	3.0 (0.1–14.5)	2.6 (0.1–12.3)	2.2 (0.0–14.5)
Any antipsychotic dose before baseline, median (range), mg/d[c,d]	353 (39–2,309)	326 (22–3,496)	565 (138–2,629)	368 (22–3,496)
Treatment with anticholinergic at baseline, n (%)	32 (40)	32 (14)	29 (60)	93 (26)
Months at risk after baseline, median (range)	30 (6–46)	29 (6–46)	29 (6–46)	30 (6–46)

[a]Haloperidol (29%), fluphenazine (14%), thiothixene (8%), perphenazine (29%), chlorpromazine (6%), thioridazine (5%), and multiple or other conventionals (10%).
[b]At baseline, includes all lifetime short-term and long-term psychiatric hospital days funded by the State of Connecticut.
[c]Chlorpromazine-equivalent dose.
[d]Median and range of each subject's lifetime mean of days with nonzero dose.

Logistic regression models on new TD present at any time during follow-up were also fitted by baseline medication status, employing as a covariate only years of total prior antipsychotic exposure or years of total prior conventional exposure, each expressed as a continuous measure. These analyses produced findings comparable to those of the unadjusted Cox regressions: a similar proportion of subjects treated with atypical antipsychotics alone at baseline developed TD as compared with subjects treated with conventional antipsychotics alone (adjusted RR = 1.00; 95% CI, 0.48–2.08; and adjusted RR = 0.94; 95% CI, 0.44–2.03, respectively), and a somewhat higher proportion of subjects treated with both types of antipsychotic at baseline developed TD as compared with subjects treated with conventionals alone (adjusted RR = 1.36; 95% CI, 0.52–3.52; and adjusted RR = 1.31; 95% CI, 0.50–3.41, respectively).

The AIMS total scores were slightly lower among incident cases appearing after recent atypical-only exposure than among recent conventional-only exposure (mean difference, −0.5; 95% CI, −1.7 to 0.8). Analyses employing single-visit Glazer-Morgenstern criteria or consecutive-visit Schooler-Kane criteria as alternate definitions of incident caseness produced adjusted RR estimates similar to those for the primary analysis (adjusted RR = 0.69; 95% CI, 0.35–1.36; and adjusted RR = 0.56; 95% CI, 0.21–1.48, respectively).

These analyses included clozapine-treated cases in the atypical antipsychotic group, our original intention. Crude analyses showed that 7 incident TD cases occurred among 55 at-risk subjects receiving clozapine who were followed for an average of 17.8 months (81.6 person-years, crude TD rate of 0.086 per year). These results include 5 incident TD cases that occurred among 23 at-risk subjects receiving clozapine as their sole antipsychotic and who were followed for an average of 23.2 months (44.4 person-years, crude TD rate of 0.111 per year). Because crude TD rates among clozapine-treated at-risk cases were unexpectedly high, clozapine-treated cases were removed and put into a separate category. These analyses are shown in Table 2.

On the basis of adjusted results from the core model, subjects treated with atypical antipsychotics alone (excluding clozapine) since the prior visit developed TD at slightly over half the rate as subjects treated with conventional antipsychotics alone (adjusted RR = 0.55; 95% CI, 0.23–1.36). The adjusted RR for combined atypical and conventional antipsychotics (excluding clozapine) was 2.21 (95% CI, 0.85–5.80).

Based on adjusted results, the TD incidence rate was also associated with age and years of previous conventional antipsychotic use (Table 2). Being African American was only weakly associated with TD, and the association with recent antipsychotic dose was not monotonic. None of the remaining planned covariates appears to have appreciably confounded individual antipsychotic effects.

