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The Impact of Olanzapine on Tardive Dyskinetic Symptoms in a State Hospital Population

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Background. *Tardive dyskinesia is a serious adverse event, which is associated mainly with the use of the first-generation antipsychotic agents. Convergent data from clinical trials suggest that second-generation antipsychotic agents are less likely to cause tardive dyskinesia. However, the data with regard to the effect of switching from first- to second-generation antipsychotic agents on pre-existing dyskinetic symptoms during routine clinical care is sparse.*

Methods. *Sixty-three patients with DSM-IV schizophrenia or schizoaffective disorder (n = 61) or bipolar I disorder (n = 2) consecutively admitted to a state hospital, who were treated either with olanzapine (n = 35) or conventional antipsychotic agents (n = 28) by physician choice, were enrolled in the study. The severity and frequency of tardive dyskinetic symptoms using the Abnormal Involuntary Movement Scale were assessed in the two medication groups at baseline, 8 weeks, and 6 months.*

Results. *There were statistically significant reductions in the prevalence and severity of dyskinetic symptoms at 8 weeks and 6 months for the group treated with olanzapine but not for those treated with conventional agents.*

Conclusions. *These preliminary data suggest that olanzapine may be a treatment option for subjects with tardive dyskinesia. However, the question whether olanzapine treats, ameliorates, or masks preexisting tardive dyskinesia was difficult to answer, as no dosage reduction or withdrawal was undertaken.*

Keywords Tardive dyskinesia, Olanzapine, Schizophrenia, State hospital, Abnormal Involuntary Movement Scale (AIMS)

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INTRODUCTION

Even though dyskinetic movements were noted and described in the pre-neuroleptic era, tardive dyskinesia (TD) has mainly been considered a long-term side effect associated with first-generation antipsychotic medications (1, 2, 3). The risk factors for tardive dyskinesia include age, gender, a higher risk in women, ethnicity, a higher risk in African Americans, affective symptoms, and history of head trauma, other serious CNS disease, or diabetes mellitus (2, 3, 4). In addition, the dose of neuroleptic medications and the duration of treatment have been considered additional risk factors. Tardive dyskinesia of varying degrees of severity may occur in approximately 20% of patients who are treated with conventional antipsychotics, although the rates among institutionalized patients at state hospitals may be considerably higher (5, 6, 7, 8).

The prototypical second-generation antipsychotic agent, clozapine, is rarely if ever associated with tardive dyskinesia. On the other hand, numerous studies have shown that clozapine improves existing tardive dyskinesia or dystonia (9, 10, 11, 12). In fact, the presence of severe and persistent tardive dyskinesia has often been an indication for a therapeutic trial of clozapine, especially in the presence of tardive dystonia or persistent akathisia (12, 13). These observations have provided an impetus for the development of several second-generation antipsychotic agents to reduce the risk of tardive dyskinesia. Several observational studies have indeed shown a reduced risk of tardive dyskinesia associated with second-generation antipsychotics (14).

Due to the structural and neuropharmacological receptor profile similarity between olanzapine and clozapine, the effects of treatment with olanzapine on existing tardive dyskinesia have also been examined. An improvement in the severity of tardive dyskinesia or complete amelioration of dyskinetic symptoms has been reported in both patients with schizophrenia as well as those with bipolar disorder (15, 16, 17, 18, 19). Some observational studies and case reports, however, have failed to show a therapeutic benefit with the addition of olanzapine (20, 21), while other reports have linked olanzapine treatment with the development of tardive dyskinesia (22, 23, 24).

We evaluated whether olanzapine could ameliorate pre-existing tardive dyskinesia in chronically ill psychiatric inpatients with several prior psychiatric hospitalizations. A retrospective cohort study of newly admitted patients to a state hospital was carried out to examine the effect of treatment with olanzapine or conventional antipsychotics on pre-existing tardive dyskinetic symptoms. The administration of the hospital intended to track all patients receiving olanzapine for several clinical outcomes in order to justify the higher acquisition costs of this agent, and so tardive dyskinesia was assessed, too, which is the focus of this study.

METHODS

Consecutively admitted state hospital patients with DSM-IV (25) schizophrenia, schizoaffective disorder, or bipolar I disorder who were initiated on olanzapine by physician choice (with patient agreement) were administered the Abnormal Involuntary Movement Scale (AIMS) (26). This scale was administered prior to olanzapine treatment and also at 8 weeks and finally at 6 months. Subjects who were discharged or discontinued sooner were seen for assessment at that time. The comparator group was those subjects admitted at approximately the same time (within a week of the olanzapine-treated subject) and also had the same diagnoses and gender as the olanzapine-treated group, but continued to receive conventional antipsychotic agents. The AIMS scale was administered to the comparator group at the same timepoints as the olanzapine-treated group. The data were delinked from the original medical records of the subjects entered into a database by a volunteer staff member independent of the study and provided to the investigative team for analyses. The study was approved by the Office of Mental Health and Substance Abuse Services of the Commonwealth of Pennsylvania and by the Institutional Review Board at the University of Pittsburgh as exempt from requiring informed consent.

