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The Incidence of Tardive Dyskinesia in the Study of Pharmacotherapy for Psychotic Depression

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Abstract

Tardive dyskinesia (TD) is a debilitating adverse effect associated with antipsychotic treatment. Older age and the presence of mood disorder have been identified as risk factors for the development of TD. Thus, we assessed the incidence of TD in younger and older patients with major depressive disorder with psychotic features who participated in a 12-week clinical trial comparing olanzapine plus sertraline versus olanzapine plus placebo. All subjects ($n = 259$) were assessed with the Abnormal Involuntary Movement Scale at baseline and after 4, 8, and 12 weeks of treatment (or at termination). We used 7 different published criteria to estimate the prevalence of TD at baseline and the incidence over the duration of the trial. We compared the incidence of TD in subjects 60 years or older and those younger than 60 years. The overall prevalence and incidence of TD varied almost 10-fold, depending on the criteria (prevalence range, 1.2%–8.9%; incidence range, 0.0%–5.9%). Tardive dyskinesia was observed as a clinical adverse event in only 1 subject (0.4%). Whereas older subjects had a higher prevalence of TD at baseline, the incidence in younger and older subjects did not differ significantly. The incidence of TD was relatively low in both younger and older patients with major depressive disorder with psychotic features treated acutely with olanzapine. However, the estimate of the risk of TD varies widely, depending on the criteria used to define TD.

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AUTHOR DISCLOSURE INFORMATION

Ms Kanellopoulos has nothing to disclose.

Keywords

psychotic depression; pharmacotherapy; tardive dyskinesia

Major depression with psychotic features (MDPsy) is a severe form of major depressive disorder (MDD) that carries significant morbidity and a poor prognosis.^{1,2} Once recognized, the treatments of choice are either combination pharmacology with an antidepressant and antipsychotic or electroconvulsive therapy.³ However, the use of antipsychotics in patients with mood disorders has been associated with an elevated risk of developing tardive dyskinesia (TD) with a shorter duration of treatment and lower cumulative dose of antipsychotic than in patients with schizophrenia and related psychoses.⁴⁻⁷ Still, patients with MDPsy who respond to an antipsychotic are at high risk for relapse, and they are often maintained on an antipsychotic for several months.⁸ Older age has also been shown to be associated with higher incidence of TD with antipsychotic treatment.⁹⁻¹¹ The emergence of TD can cause psychological distress and severe functional impairment.^{12,13} Thus, it is important for clinicians to be able to inform patients with MDPsy and their family of the risks of TD. However, there is a paucity of prospective data to quantify the risk of emergence of TD in these patients. Most data on the risk for TD pertain to younger patients with schizophrenia or older patients with dementia who may have a different risk and, typically, are exposed to antipsychotics for longer durations.¹⁴⁻¹⁶ Furthermore, there is much variability in diagnosing TD based on different criteria.^{17,18}

This article assesses the extent to which different criteria for capturing TD result in different TD rates: we apply different criteria sets to estimate a range for the prevalence of TD at baseline and its incidence during short-term exposure to olanzapine in a sample of younger and older subjects who participated in the National Institute of Mental Health Study of Pharmacotherapy for Psychotic Depression (STOP-PD).¹⁹ We hypothesized that more stringent criteria would be associated with lower baseline and incident rates of TD. Using the standard Schooler-Kane criteria,²⁰ we hypothesized that the incidence of TD would be higher than the incidence reported in previous olanzapine studies conducted in patients with schizophrenia.²¹⁻²⁵ We also hypothesized that, regardless of the criteria, older age would be associated with a higher baseline and incident rates of TD.^{11,25,26}

METHODS

Subjects

The methods of STOP-PD and the characteristics of the sample have been described in detail in several other manuscripts (eg, see Meyers et al¹⁹). Briefly, STOP-PD was a double-blind randomized clinical trial comparing a combination of olanzapine plus sertraline versus olanzapine plus placebo,¹⁹ referred to in this article as combination and monotherapy. Patients 18 years or older admitted to the inpatient or ambulatory services of 4 academic sites between December 2002 and June 2007 were eligible for participation in the study. The institutional review boards of the 4 institutions and a Data Safety Monitoring Board at the National Institute of Mental Health approved the study consent forms and monitored the

study's progress. Written informed consent was obtained either from the subjects or from their substitute decision makers.

