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Incidence of Tardive Dyskinesia with Atypical and Conventional Antipsychotic Medications: Prospective Cohort Study

Scott W. Woods, M.D.[1], **Hal Morgenstern, Ph.D.**[2], **John R. Saksa, Psy.D.**[1], **Barbara C. Walsh, Ph.D.**[1], **Michelle C. Sullivan, R.N.**[1], **Roy Money, M.S.**[1], **Keith A. Hawkins, Psy.D.**[1], **Ralitza V. Gueorguieva, Ph.D.**[1,3], and **William M. Glazer, M.D.**[4]

Scott W. Woods: scott.woods@yale.edu

[1] Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA. Dr. Woods may be reached at 34 Park Street, New Haven, CT, USA 06519, tel 203 974-7038, fax 203 974-7057

[2] Departments of Epidemiology and Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor, MI USA

[3] Department of Epidemiology and Public Health, Biostatistics Division, Yale University School of Medicine

[4] Glazer Medical Solutions, Menemsha, MA USA

Abstract

Objective—Most previous studies of the incidence of tardive dyskinesia with atypical compared to 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—352 initially tardive dyskinesia-free psychiatric outpatients were examined for a new diagnosis of tardive dyskinesia 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.

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% confidence interval 0.29 to 1.64). The incidence and prevalence of tardive dyskinesia was similar to previous findings at this site in the 1980s.

Conclusion—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.

When the atypical antipsychotics became available, it was hoped that they would be associated with a lower risk of tardive dyskinesia (TD) than the older conventional

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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 November 2000 through May 2003. Following baseline, subjects at risk for TD were followed prospectively with examinations every six 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 neurological disease (such as Huntington's). With institutional review board approval, we asked clinicians for permission to approach eligible patients for consent. Consenting subjects 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 for dyskinesia.[6] These criteria require the total AIMS score be ≥3, with at least one body area rated ≥2 (mild), on both AIMS exams at that visit. Glazer-Morgenstern criteria are slightly more inclusive than the Schooler-Kane criteria,[7] which require at least two body areas be ≥2 or one body area rated ≥3 (moderate). 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 (WMG) and project coordinator conducted a full-day training session on 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 5 raters per examination, the intraclass correlation for agreement among raters[8] on the AIMS total scores was 0.93.

We considered subjects *prevalent cases* of persistent TD when Glazer-Morgenstern criteria were met at the first visit if there were 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 two consecutive visits.

At-risk cases were defined based on history and baseline examination. Prevalent cases and patients who previously received a Glazer-Morgenstern (GM) research diagnosis of persistent TD in the first Yale TD study (1985–1993)[3, 4, 6] or in the CMHC 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 GM criteria at the initial but not at the second examination. These cases were considered instances of transient dyskinesia and therefore still at risk for developing persistent TD. All at-risk cases were scheduled for follow-up evaluation every six months.

Incident cases of persistent TD were those who, having first met at-risk criteria at baseline, subsequently met Glazer-Morgenstern criteria at two consecutive follow-up visits for both examinations at each visit and on verification exam 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 are supported by empirical studies.[12–14] Drug exposure variables derived from these data included antipsychotic type and years of exposure to, and average 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 non-overlap 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 (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 two groups (0.102/year and 0.092/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 types with recent users of conventional antipsychotics only, controlling for potential confounders (i.e., TD risk factors associated with type of antipsychotic exposure). Proportional hazards analysis was used to estimate drug-type effects (rate-ratios, RR; and their 95% confidence intervals, CI), 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 CPZ-equivalent dose.[4] The other reported risk factors were then added to the core model one 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 effects of lifetime use (available on request from SWW).