The adjusted RR for atypicals vs conventionals (0.55) was lower than the crude RR (0.94) in Table 2 due to apparent confounding by years of conventional antipsychotic exposure. Subjects receiving atypicals had shorter durations

Table 2. Crude (unadjusted) and Adjusted Estimated Effects (RR and 95% CI) of Antipsychotic Type and Other Covariates in the Core Model on the Incidence Rate of Persistent Tardive Dyskinesia (TD)

Model Variable	n/N[a]	Months at Risk Per Subject	Years at Risk	Crude TD Rate	Crude Estimated Effects RR	Crude Estimated Effects 95% CI	Adjusted Estimated Effects[b] RR	Adjusted Estimated Effects[b] 95% CI	*P* Value[c]
Antipsychotic dose since prior visit, mg/d[d,e]									.004
Conventional only[f]	8/81	21.0	141.8	0.056	1	…	1	…	
Atypical only[g]	22/194	25.7	415.6	0.053	0.94	0.44–2.04	0.55	0.23–1.36	
Atypical + conventional	15/93	18.6	144.0	0.104	1.85	0.82–4.16	2.21	0.85–5.80	
Any clozapine	7/55	17.8	81.6	0.086	1.52	0.59–3.92	2.27	0.68–7.59	
Age at baseline, y									.019
< 35[f]	9/87	26.2	189.6	0.048	1	…	1	…	
35–49	31/194	27.4	443.1	0.070	1.47	0.73–3.01	1.82	0.84–3.97	
≥ 50	12/71	25.4	150.2	0.080	1.68	0.74–3.82	3.31	1.23–8.96	
Race									.251
Others[f]	29/226	26.4	498.3	0.058	1	…	1	…	
African American	23/126	27.1	284.6	0.081	1.39	0.82–2.34	1.40	0.79–2.48	
Conventional antipsychotic use at prior visit, y[e]									.020
< 5[f]	20/158	23.3	307.3	0.065	1	…	1	…	
5 to < 10	12/71	26.5	156.6	0.077	1.18	0.60–2.31	0.86	0.41–1.84	
10 to < 20	16/92	25.9	198.7	0.080	1.24	0.66–2.31	0.78	0.37–1.64	
≥ 20	4/49	29.4	120.2	0.033	0.51	0.18–1.39	0.23	0.07–0.80	
Recent antipsychotic dose, mg/d[d,e]									.010
< 200[f]	15/163	19.9	270.8	0.055	1	…	1	…	
200–499	22/176	18.7	274.0	0.080	1.45	0.78–2.72	1.82	0.89–3.73	
≥ 500	15/134	21.3	238.2	0.063	1.14	0.57–2.25	0.60	0.23–1.52	

[a]n indicates number of new TD incident cases during follow-up; N indicates number of at-risk subjects. Ns do not sum to 352 for time-dependent predictors (see footnote e) because individual subjects can contribute person-time in more than 1 category.
[b]Adjusted for all other variables in this table.
[c]Reflects a 2-sided test of the hypothesis that there is no association (antipsychotic type, race, and antipsychotic mean dose) nor linear trend (age and conventional lifetime years of use). To generate the adjusted rate-ratios shown, alternative models were built that categorized the continuous measures as shown.
[d]Chlorpromazine-equivalent dose.
[e]Time-dependent predictor; subjects at risk do not sum to 352 because some subjects contributed person-time in more than 1 category.
[f]Reference category.
[g]Atypical antipsychotics other than clozapine.
Abbreviation: RR = rate-ratio.

Table 3. Estimated Crude and Adjusted Rate-Ratio (RR) for Tardive Dyskinesia (TD) Comparing Each Atypical Antipsychotic With Conventional Antipsychotic Since the Prior Visit[a]

Model Variable[b]	n/N[c]	Mean Chlorpromazine-Equivalent Dose, mg/d	Months at Risk Per Subject	Years at Risk	Crude TD Rate	Crude Estimated Effects RR	Crude Estimated Effects 95% CI	Adjusted Estimated Effects[d] RR	Adjusted Estimated Effects[d] 95% CI	*P* Value[e]
Risperidone only	10/64	213	20.5	109.4	0.091	1.62	0.68–3.89	0.98	0.36–2.71	.188
Olanzapine only	8/108	268	23.1	208.3	0.038	0.68	0.27–1.72	0.46	0.16–1.34	
Quetiapine only	2/19	327	15.8	25.1	0.080	1.41	0.34–5.43	0.81	0.16–4.17	
Ziprasidone only	0/2	60	12.3	2.0	0	…	…	…	…	
Aripiprazole only	0/6	160	9.0	4.5	0	…	…	…	…	