Strategies to identify eligible patients included review of new admissions, advertisements, and direct referrals by community psychiatrists. Subjects were assessed with the Structured Interview for Clinical Diagnosis²⁷ to ensure that *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* criteria for unipolar MDPsy were met. Other inclusion and exclusion criteria are detailed in the original report.¹⁹ Exclusion criteria potentially related to the incidence of TD included a dementia or a history of cognitive impairment before the current depressive episode; meeting criteria for Axis I substance abuse during the preceding 3 months; the presence a neurological disease, such as Parkinson disease, that might affect neuromuscular functioning; having received olanzapine 15 mg/d or more for a minimum of 4 weeks during the current episode. Screening also involved baseline laboratory assessments, including thyroid-stimulating hormone, folates, and B₁₂ levels; an electrocardiogram; and a toxicology screen to detect undisclosed illicit drug use.

Intervention

Eligible subjects were randomized using computer-generated lists with investigators and raters blind to treatment assignments. Randomization was stratified by site and age 60 years or older with a block size of 4. Subjects taking antidepressant or antipsychotic medications at entry had these tapered before randomization, but a washout period was not enforced because of the severity of illness anticipated in study participants. Subjects began 2.5 to 5 mg/d of olanzapine and 25 to 50 mg/d of sertraline or matching placebo, with dose increases permitted every 3 days as tolerated. Olanzapine was administered openly and sertraline or placebo under double-blind conditions. An attempt was made to reach minimum doses of 10 mg/d of olanzapine and 100 mg/d of sertraline or placebo before the end of week 1. Doses were increased to 15 mg/d of olanzapine and 150 mg/d of sertraline or placebo during week 2, with further increases allowed to a maximum of 20 mg/d of olanzapine or 200 mg/d of sertraline, as tolerated, beginning in week 3. Slower titration or dose reductions of 1 or both medications were allowed if adverse effects were suspected; however, subsequent attempts to achieve minimum daily target doses of 15 mg/d of olanzapine and 150 mg/d of sertraline or placebo were required. Adjunctive lorazepam up to 4 mg/d was allowed to control anxiety or agitation and benztropine up to 2 mg/d to control extrapyramidal symptoms. No other psychotropics were allowed.

Assessment of TD and Data Analysis

Baseline assessments were completed within 7 days of obtaining consent. Follow-up research assessments were conducted weekly for the first 6 weeks and then every other week until week 12 or termination. The Abnormal Involuntary Movement Scale (AIMS)²⁸ was performed at baseline and at weeks 4, 8, and 12 (or at the final visit for subjects who terminated the study prematurely).

In the corrected original report of the main outcomes of STOP-PD, TD was reported in 11 subjects (4.3% of the entire sample) comprising 6 older patients (4.2%) and 5 younger patients (4.3%) ($\chi^2_1 = 0.0004$; $P = 0.99$).²⁹ However, these rates of TD aggregated both TD

observed at baseline or during the trial, and they did not include end point assessment for subjects who exited the trial at other time points.^{19,29} For this analysis, we determined and compared the incidence of TD using several operationalized criteria listed in Table 1. The rate that TD was considered an adverse event by the study investigators was included to capture the clinically meaningful emergence of TD. We selected a broad range of criteria that capture both the rates of emergent and persistent TD. For each set of criteria, we determined which subjects met criteria for TD at baseline. These subjects were excluded from further analysis, and we then applied the criteria to the other subjects to assess the incidence of TD during the study. Finally, using each set of criteria, we compared the prevalence of TD at baseline and the incidence of new cases in patients younger or older than 60 years using a Fisher exact test.