Literature Review Methods

We searched Pub Med for studies with the words “tardive,” “clozapine,” “risperidone,” “olanzapine,” quetiapine,” “aripiprazole,” or “ziprasidone” in the title, as well as bibliographies and subsequent citations (in 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 on atypical antipsychotic to incidence on conventional antipsychotic. 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, e.g. present on two 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 follow-up time, or calculated these quantities from published data. Atypical/conventional rate-ratios (RRs) and their 95% confidence intervals were then calculated, and RRs were synthesized across study using a random effects Mantel-Haentzel model in Review Manager 5.[32] In studies where several atypical arms were compared to a single conventional arm, the atypical arms were first weighted by person-years of follow-up and 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 to 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 whom 352 were re-examined at least once during follow-up (the study population). Demographic, diagnostic, and treatment characteristics of the study population are shown in Table 1. Female gender 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 qualified as at-risk by virtue of both negative clinical histories and negative initial research examinations (81%). The remainder had no clinical history but a positive research examination that was negative on repeat (3%) or a positive clinical history but negative baseline research examination (17%). The distribution of conventional medications at baseline is shown in Table 1.

At-risk individuals underwent 1344 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/year. TD risk (cumulative incidence) after 3.9 years of follow-up was 19.7% (95% CI 15.2 to 25.1%). The average of the four total AIMS scores leading to 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 TD

Crude analyses revealed that patients receiving conventional antipsychotic 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, 0.056/year), patients receiving atypical antipsychotic alone developed TD at a rate of 0.059/year (28 cases per 475.2 patient-years), and patients receiving both types since the prior visit developed TD at a rate of 0.096/year (16 cases in 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 conventionals alone (crude RR=1.04; 95% CI 0.50 to 2.22). Subjects treated with both types of antipsychotic since the prior visit developed TD at a somewhat higher rate as subjects treated with conventionals alone (crude RR=1.71; 95% CI 0.77 to 3.82).

Based on 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 to 1.64). Subjects treated with both types of antipsychotic since the prior visit developed TD at nearly double the rate as subjects treated with conventionals alone (adjusted RR=1.85; 95% CI 0.72 to 4.75).

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 subjects treated with conventionals alone (adjusted RR=1.00, 95% CI 0.48 to 2.08 and 0.94, 95% CI 0.44 to 2.03) and a somewhat higher proportion of subjects treated with both types of antipsychotic at baseline developed TD as subjects treated with conventionals alone (adjusted RR=1.36, 95% CI 0.52 to 3.52 and 1.31, 95% CI 0.50 to 3.41).

AIMS total scores were slightly lower among incident cases appearing after recent atypical only exposure than 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 (0.69, 95% CI 0.35 to 1.36 and 0.56, 95% CI 0.21 to 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 an average of 17.8 months (81.6 person-years, crude TD rate 0.086/year). These results include 5 incident TD cases occurred among 23 at-risk subjects receiving clozapine as their sole antipsychotic followed an

average of 23.2 months (44.4 person-years, crude TD rate 0.111/year). Because crude TD rates among clozapine-treated at-risk cases were unexpectedly high, clozapine-treated cases were removed into a separate category. These analyses are shown in Table 2.

Based on 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 conventionals alone (adjusted RR=0.55, 95% CI 0.23 to 1.36). The adjusted RR for combined AT and CV antipsychotics (excluding clozapine) was 2.21 (95% CI 0.85 to 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 appear 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 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 otherwise-adjusted RR for atypical antipsychotic was very similar to the unadjusted RR. The relative effect of atypicals vs conventionals did not appear confounded by years of previous lifetime atypical exposure when this variable was added to the model. None of the remaining planned covariates, including gender, appreciably changed 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 to 0.71) than among schizophrenia subjects (RR=0.97, 95% CI 0.31 to 3.04, p for interaction term 0.050). The stronger advantage among affective patients appeared partly due to lower risk among affective patients exposed to atypicals (crude rate 0.028/year, 4 cases in 142.5 person-years) and partly due to higher risk among affective patients exposed to conventionals (crude rate 0.100/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 one atypical only for the entire time since the prior visit.

Estimated Effects of Duration of Antipsychotic Use by Type

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

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 SWW).