[a]Compared to conventional-only as the reference group.
[b]Data are not shown for other antipsychotics or for subjects receiving multiple antipsychotics in the same interval.
[c]n indicates number of new TD incident cases during follow-up; N indicates number of at-risk subjects. Individual subjects can contribute person-time in more than 1 category.
[d]Adjusted for age at baseline, race, years of conventional antipsychotic use, and mean antipsychotic dose since the prior visit. Age and years of conventional antipsychotic use are treated as continuous variables.
[e]*P* value reflects a test of the hypothesis that the adjusted tardive dyskinesia rate is the same for all medication groups.

of prior (TD-free) conventional exposure than subjects receiving conventionals (Table 1), and shorter durations of prior TD-free conventional exposure were associated with a higher rate of TD (Table 2), as in our prior report.[4] Thus, adjusting for this confounder lowered the RR for atypicals. When this variable was omitted from the core model, the RR for atypical antipsychotic adjusted for the remaining terms was very similar to the unadjusted RR. The relative effect of atypicals vs conventionals did not appear to be confounded by years of previous lifetime atypical exposure when this variable was added to the model. None of the remaining planned covariates, including sex, appreciably changed the antipsychotic effects on TD incidence after adjustment for core model variables.

The overall modest advantage of atypical antipsychotics (excluding clozapine) since the prior visit on TD incidence was stronger among affective disorder subjects (RR = 0.15; 95% CI, 0.03–0.71) than among schizophrenia subjects

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Table 4. Previous Studies Comparing Newly Identified Tardive Dyskinesia in Atypical Antipsychotic–Treated and Conventional Antipsychotic–Treated Groups Compared With the Current Study

			Tardive Dyskinesia Acquisition			Conventional Antipsychotics					
Study[a]	Mean Age, y[b]	Study Design[c]	Examination Method[d]	Rater ICC[e]	Baseline Prevalence, %	Medication	Dose, mg/d[f]	n/N[g]	Months of Follow-Up[h]	Patient-Years[i]	Annual Incidence[j]
Beasley et al[33] and refs 70 and 71	37	R	AIMS	NR	NR	Haloperidol	695	5/114	7.3	69	0.072
Csernansky et al[34,m]	40	R	AE	NR	NR	Haloperidol	585	5/188	8.4	132	0.038
Dossenbach et al[35]	35	R	AIMS	NR	10.0	Fluphenazine	585	2/28	4.8	11	0.182
Lieberman et al[36] and ref 72	41	R	AIMS global	NR	14.5	Perphenazine	208	41/237	9.1	180	0.228
Tenback et al[37] and refs 73 and 74[n]	40	C	Yes/No	NR	9.4	Conventionals	NR	36/943	6.0	472	0.076
Dossenbach et al[38] and refs 75 and 76	36	C	Yes/No	NR	8.9	Haloperidol	590	10/104	12.0	104	0.096
Gharabawi et al[39] and ref 77[p]	25	R	ESRS	NR	3.1	Haloperidol	160	5/215	15.1	267	0.019
Miller et al[40]	37	R	AIMS	NR	9.0	Haloperidol	456	16/391	5.5	176	0.091
Gaebel et al[41]	32	R	AIMS	NR	3.2	Haloperidol	180	3/67	6.1	34	0.088
Summary of previous studies[q]	38	7R/2C		NR	8.7	Conventionals	402	123/2,287	7.6	1,436	0.085
Current study	42	C	AIMS	0.93	31.5	Conventionals	576	8/81	21.0	142	0.056