RESULTS

The intent-to-treat sample included 259 subjects who were randomized to combination therapy or monotherapy with olanzapine.¹⁹ The demographic and clinical characteristics of these 259 subjects are described in the original report.¹⁹ Prior medication treatments are outlined in more detail in 2 other publications.^{32,33} The baseline prevalence and incidence rates of TD based on the operationalized criteria are presented in Table 2. Using the operationalized criteria, the prevalence of TD at baseline ranged from 1.2% to 8.9%, and the incidence of TD ranged from 0.4% to 5.9%. Using the Schooler-Kane Criteria for probable TD, 11 (4.2%) of 259 subjects met criteria for prevalent TD at baseline, and 9 (3.6%) of 248 subjects met criteria for incident TD. Using the original Schooler-Kane research criteria (including a 2-consecutive assessment requirement), only 2 (0.8%) of 259 subjects met criteria for incident TD. Based on reported adverse events, 1 (0.4%) of 259 subjects had incident TD; this occurred in an older subject. In the subjects 60 years or older, the baseline prevalence rate of TD ranged from 2.1% to 13.4%, and the incidence ranged from 0.7% to 6.5%. In those younger than 60 years, the baseline prevalence rate of TD ranged from 0% to 3.4%, and the incidence ranged from 0% to 7.0%. Regardless of the criteria used, there were no statistical differences in the incidence rates between the group 60 years or older and that younger than 60 years. The incident rates of TD in the olanzapine monotherapy and combination olanzapine plus sertraline groups are presented in Table 3; there was no statistical difference in the incidence rates between the 2 groups on any of the criteria. Observed dyskinetic movements could be due to withdrawal dyskinesia (ie, unmasking of dyskinetic movements following a switch from one antipsychotic to olanzapine). Thus, we reviewed when the 9 subjects met Schooler-Kane criteria for probable TD and assessed whether these 9 subjects had received an antipsychotic before the study: 4 subjects met criteria for probable TD in weeks 1 to 4, 3 during weeks 5 to 8, and 2 during weeks 9 to 12. The 4 subjects who met Schooler-Kane criteria for probable TD during the first 4 weeks of the trial had received an antipsychotic in the 6 months before enrolling in the study (1 subject had received a typical antipsychotic and an atypical antipsychotic, and 3 had received moderate doses of atypical antipsychotics). Two of the 3 subjects who met TD criteria during weeks 5 to 8 had received an atypical antipsychotic in the 6 months before enrolling in the study (1 low dose and 1 moderate dose). Finally, both subjects who met TD

criteria during weeks 9 to 12 had received a low-dose atypical antipsychotic in the 6 months before enrolling in the study.

DISCUSSION

To our knowledge, this is the first study to compare the incidence of TD based on various published criteria in a relatively large sample of subjects treated with an atypical antipsychotic under protocolized conditions. We found that the incidence of TD over this 12-week treatment study ranged from 0.0% to 5.9%. Clinically identified TD was reported as an adverse event in only 1 subject, yielding a very low incidence rate of 0.4%. Standardized criteria that required the persistence of symptoms yielded low incidence rates, ranging from zero new cases (using the modified Glazer-Morgenstern criteria) to only 2 new cases (0.8% incidence rate based on the Schooler-Kane research criteria). Standardized criteria that did not require persistence of symptoms yielded incidence rates that were higher, ranging from 1.6% to 5.9%.