Loss to Follow-Up

Among 401 TD-free subjects enrolled, 49 (12%) were never re-examined 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 nine previous studies in adult patients that reported TD incidence with atypical compared to conventional antipsychotics.[33–41] Table 4 shows the mean age, design, TD acquisition methods, baseline TD prevalence, average 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 for the nine studies taken together and the present study. The 7 randomized and 2 cohort studies together reported 123 incident cases of TD among 2287 patient years of conventional antipsychotic exposure (0.085/year) and 247 incident cases of TD among 12,018 patient years of atypical antipsychotic exposure (0.031/year, RR 0.24, 95% CI 0.12 to 0.48). About three-quarters of the exposure time was accounted for by the two large cohort studies.[37, 38] The present study reports on more atypical antipsychotic exposure time than any of the previous studies except the two previous cohort studies and one of the seven randomized studies.[36] Average 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 CMHC was more similar to that for conventional antipsychotics than in 8/9 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 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 nine previous studies (all of schizophrenia patients) in Table 4.

Strengths and Limitations

Methodologic 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-naïve. In addition very few patients in our study were exposed to only one 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 5/7 of the nine previous comparative TD incidence studies found

by out review.[33, 34, 36–38] The two 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 gender, anticholinergic use, and negative symptoms. One might speculate that our conventional-treated cohort had been selected by prescribers to remain on conventional antipsychotic based on 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/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 four-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.

Lastly, 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 antipsychotic, Table 2, and 5 cases among 23 exposed to clozapine alone). Because of the surprising findings, an investigator (JRS or SWW) thoroughly re-reviewed 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 five incident cases with clozapine alone did have a clinical history of TD on at least one examination, but in one case only on one examination of four recorded lifetime before clozapine and in the other only on 1/17 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 been 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 three studies, none of which are impressively larger than ours, only one of which unequivocally found very low risk.[44] In this study, single study, two of 28 patients developed TD during an average 7.7 years of clozapine treatment, yielding a rate roughly one-tenth of ours in 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 roughly 4 year follow-up of 25 clozapine-treated patients (approximately 0.070/year).[45] In the other study, a possibly increased crude TD risk with clozapine (among only 13 patients, however) was reduced when the model 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 neurological effects that could themselves have conferred an increased risk of TD.

Comparison with Previous Studies Comparing Atypicals and Conventionals

Table 4 shows that the differing relative risk in our study vs previous studies is accounted for by the previous studies finding a somewhat higher TD incidence rate with conventionals than we did (0.085 vs 0.056/year) and a somewhat lower incidence rate with atypicals (0.031 vs 0.059/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 substantial lower proportions of TD at baseline than we did (8.7% vs 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 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 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 antipsychotic.

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, two 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 two 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 antipsychotic could experience new EPS, which could be sometimes 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 4 shows substantial variability among the nine previous studies. Annualized incidence for conventional antipsychotic varied from 0.019/year to 0.228/year. Annualized incidence for atypical antipsychotic varied from 0.000/year to 0.206/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 a meeting criteria on one occasion across as many as 7 follow-up

time points. The other studies either required criteria be met twice on consecutive occasions or one occasion but at a single specified time point[38] or at one of two follow-up time points.[37] The study requiring only one occasion but at a single specified time point[38] (12 months) also reported rates based on meeting criteria at any of three time points (3, 6, and 12 months); these rates were 2–3 times higher.

Comparison with Our Previous Study 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 10–12% during the atypical era; the studies compared used the same rating and training methods but were not conducted at the same sites.

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 average daily CPZ 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. 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 with atypicals relative to conventionals in affective disorder subjects.

Implications for Specific Atypical Antipsychotics

Little 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 two studies that compared multiple atypicals to conventionals in Table 4, olanzapine had the lowest rate-ratio in both.[36, 38] Additional studies comparing TD risk among atypical antipsychotics are needed.

Overall Risk of TD 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-naïve. 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 70s there was some well-intentioned resistance and skepticism about conventionals 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.