[a]Studies are listed with first author of primary publication plus secondary publications as applicable.
[b]Mean age of full sample[33–41]; for current study, mean age of at-risk sample.
[c]Most or all patients were receiving antipsychotic medication prior to baseline, and follow-up began after an antipsychotic medication change or initiation.[33–40] In 1 study, the first lifetime antipsychotic was begun 8 weeks before baseline.[41] In the current study, no medication changes were required at entry. Double-blind studies[33–36,39–41]; open-label studies[37,38]; current study was single-blind.
[d]Consecutive ratings by Glazer-Morgenstern criteria[33] (and current study); tardive dyskinesia data reported from adverse event reports[34]; consecutive ratings by Schooler-Kane criteria[35,39–41]; AIMS global rating ≥ 2, single rating[36]; single rating, unspecified criteria[37,38]; raters blind to medication identity[33–36,39–41] (and current study); raters not blind.[37,38]
[e]Raters not trained systematically[33]; reported tardive dyskinesia rates not from raters[34]; raters trained initially at a study start-up meeting[35,36,39,40]; raters not trained[37]; initial rater training program[38]; several rater trainings (not specifically on TD content).[41]
[f]Chlorpromazine-equivalent dose: conventionals,[10] atypicals.[11] Mean dose after 6 weeks[33]; mean modal dose[34,36,39]; mean dose at 22 weeks[35]; mean dose at 12 months[38]; mean dose[40]; mean dose for the first year[41]; mean baseline dose in current study.
[g]n = number of incident TD cases, defined as new-onset cases at any time point during reported follow-up,[34,36,41] new-onset cases at the final time point,[35,37,38,40] excluded cases appearing in the first 6 weeks,[33] or those appearing within 4 weeks[39] of discontinuing or switching an antipsychotic. N = sample size for subjects initially at risk for incident tardive dyskinesia[33,35–41] or full sample.[34]
[h]Mean length of follow-up, as reported[37,38,41] (and current study), as calculated from published data,[33,34,39,40] and as estimated from published completion rates assuming a constant drop hazard.[35,36]
[i]Person-years of follow-up, as published[33,37–40] (and current study) or as calculated from published data.[34–36,41] Calculation requires assumption that average follow-up time for sample at risk for TD is the same as published data for full sample.
[j]Incidence rate of new cases per person-year of exposure, as published[33,39] and as calculated from published incident cases and person years of follow-up per footnote i.[41]
[k]Includes clozapine in current study but not patients receiving conventional in combination.

(RR = 0.97; 95% CI, 0.31–3.04; $P = .050$ for interaction term). The stronger advantage among affective patients appeared to be partly due to lower risk among affective patients exposed to atypicals (crude rate, 0.028 per year; 4 cases in 142.5 person-years) and partly due to higher risk among affective patients exposed to conventionals (crude rate, 0.100 per year; 3 cases in 29.9 person-years). None of the remaining variables appreciably modified the estimated atypical antipsychotic effect on TD incidence.

Results for individual atypical antipsychotics are shown in Table 3. Estimates were imprecise in this analysis since fewer subjects had received only 1 atypical antipsychotic for the entire time since the prior visit.

Estimated Effects of Duration of Antipsychotic Use by Type

Only 26 subjects were naive to conventional antipsychotic exposure over their lifetimes. Among these, 2 incident cases of persistent TD appeared during 51.3 person-years of atypical antipsychotic exposure (crude rate, 0.039 per year). Comparing that rate to the crude rate for conventionals only yields a crude RR of 0.69 (95% CI, 0.15–3.25).

Atypical Antipsychotics						Atypical/ Conventional RR[l] (95% CI)
Medication[k]	Dose, mg/d[f]	n/N[g]	Months of Follow-Up[h]	Patient-Years[i]	Annual Incidence[j]	
Olanzapine	270	2/513	7.7	328	0.006	0.08 (0.02–0.43)
Risperidone	245	1/177	11.0	162	0.006	0.16 (0.02–1.04)
Olanzapine	296	1/26	5.1	11	0.091	0.50 (0.07–3.53)
Olanzapine	402	32/236	10.8	212	0.151	0.66 (0.44–1.00)
Quetiapine	725	30/236	7.8	153	0.196	0.86 (0.57–1.30)
Risperidone	195	38/238	9.3	184	0.206	0.91 (0.61–1.33)
Ziprasidone	188	18/126	8.4	88	0.204	0.90 (0.54–1.45)
Atypicals	NR	61/6,770	6.0	3,385	0.018	0.24 (0.16–0.35)
Olanzapine	216	29/1,978	12.0	1,978	0.015	0.15 (0.08–0.30)
Quetiapine	200	4/81	12.0	81	0.049	0.51 (0.17–1.49)
Risperidone	445	27/554	12.0	554	0.049	0.51 (0.26–1.01)
Risperidone	170	2/229	14.8	278	0.007	0.38 (0.09–1.70)
Aripiprazole	384	2/786	6.9	444	0.004	0.05 (0.01–0.19)
Risperidone	195	0/68	6.3	35	0.000	0.00 (0.00–1.19)
Atypicals	299	247/12,018	7.9	7,893	0.031	0.24 (0.12–0.48)
Atypicals	379	29/249	24.0	497	0.059	0.68 (0.29–1.36)

[l]RR in this table indicates either relative rate or relative risk; RR elsewhere in the article refers specifically to relative rate (rate-ratio). Tardive dyskinesia incidence RRs and 95% CIs are shown as published[33] or are shown as adjusted RR (from current study) or crude RR and 95% CI calculated from incidence risk data per footnote j.