The incidence rates observed using these single-time-point criteria are similar to rates reported in studies of mixed age samples with schizophrenia spectrum disorders treated with second-generation antipsychotics for 1 year,³⁴ but are less than the incidence reported in the CATIE trial (9.3% for probable TD using single-time-point assessment). However, the rate for emergent TD observed in this trial was consistent with that observed in the CATIE trial (1.1%) when emergent TD is defined using 2 consecutive assessments.²⁴ The rates in the current study are higher than those reported in trials of olanzapine augmentation of fluoxetine in treatment-resistant nonpsychotic depression^{35,36} or in psychotic major depression.³⁷ Thus, it seems that, at least over the short term, patients with MDPsy treated with olanzapine may experience an incidence of TD commensurate with that of patients with schizophrenia. In our sample, more than half of the subjects were older than 60 years. However, the incident rates of TD in younger and older patients were not significantly different. Thus, the incident rates in our sample cannot be explained by the older age of our sample. Criteria based on single assessments may be too sensitive and may include non-TD-related movements. However, it is also possible that continuing treatment with an antipsychotic temporarily masks emergent TD. Mild TD may also vary from week to week. Using more sensitive criteria may be desirable if the goal is to detect abnormal movements early during treatment in order to prevent permanent TD, for example, by decreasing antipsychotic doses or switching a patient to an antipsychotic that is less likely to cause TD. This issue is particularly germane in patients with MDPsy or other mood disorders in whom the risk-benefit of treatment with high-dose antipsychotic is different from the risk-benefit in patients with a schizophrenia spectrum disorder: some patients with MDPsy may respond to an antidepressant alone, and more than two-thirds to electroconvulsive therapy.^{38–41} Also, some patients with MDPsy who require acute treatment with an antipsychotic may not need to be maintained on one.³⁸ However, we do not know of any published controlled data on which to compare the potential benefit of decreased relapse and recurrence rates versus the risk of higher TD rates with longer exposure to antipsychotic medications in patients with MDPsy. The risk-benefit issue with respect to TD has become more relevant to treatment of major depression without psychosis where augmentation with an antipsychotic has become

increasingly common and a larger armamentarium of treatment alternatives exist that do not carry risk of TD.

In contrast to previous reports, the incidence of TD in this sample was the same in subjects older than 60 years as in those younger than 60 years. With typical antipsychotics, the incident rates of TD have been reported to be 5 times higher in the elderly than in younger subjects using the Schooler-Kane criteria for probable TD.^{10,42} Using the Schooler-Kane criteria for probable TD, the 1-year incidence of TD has been reported to be 6.7% in adults older than 55 years treated with olanzapine for a diagnosis of dementia or mood disorder.⁴³ In our study, a higher proportion of older subjects presented with abnormal movements at baseline, and the exclusion of these subjects may have contributed to the similarly low incidence of TD in both younger and older subjects.

The limitations of this study need to be considered when interpreting our findings. First, all our subjects were treated with olanzapine, and thus we cannot compare the incidence of TD in patients taking or not taking an antipsychotic. Because almost all patients presenting with psychosis are treated with antipsychotics, this is a limitation of almost all large longitudinal studies of the incidence of TD. Also, although our raters were physicians who had been trained in the AIMS, we did not formally assess their interrater reliability. Subjects who dropped out had their final rating at the time of dropout, and we did not correct the incidence rates based on length of observation because the relationship between TD and duration of antipsychotic exposure is probably not linear and is determined by multiple factors.^{24,34} Thus, the incident rates of TD we report do not reflect an exposure of 12 weeks in all subjects. Furthermore, the duration and intensity of prior antipsychotic exposure varied among the subjects. The data raise the possibility that subjects on higher-dose antipsychotic before enrolling the study may have experienced withdrawal dyskinesia: all but 1 subject who met Schooler-Kane criteria for probable TD had received antipsychotics before study entry, and those who presented with probable TD during the first 4 weeks of the trial had received higher doses before enrolment than did those who developed TD later in the trial.

In conclusion, we observe clinically meaningful emergence of TD in less than 1% of our young and old MDPsy patients treated with olanzapine over up to 3 months. Our results highlight the need for greater consistency in measuring the emergence of TD in antipsychotic trials for indications other than schizophrenia, as the incidence rates varied widely, depending on the criteria used. Our results also highlight that single assessment criteria may lead to an overestimation of emergent TD: using the Schooler-Kane criteria for a single assessment yielded a rate 4 times higher than the rate when consecutive assessments were used. There is a significant amount of point-to-point variability when patients have mild symptoms. If a single assessment is going to be used to estimate the incidence of TD, then the operationalized criteria of Sweet et al³¹ seem to be sufficiently stringent to detect true “cases” of TD.