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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 AT+CV N=48 (14%)	Total N=352
Age, years[b]	43 (18–78)	41 (20–75)	38 (22–66)	42 (18–78)
Gender female[c]	48 (60%)	87 (39%)	20 (42%)	155 (44%)
Race[c]				
Caucasian	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[c]				
Schizophrenia	35 (44%)	79 (35%)	21 (44%)	135 (38%)
Schizoaffective	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[b,d]	32 (0–1664)	46 (0–6067)	67 (0–3115)	47 (0–6067)
AP dose at baseline[b,e]	275 (25–3500)	300 (12–2000)	700 (200–5157)	300 (12–5157)
Years CV use before baseline[b]	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 AT use before baseline[b]	0.1 (0.0–4.3)	3.0 (0.1–14.5)	2.6 (0.1–12.3)	2.2 (0.0–14.5)
AP dose before baseline[b,e,f]	353 (39–2309)	326 (22–3496)	565 (138–2629)	368 (22–3496)
Anticholinergic at baseline[c]	32 (40%)	32 (14%)	29 (60%)	93 (26%)
Months at risk after baseline[b]	30 (6–46)	29 (6–46)	29 (6–46)	30 (6–46)

AT—atypical antipsychotic, CV—conventional antipsychotic, AP—any antipsychotic

[a] haloperidol (29%), fluphenazine (14%), thiothixene (8%), perphenazine (29%), chlorpromazine (6%), thioridazine (5%), multiple or other conventionals (10%)

[b] values show median (range)

[c] values show number (proportion)

[d] at baseline, includes all lifetime short- and long-term psychiatric hospital days funded by the State of Connecticut

[e] chlorpromazine equivalent dose

[f] median and range of each subject's lifetime mean of days with nonzero dose

Table 2

Crude (unadjusted) and adjusted estimated effects (rate-ratio, RR; and 95% CI) of antipsychotic type and other covariates in the core model on the incidence rate of persistent tardive dyskinesia.

Model Variable[a]	n/N	Mos. At Risk /Subj	Subj Years At Risk	Crude TD Rate	Crude		Adjusted[b]		
					RR	95% CI	RR	95% CI	p[c]
AP since prior visit[d]									.004
Conventional only*	8/81	21.0	141.8	0.056	1	…	1	…	
Atypical[e] only	22/194	25.7	415.6	0.053	0.94	0.44–2.04	0.55	0.23–1.36	
AT + CV	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									.019
<35*	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*	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	
CV use at prior visit[d]									.020
<5 yrs*	20/158	23.3	307.3	0.065	1	…	1	…	
5–<10 yrs	12/71	26.5	156.6	0.077	1.18	0.60–2.31	0.86	0.41–1.84	
10–<20 yrs	16/92	25.9	198.7	0.080	1.24	0.66–2.31	0.78	0.37–1.64	
≥20 yrs	4/49	29.4	120.2	0.033	0.51	0.18–1.39	0.23	0.07–0.80	
Recent AP dose[d]									.010
<200*	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	

* reference category

TD – tardive dyskinesia

CV – conventional antipsychotic

AP – antipsychotic, chlorpromazine-equivalent, mg/day

[a] n indicates number to 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 note d) because individual subjects can contribute person-time to more than one category

[b] adjusted for all other variables in this Table.

[c] reflects a two-sided test of the hypothesis that there is no association (antipsychotic type, race, and antipsychotic mean dose) or no 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] time-dependent predictor, subjects at risk do not sum to 352 because some subjects contributed person-time to more than one category

[e] atypical antipsychotics other than clozapine

Table 3

Estimated crude and adjusted rate-ratio (RR, 95% CI) for tardive dyskinesia comparing each atypical antipsychotic with conventional antipsychotic since the prior visit.