[m]Mahmoud R. TD assessment procedures for Csernansky et al (*NEJM* 2002;346:16–22). Personal communication on June 7, 2006.

[n]Tenback DE. Proportion of patients with TD at 6 months who did not have TD at baseline. Personal communication regarding Tenback et al (*J Clin Psychiatry* 2005;66:1130–1133) to S.W.W. on October 16, 2005.

[p]Rabinowitz J. TD rater training procedures for Schooler et al (*Am J Psychiatry* 2005;162:947–953). Personal communication to S.W.W. on June 15, 2006.

[q]Summary of previous studies is indicated as total (n, N, patient-years), mean weighted by sample size (age, baseline prevalence, dose, months of follow-up), mean weighted by person-years of follow-up (annual incidence), and meta-analysis of atypical/conventional RR using RevMan 5 software.[32] Meta-analysis of RR excludes the current study.

Abbreviations: AE = spontaneous adverse event reports, AIMS = Abnormal Involuntary Movement Scale, C = cohort, ESRS = Extrapyramidal Symptom Rating Scale, ICC = intraclass correlation coefficient, NR = not reported, R = randomized, SDS = Simpson Dyskinesia Scale, TD = tardive dyskinesia, Yes/No = simple rating of tardive dyskinesia present vs not present.

Models focusing on lifetime duration of antipsychotic use at the current visit by drug type revealed estimated antipsychotic effects similar to those from the recent exposure analyses (available on request from S.W.W.).

Subjects Lost to Follow-Up

Among 401 TD-free subjects enrolled, 49 (12%) were never reexamined and 133 (33%) withdrew sometime later during follow-up before developing TD. Analyses omitting the partial data for dropouts produced results that were not appreciably different from the primary analysis.

Literature Review

We identified 9 previous studies in adult patients that reported TD incidence during treatment with atypical compared to conventional antipsychotics.[33–41] Table 4 shows the mean age, design, TD acquisition methods, baseline TD prevalence, mean antipsychotic doses, incident cases, mean follow-up time, patient-years of exposure, annual incidences, and the atypical/conventional RRs and 95% CIs for each study as well as the 9 studies taken together and the present study. The 7 randomized and 2 cohort studies together reported 123 incident cases of TD among 2,287 patient-years of conventional antipsychotic exposure (0.085 per year) and 247 incident cases of TD among 12,018 patient-years of atypical antipsychotic exposure (0.031 per year, RR = 0.24; 95% CI, 0.12–0.48). About three-quarters of the exposure time was accounted for by the 2 large cohort studies.[37,38] The present study reports on more atypical antipsychotic exposure time than any of the previous studies except the 2 previous cohort studies and 1 of the 7 randomized studies.[36] Mean length of follow-up in the previous studies was about one-third that for the present study.

DISCUSSION

The major finding of this study is that the incidence of TD with recent exposure to atypical antipsychotics alone at our Connecticut Mental Health Center was more similar to that for conventional antipsychotics than in 8 of 9 previous studies. Taken together, the previous studies suggest that the risk of TD with atypicals is one-quarter that of conventionals (Table 4); our findings suggest that the risk with atypicals is more than half that of conventionals when clozapine patients are excluded (Table 2) or more than two-thirds the risk when clozapine patients are included. Furthermore, our adjusted TD rate-ratio of 0.97 among schizophrenia patients suggests less of an advantage for atypicals than reported in any of the 9 previous studies (all schizophrenia patients) in Table 4.

Study Strengths and Limitations

Methodological strengths of this study include the prospective cohort design with multiple years of follow-up, careful screening for previous and current TD symptoms at baseline, systematic identification of new TD cases periodically during follow-up, careful compilation of medication histories, and appropriate multivariable analysis

that controlled for multiple potential confounders and treated type and dose of antipsychotic medications as time-dependent covariates.