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TABLE 1

Operationalized Criteria Used to Define TD Cases

TD Criteria	AIMS Criteria	Duration Criteria
Schooler-Kane criteria for probable TD ²⁰	(i) AIMS score 3 in 1 body region (AIMS items 1–7) OR (ii) Score 2 in 2 body regions (AIMS items 1–7)	Single assessment
Schooler-Kane research criteria ²⁰	(i) AIMS score 3 in 1 body region (AIMS items 1–7) OR (ii) Score 2 in 2 body regions (AIMS items 1–7)	Two consecutive assessments [*]
Modified Glazer-Morgenstern criteria ³⁰	(i) AIMS total score 3 AND (ii) Score 2 in 1 body regions (AIMS items 1–7)	Two consecutive assessments [†]
Modified Schooler-Kane criteria (as described in footnote 1 to Table 2) ¹⁹	(i) Increase from baseline of 2 points in 1 body region (AIMS items 1–7) OR (ii) Score 2 in 2 body regions (AIMS items 1–7)	Single assessment
AIMS global rating (item 8)	(0) None (1) Minimal, may be extreme normal (2–4) Mild to severe	Single assessment
Operationalized global rating ³¹	Based on AIMS items 1–7 (0) None: not meeting criteria 1–4 below (1) Minimal: any movements of severity 2, but no more than 1 body region with movements of severity 3 (2) Mild: movements of severity 3 in 2 body areas or severity 4 in 1 body region (3) Moderate: severity of 4 in 2 body areas or severity 5 in 1 area (4) Severe: movements of severity 5 in >1 body area	Single assessment
Adverse event data	TD recorded as an adverse event	Single assessment

^{*} The interval for consecutive assessments was not specified. In the current study, consecutive assessments occurred at baseline and after 4, 8, and 12 weeks (or study termination).

[†] The time interval specified for consecutive assessments required separation by 6 months. In the current study, consecutive assessments occurred at baseline and after 4, 8, and 12 weeks (or study termination).

TABLE 2
Baseline and Incident Cases of TD According to Operationalized Criteria Revised

TD Definition	AIMS Criteria*	Total Baseline Cases	Total Incident Cases	Baseline Cases 60	Incident Cases 60	Baseline Cases <60	Incident Cases <60
Schooler-Kane criteria for probable TD	(i)	9/259	6/250	8/142	2/134	1/117	4/116
	(ii)	7/259	5/252	7/142	2/135	0/117	3/117
Schooler-Kane research criteria	(i) or (ii)	11/259 (4.2%)	9/248 (3.6%)	10/142 (7.0%)	3/132 (2.3%) [†]	1/117 (0.9%)	6/116 (5.2%) [†]
	(i)	Not applicable [‡]	2/250	Not applicable [‡]	2/134	Not applicable [‡]	0/116
	(ii)		0/252		0/135		0/117
	(i) or (ii)		2/248 (0.8%)		2/132 (1.5%) [§]		0/116 (0.0%) [§]
Glazer-Morgenstern criteria	(i)	Not applicable [‡]	0/246	Not applicable [‡]	0/133	Not applicable [‡]	0/112
	(ii)		0/252		0/135		0/117
Modified Schooler-Kane criteria	(i) AND (ii)		0/252 (0.0%)		0/135 (0.0%) ^{//}		0/117 (0.0%) ^{//}
	(i)	22/259	14/237	18/142	8/124	4/117	6/113
	(ii)	7/259	5/252	7/142	2/135	0/117	3/117
	(i) or (ii)	23/259 (8.9%)	14/236 (5.9%)	19/142 (13.4%)	8/123 (6.5%) [¶]	4/117 (3.4%)	6/113 (5.3%) [¶]
AIMS global rating (item 8)	(0) None	226/257		118/141		108/116	
	(1) Minimal	21/257	12/236	14/141	6/127	7/116	6/109
	(2-4) Mild to severe	10/257 (3.9%)	14/247 (5.7%)	9/141 (6.4%)	6/132 (4.5%) [#]	1/116 (0.9%)	8/115 (7.0%) [#]
	(0) None	242/259		128/142		114/117	
Operationalized Global AIMS rating ³²	(1) Minimal	14/259	9/245	11/142	6/131	3/117	3/114
	(2-4) Mild to severe	3/259 (1.2%)	4/256 (1.6%)	3/142 (2.1%)	2/139 (1.4%) ^{**}	0/117 (0.0%)	2/117 (1.7%) ^{**}
	Present	Not applicable	1/259 (0.4%)	Not applicable	1/142 (0.7%) ^{††}	Not applicable	0/117 (0.0%) ^{††}