Antipsychotic since prior visit[a]	n/N[b]	Mean CPZ Equiv Dose	Mos. At Risk /Subj	Subj Years At Risk	Crude TD Rate	Crude		Adjusted[c]		
						RR*	95% CI	RR*	95% CI	p[d]
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	…	…	…	…	

TD – tardive dyskinesia

*compared to conventional only as the reference group

[a]Data are not shown for other antipsychotics or for subjects receiving multiple antipsychotics in the same interval.

[b]n indicates number to new TD incident cases during follow-up, N indicates number of at-risk subjects. Individual subjects can contribute person-time to more than one category.

[c]adjusted for age at baseline, race, years of conventional use, and average antipsychotic dose since the prior visit. Age and years of conventional use are treated as continuous variables.

[d]P value reflects a test of the hypothesis that the adjusted tardive dyskinesia rate is the same for all medication groups.

Table 4

Previous studies comparing newly identified tardive dyskinesia in atypical- and conventional-treated groups, compared to current study.

Study[a]	Mean Age[b]	Design[c]	TD Acquisition		Baseline Prevalence	Conventionals						Atypicals						AT/CV RR[l] (95% C.I.)
			Exam Method[d]	Rater ICC[e]		Medication(s)	Dose[f]	n/N[g]	FU Months[h]	Pt-Yrs[i]	Annual Incidence[j]	Medication(s) [k]	Dose[f]	n/N[g]	FU Months[h]	Pt-Yrs[i]	Annual Incidence[j]	
Beasley et al 1999[33, 70, 71]	37	R	AIMS	nr	nr	Haloperidol	695	5/114	7.3	69	0.072	Olanzapine	270	2/513	7.7	328	0.006	0.08 (0.02 to 0.43)
Csernansky et al 2002[34, 72]	40	R	AE	nr	nr	Haloperidol	585	5/188	8.4	132	0.038	Risperidone	245	1/177	11.0	162	0.006	0.16 (0.02 to 1.04)
Dossenbach et al 2004[35]	35	R	AIMS	nr	10.0%	Fluphenazine	585	2/28	4.8	11	0.182	Olanzapine	296	1/26	5.1	11	0.091	0.50 (0.07 to 3.53)
Lieberman et al 2005[36, 73]	41	R	AIMS global	nr	14.5%	Perphenazine	208	41/237	9.1	180	0.228	Olanzapine	402	32/236	10.8	212	0.151	0.66 (0.44 to 1.00)
												Quetiapine	725	30/236	7.8	153	0.196	0.86 (0.57 to 1.30)
												Risperidone	195	38/238	9.3	184	0.206	0.91 (0.61 to 1.33)
												Ziprasidone	188	18/126	8.4	88	0.204	0.90 (0.54 to 1.45)
Tenback et al 2005[37, 74–76]	40	C	Yes/No	nr	9.4%	Conventionals	nr	36/943	6.0	472	0.076	Atypicals	nr	61/6770	6.0	3385	0.018	0.24 (0.16 to 0.35)
Dossenbach et al 2005[38, 77, 78]	36	C	Yes/No	nr	8.9%	Haloperidol	590	10/104	12.0	104	0.096	Olanzapine	216	29/1978	12.0	1978	0.015	0.15 (0.08 to 0.30)
												Quetiapine	200	4/81	12.0	81	0.049	0.51 (0.17 to 1.49)
												Risperidone	445	27/554	12.0	554	0.049	0.51 (0.26 to 1.01)
Gharabawi et al 2006[39, 79, 80]	25	R	ESRS	nr	3.1%	Haloperidol	160	5/215	15.1	267	0.019	Risperidone	170	2/229	14.8	278	0.007	0.38 (0.09 to 1.70)
Miller et al 2007[40]	37	R	AIMS	nr	9.0%	Haloperidol	456	16/391	5.5	176	0.091	Aripiprazole	384	2/786	6.9	444	0.004	0.05 (0.01 to 0.19)
Gaebel et al 2007[41]	32	R	AIMS	nr	3.2%	Haloperidol	180	3/67	6.1	34	0.088	Risperidone	195	0/68	6.3	35	0.000	0.00 (0.00 to 1.19)