The major limitation of our study is that nearly all of our CMHC subjects had lifetime histories of conventional antipsychotic exposure, often extensive and most of it occurring before baseline examination. It is possible that prior conventional antipsychotic use could sensitize patients subsequently receiving atypicals to be at higher risk than if they had been conventional antipsychotic–naive. In addition, very few patients in our study were exposed to only 1 antipsychotic over their lifetime, which also complicates interpretation in attributing newly emergent TD to current medication vs possible lingering effects of previous treatment. These limitations are not unique to our study but are characteristic of most other modern attempts to estimate differential risks of TD with conventional and atypical antipsychotic drugs,[42] including at least 5 of 7 of the 9 previous comparative TD incidence studies found by our review.[33,34,36–38] The 2 recently reported first-episode risperidone vs haloperidol analyses are exceptions.[39,41]

A second important limitation of the present study is our use of a cohort design. This design carries the advantage of not artificially requiring treatment change at the start of the study but can lead to imbalances in the treated groups, such as the markedly shorter observed median exposure to conventional antipsychotics among persons currently treated with atypical agents (3.6 years) vs those currently treated with conventionals (12.9 years; Table 1) and the far shorter prior exposure to atypical agents among those currently given conventional antipsychotics (0.1 vs 3.0 years; Table 1). Our analyses, however, adjusted for lifetime duration of conventional antipsychotic use as well as other measured potentially confounding variables such as sex, anticholinergic use, and negative symptoms. One might speculate that our conventional-treated cohort had been selected by prescribers to remain on conventional antipsychotic treatment on the basis of some unmeasured protective factor for which we cannot adjust. For such selection to account for our findings, however, we would expect a low crude TD incidence rate among our conventional-treated patients, and the observed rate of 0.056 per year (Table 2) was not unexpectedly low.[4,43]

Another limitation of our study is that we lost 45% of our initial cohort during the 4-year follow-up. Examination of sample size and follow-up length data in Table 4 suggests, however, that the differences between our findings and those of most previous studies are unlikely to be explained by differences in follow-up time. Measured differences between conventional-treated dropouts and atypical-treated dropouts are unlikely to have biased our findings since we adjusted for these variables.

Last, the relatively high rate of emerging TD we observed among clozapine-treated patients was surprising given our expectations that clozapine would be associated with minimal risk of TD. Important caveats are that we estimated the RR for clozapine alone very imprecisely (7 cases among 55 patients exposed to clozapine with or without concomitant other antipsychotics [Table 2] and 5 cases among 23 patients exposed to clozapine alone). Because of the surprising findings, an investigator (J.R.S. or S.W.W.) thoroughly rereviewed all available medical records for the 5 incident cases appearing in patients treated with clozapine alone. Previous history of TD despite negative baseline research examination did not appear to account for the high rate. Three of these cases had previously participated in the earlier Yale TD Incidence Study (no TD throughout). Two of the 5 incident cases treated with clozapine alone did have a clinical history of TD on at least 1 examination, but TD was not observed consistently. In 1 of these cases, TD was observed on only 1 examination among 4 recorded lifetime before clozapine, and, in the other, on only 1 of 17 clinical examinations before clozapine. Neither of these positive clinical examinations was the last one before beginning clozapine. Still, it is possible that previous clinical or research examinations could have overlooked previous TD or that records reporting previous TD could have existed but were unavailable for our review.

It is worth mentioning that the expected minimal risk of TD with clozapine is supported by a surprisingly small direct incidence database. We are aware of only 3 studies, none of which are impressively larger than ours, and only 1 of which unequivocally found very low risk.[44] In this single study, 2 of 28 patients developed TD during a mean of 7.7 years of clozapine treatment, yielding a rate roughly one-tenth of ours (Table 2). Two other small studies, however, have reported clozapine findings similar to ours.[17,45] In one of these, 7 cases of dyskinesia emerged during a roughly 4-year follow-up of 25 clozapine-treated patients (approximately 0.070 per year).[45] In the other study, a possibly increased crude TD risk with clozapine (among only 13 patients, however) was reduced when the model was adjusted for response to treatment of the first episode.[17] Unfortunately, we did not collect data permitting us to adjust for first-episode treatment response. Thus, it is not clear whether clozapine increased the risk for dyskinesia in our cases or whether our clozapine-treated cases were at greater risk for illness-related dyskinesia. Current use of clozapine could potentially also have been confounded by indication if it were prescribed because of earlier, and unmeasured, intolerable adverse neurologic effects that could themselves have conferred an increased risk of TD.