* Definitions of (i) and (ii) are shown in Table 1.

[†] Incident cases, 60 versus <60: Fisher exact $P = 0.31$.

[‡] The 2 consecutive assessment criteria cannot be applied at baseline because only 1 AIMS rating was completed before initiation of study medications. However, subjects who met the criteria at baseline were excluded from the determination of incident cases.

[§] Incident cases, 60 versus <60: Fisher exact $P = 0.50$.

^{//} Incident cases, 60 versus <60: Fisher exact, $P = 1.00$.

[†] Incident cases, 60 versus <60; Fisher exact $P = 0.79$.
[#] Incident cases, 60 versus <60; Fisher exact $P = 0.43$.
^{**} Incident cases, 60 versus <60; Fisher exact $P = 1.00$.
^{††} Incident cases, 60 versus <60; Fisher exact $P = 0.45$.

TABLE 3

Baseline and Incident Cases of TD Based on Treatment Condition

TD Definition	AIMS Criteria *	Olanzapine/Placebo (n = 130)		Olanzapine/Sertraline (n = 129)		Comparison (Fisher Exact Test)
		Baseline Cases	Incident Cases	Baseline Cases	Incident Cases	
Schooler-Kane criteria for probable TD	(i)	5/130	3/125	4/129	3/125	$P = 0.50$
	(ii)	3/130	4/127	4/129	1/125	
	(i) or (ii)	6/130 (4.6%)	6/124 (4.8%)	5/129 (3.9%)	3/124 (2.4%)	
Schooler-Kane research criteria	(i)	Not applicable [†]	0/125	Not applicable [†]	2/125	$P = 0.50$
	(ii)		0/127		0/125	
	(i) or (ii)		0/124 (0%)		2/124 (1.6%)	
Modified Glazer-Morgenstern criteria	(i)	Not applicable [†]	0/122	Not applicable [†]	0/124	n/a
	(ii)		0/127		0/125	
	(i) AND (ii)		0/127 (0%)		0/125 (0%)	
Modified Schooler-Kane	(i)	14/130	7/116	8/129	7/121	$P = 1.00$
	(ii)	3/130	3/127	4/129	2/125	
	(i) or (ii)	14/130 (10.8%)	7/116 (6.0%)	9/129 (7.0%)	7/120 (5.8%)	
AIMS global rating (item 8)	(0) None	110/129		116/128		$P = 0.29$
	(1) Minimal	13/129	5/116	8/128	7/120	
	(2-4) Mild to severe	6/129 (4.7%)	9/123 (7.0%)	4/128 (3.0%)	5/124 (4.0%)	
Operationalized global AIMS rating	(0) None	119/130		123/129		$P = 0.35$
	(1) Minimal	10/130	4/120	4/129	5/125	
	(2-4) Mild to severe	1/130 (0.8%)	1/129 (0.8%)	2/129 (1.6%)	3/127 (2.3%)	
Adverse event data	Present	Not applicable	0/130	Not applicable	1/129 (0.8%)	$P = 0.50$

* Definitions of (i) and (ii) are shown in Table 1.

[†] The 2 consecutive assessment criteria cannot be applied at baseline because only 1 AIMS rating was completed before initiation of study medications. However, subjects who met the criteria at baseline are excluded from the determination of incident cases.