Study[a]	Mean Age[b]	Design[c]	TD Acquisition		Baseline Prevalence	Conventionals						Atypicals						AT/CV RR[l] (95% C.I.)
			Exam Method[d]	Rater ICC[e]		Medication(s)	Dose[f]	n/N[g]	FU Months[h]	Pt-Yrs[i]	Annual Incidence[j]	Medication(s) [k]	Dose[f]	n/N[g]	FU Months[h]	Pt-Yrs[i]	Annual Incidence[j]	
Previous Studies[m]	38	7R/2C		nr	8.7%	Conventionals	402	123/2287	7.6	1436	0.085	Atypicals	299	247/12,018	7.9	7893	0.031	0.24 (0.12 to 0.48)
Current Study	42	C	AIMS	0.93	31.5%	Conventionals	576	8/81	21.0	142	0.056	Atypicals	379	29/249	24.0	497	0.059	0.68 (0.29 to 1.36)

[a] first author and year of primary publication.

[b] mean age of full sample.[33–41] Current study at-risk sample.

[c] Most or all patients were receiving antipsychotic prior to baseline, and follow-up began after an antipsychotic medication change or initiation.[33–40] One study first lifetime antipsychotic began eight weeks before baseline.[41] Current study no medication changes required at entry. Double-blinded,[33–36, 39–41] open-label,[37, 38] (current study single-blind).

[d] AIMS – Abnormal Involuntary Movement Scale, AE spontaneous adverse event reports, Yes/No – simple rating of tardive dyskinesia present vs not present, ESRS – Extrapyramidal Symptom Rating Scale, SDS – Simpson Dyskinesia Scale. 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), not blind.[37, 38]

[e] nr – not reported. 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] dose – CPZ equivalent dose, for conventionals,[10] for 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 (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 six 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] for current study, and as calculated from published data,[33, 34, 39, 40] 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 in 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 in new cases per person-year of exposure as published,[33, 39] as calculated from published incident cases and person years of follow-up per note i.[41]

[k] includes clozapine in current study but patients receiving conventional in combination.

[l] RR in this Table indicates either relative rate or relative risk, RR elsewhere in the paper refers specifically to relative rate (rate-ratio). Tardive dyskinesia incidence relative rates and 95% CI are shown as published,[33] or adjusted RR (from current study), or crude RR and 95% CI calculated from incidence risk data per note j.

[m] summary of previous studies indicated as total (n, N, Pt Yrs), mean weighted by sample size (age, baseline prevalence, dose, follow-up months), mean weighted by person-years of follow-up (annual incidence), or meta-analysis of AT/CV RR using RevMan 5.[32] Meta-analysis of RR excludes this study.

Table 5

Comparison between tardive dyskinesia at CMHC in 1980s and 2000s.

Comparison	1980s[a]	2000s[b]
Proportion on conventional at baseline	100%	23–36%*
Patients at risk	362	352
Patient-years of follow-up	1127	783
Age at baseline, median	41 years	42 years
Sample % African-American	23%	35%
Sample % schizophrenia**	58%	67%
CPZ eq dose at baseline, median	250 mg	300 mg
Lifetime CV exposure at baseline, median	6.1 years	6.0 years
Lifetime AT exposure at baseline, median	0	2.2 years
Tardive dyskinesia prevalence	33%	32%
Tardive dyskinesia incidence	0.053/year	0.066/year
Severity of incident cases***	4.8	4.8

all data except prevalence estimates from the at-risk samples

[a] prevalence data 1982–1983 as published [3]; at-risk baseline and incidence data 1985–1990 as published [4].

[b] data from present study 2000–2005

* 23% conventional alone at baseline in the at-risk sample, 36% including conventional in combination with atypical

** schizophrenia or schizoaffective disorder

*** mean of average AIMS total scores across four exams contributing to incident case detection