Comparison With Previous Studies

Comparing Atypical and Conventional Antipsychotics

Table 4 shows that the differing relative risk in our study versus previous studies is accounted for by the previous studies' finding a somewhat higher TD incidence rate with conventionals than we did (0.085 per year versus 0.056 per year) and a somewhat lower incidence rate with atypicals

(0.031 per year versus 0.059 per year). The incidence rate we observed with conventionals is similar to those from large studies from the conventional era.[4,43] Previous studies in Table 4 reporting prevalence found substantially lower proportions of TD at baseline than we did (8.7% versus 31.5%).

The limitation of our study that nearly all our subjects had lifetime histories of conventional antipsychotic exposure is unlikely to account for differences between our findings and the findings of others, since most subjects had extensive prior conventional exposure histories in many previous studies that did find lower rates of TD with atypicals.[33,34,37,38] Our use of a cohort design is also unlikely to explain differences between our findings and the findings of others, since previous cohort studies[37,38] agree with most previous randomized studies in reporting a stronger TD advantage for atypicals than we do (Table 4). Similarly, many previous studies appear to have experienced higher attrition rates than ours, and none adjusted for the possibility of TD risk differing between dropouts from atypical versus conventional antipsychotics.

Likely explanations for the difference between our findings and those obtained previously relate to study design features. The previous studies all articulated broad efficacy and safety aims and therefore did not focus substantial attention on training raters to detect TD accurately (Table 4). None of the previous studies report more than initial training for TD ratings, and no previous study reports TD interrater reliability data. In the absence of careful training and ongoing monitoring, 2 types of errors have been previously reported. First, true TD can be missed fairly often.[46] Second, cases of extrapyramidal syndrome (EPS) movement such as jaw tremor, hand tremor, or leg restlessness can be misidentified as TD.[47–52] These 2 types of error could explain the pattern of findings among previous studies in Table 4: missed true TD in the previous studies could explain the low baseline prevalence and low incidence in the atypical-treated patients. Patients assigned to conventional antipsychotics could experience new EPS, which could sometimes be misidentified as TD, leading to higher than expected rates of "TD" in the conventional group. Among atypical-treated patients, misidentification of EPS as TD would not inflate the TD incidence rate to a similar degree because these patients would be expected to be less likely to experience EPS that could be misidentified. The propensity of a study to falsely detect "TD" in conventional-treated patients (despite missing it at baseline) would be particularly high if the design called for forced antipsychotic change or initiation at entry (all previous studies), change to or initiation of high-EPS conventionals at entry,[33–35,38–41] or proscription or discouragement of anticholinergic medication after entry.[33–35] This propensity would also be magnified if movements emerging in the first 3 months after antipsychotic initiation or change were permitted to qualify as TD.[33–36,39–41]

Table 5. Comparison Between Tardive Dyskinesia in the 1980s and 2000s at the Connecticut Mental Health Center

Comparison[a]	1980s[b]	2000s[c]
Proportion receiving conventional antipsychotic at baseline, %	100	23–36[d]
Patients at risk, N	362	352
Patient-years of follow-up	1127	783
Age at baseline, median, y	41	42
Percent of sample African American	23	35
Percent of sample with schizophrenia[e]	58	67
Chlorpromazine-equivalent dose at baseline, median, mg/d	250	300
Lifetime conventional antipsychotic exposure at baseline, median, y	6.1	6.0
Lifetime atypical antipsychotic exposure at baseline, median, y	0	2.2
Tardive dyskinesia prevalence, %	33	32
Tardive dyskinesia incidence per year	0.053	0.066
Severity of incident cases[f]	4.8	4.8

[a]All data except prevalence estimates are from the at-risk samples.
[b]Prevalence data are from 1982–1983 as published[3]; at-risk baseline and incidence data are from 1985–1990 as published.[4]
[c]Data are from present study, conducted from 2000 to 2005.
[d]Twenty-three percent conventional alone at baseline in the at-risk sample; 36% including conventional in combination with atypical.
[e]Includes schizophrenia or schizoaffective disorder.
[f]Mean of average Abnormal Involuntary Movement Scale (AIMS) total scores across 4 examinations contributing to incident case detection.

Table 4 shows substantial variability among the 9 previous studies. Annualized incidence for conventional antipsychotics varied from 0.019 per year to 0.228 per year. Annualized incidence for atypical antipsychotics varied from 0.000 per year to 0.206 per year. Some of the variability may be methodological. The previous study with the highest incidence rates[36] was the only one to report rates based on meeting criteria on 1 occasion across as many as 7 follow-up time points. The other studies required criteria to be met either twice on consecutive occasions or on 1 occasion but at a single specified time point[38] or at 1 of 2 follow-up time points.[37] The study requiring only 1 occasion but at a single specified time point[38] (12 months) also reported rates based on meeting criteria at any of 3 time points (3, 6, and 12 months); these rates were 2 to 3 times higher.

Comparison With Our Previous Study Conducted During the Conventional Era

Another finding of the present study is that overall TD prevalence, incidence, and incident case severity in the current cohort differed little from estimates obtained from a similar cohort studied at our site with similar methods before the introduction of atypical antipsychotics (Table 5). Other researchers have also reported persistence of substantial TD prevalence despite widespread atypical antipsychotic use.[53–57] One group[58] has recently published evidence of a decline in TD prevalence from 31% during the conventional era to 10% to 12% during the atypical era; the compared studies used the same rating and training methods but were not conducted at the same sites.

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Implications for Combination Prescribing

The incidence of TD with atypical and conventional antipsychotics in combination was somewhat higher than for conventional antipsychotics alone (Table 2). The mean daily chlorpromazine-equivalent dose was strikingly higher in patients receiving combination prescribing (Table 1), but the association between combination prescribing and risk of TD was unchanged after adjusting for dose. Although combination prescribing is common,[59–66] TD risk with combination prescribing has not previously been studied, to our knowledge. The TD risk associated with this practice should be balanced against the infrequently studied likelihood of benefit.[67,68]

Implications of Psychiatric Diagnosis

Little TD advantage for atypicals was apparent in schizophrenia subjects, while a relatively strong advantage was estimated in affective disorder subjects. Since numerous interactions were examined, and power was low for detecting them in this study, caution is indicated in interpreting these findings. We are not aware of other TD incidence data for atypicals relative to conventionals in affective disorder subjects.

Implications for Specific Atypical Antipsychotics

Few data were available for ziprasidone or aripiprazole. Among other atypical antipsychotics, olanzapine showed the lowest relative TD rate (Table 3). Confidence intervals in the present study for specific medications were wide, however. These findings do agree with some previous studies (Table 4). For example, in the other 2 studies[36,38] that compared multiple atypicals to conventionals (Table 4), olanzapine had the lowest rate-ratio in both. Additional studies comparing TD risk among atypical antipsychotics are needed.

Overall Risk of Tardive Dyskinesia With Atypical Antipsychotics

While our findings differ from most previous TD studies from the atypical era, ours is the first incidence study to focus primary investigative attention on the TD question, and previous studies may have consistently been susceptible to ascertainment bias. Our findings suggest that the incidence rate of TD with atypical antipsychotics, while modestly reduced, remains substantial, at least in patients with prior conventional antipsychotic exposure who currently constitute the large majority of patients at our facility. Risk appeared little different among the few patients who were conventional antipsychotic–naive. Future studies should investigate TD incidence in large samples with no conventional exposure history. Comparison of findings from the current study with those from our site prior to the atypical era reveal little impact on TD from a decade of increasing atypical antipsychotic prescription.

Despite the feeling among some clinicians that TD is much less of a problem now in the atypical era, such a conclusion may unfortunately be premature. In the 1960s and 1970s, there was some well-intentioned resistance and skepticism about conventional antipsychotics being associated with risk of TD,[69] and now, during the atypical era, we are perhaps not immune to some of the same forces. Until we are certain we have developed antipsychotics that carry minimal risk, we should continue to inform patients prescribed antipsychotics about TD and continue monitoring for it. Research efforts should continue to discover novel antipsychotics that are free of TD risk as well as to discover new treatments that can help patients who already have TD.

Drug names: aripiprazole (Abilify), clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), thiothixene (Navane and others), ziprasidone (Geodon).

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