Data Analyses

Descriptive statistics were used to examine the demographic and clinical characteristics of the study sample, and correlational statistics were employed to explore the relationship, if any, between these variables and measures of tardive dyskinesia. The prevalence of tardive dyskinesia, as defined by Schooler and Kane (27), and the severity, as defined by the AIMS total score (items 1 through 7), were examined at each visit (baseline, 8 weeks, and 6 months) in two groups of patients in the study sample. According to these criteria, patients were determined to have tardive dyskinesia if they scored at least moderate severity (3) in one body region (items 1 to 7) or at least mild severity (2) in two or more body regions (items 1 to 7), persisting for at least one month during the evaluation period. Patients in both treatment groups were then categorized on the basis of the TD criteria (TD and non-TD (27)) and categorical comparisons were done using contingency statistics, chi-square for between-group comparisons, i.e., olanzapine vs. conventional. The severity of dyskinetic movements represented by the AIMS total scores at each visit was also compared between groups using independent group t-tests. Differences between the global severity of tardive dyskinesia (item #8 on the AIMS scale) between the two groups was also examined using an independent t-test.

Two strategies were used for statistical analysis. The first strategy, also referred to as an intent-to-treat analysis, included all patients who had been enrolled in the study and had received a baseline assessment. This is a conservative analysis technique that uses the last obtained measurement or assessment as the study end-point (last observation carried forward, LOCF). The second strategy, referred to as completer (or on-treatment) analysis, was based upon observed data and included those

patients who completed all the assessments in the study. The concordance (or discordance) of results from the two analytic strategies was examined to explore the magnitude of the treatment effect (effect of olanzapine treatment on tardive dyskinetic symptoms).

RESULTS

The demographic characteristics of the study sample are presented in Table 1. The subjects represented a treatment-resistant or refractory chronically ill group with more than 17 years of illness, the diagnosis was schizophrenia mainly, and on average they had been hospitalized more than 10 times. There were no significant differences between the two groups for any of the demographic characteristics. We did not obtain the duration of TD for patients in the study because it was difficult to assess reliably. The treatment groups, however, did not differ with respect to other surrogate markers of illness severity, namely, age of onset (of psychosis), duration of illness, and number of previous hospitalizations. We examined the use of concomitant medications, including those used for treatment of tardive dyskinesia, in the two study groups at baseline and during the study (data not shown). There were no significant differences in the use of any medication with the exception of PRN antipsychotics (as needed) that were used more frequently for patients treated with conventional antipsychotic agents (Wilcoxon signed rank test, $z = 2.25$, $p = 0.024$).

Differences in the prevalence of presumptive tardive dyskinesia, i.e., the number of patients meeting the Schooler-Kane research diagnostic criteria, were examined at baseline, at 8 weeks, and at 6 months (Table 2). While there were no significant differences in the prevalence of tardive dyskinesia between the two study groups at baseline, there was a trend ($p = 0.051$) suggesting a lower prevalence of tardive dyskinesia in the olanzapine group at 8 weeks as compared to the group treated with conventional antipsychotic agents. These

Table 1 Demography and Illness Characteristics of the Study Cohort[a]

	Olanzapine Group ($n = 35$)	Conventional Antipsychotics Group ($n = 28$)
Age (years): (mean ± SD)	41.5 ± 9	43.7 ± 9.9
Gender: male/female	19/16	13/15
Ethnicity: Caucasian/African American/ Asian	25/10/0	19/8/1
Diagnosis: Schizophrenia or schizoaffective disorder	33	28
Bipolar I disorder	2	
Age at onset (years): (mean ± SD)	23.1 ± 7	22.5 ± 9
Length of illness (years): (mean ± SD)	17.6 ± 9	19.1 ± 10
Number of previous hospitalizations: (mean ± SD)	13.6 ± 15.7	10.4 ± 6

[a]None of the demography and illness characteristics were significantly different between the two treatment groups.

Table 2 Subjects Meeting the Schooler-Kane Tardive Dyskinesia Criteria: Olanzapine vs. Conventional Antipsychotic Agents[a]

	Group		
Time	Olanzapine	Conventional	Statistics
Baseline (%)	14/35 (40%)	14/28 (50%)	Not significant
8 weeks (%)	6/33 (18%)	10/24 (42%)	$\chi^2 = 3.8$ $df = 1$ $p = 0.051$
6 months (%)	4/20 (20%)	10/14 (71%)	$\chi^2 = 9.0$ $df = 1$ $p = 0.003$

[a]AIMS data for some subjects were unavailable at different time points.

differences between the two treatment groups reached statistical significance at 6 months.

The severity of tardive dyskinesia as defined by the sum of region-specific dyskinetic symptoms (sum of AIMS items 1 through 7) is presented in Table 3. There were no differences between the two groups in the severity of dyskinetic symptoms at baseline. However, at 8 weeks and 6 months, the severity of dyskinetic symptoms in the olanzapine group was significantly lower than in the group treated with conventional antipsychotic agents. Similar trends were also observed by examining the global severity of tardive dyskinesia (AIMS item 8) alone (Table 4, Figure 1).

It is important to note that patients from both groups were discharged during the course of the study. In the olanzapine group, 33 of 35 patients received AIMS assessment at 8 weeks, and only 20 received the final AIMS assessment at 6 months. Subject attrition in this group was primarily due to discharge from the hospital. In the group treated with conventional agents, 24 of 28 patients received AIMS assessments at 8 weeks, and only 14 received the final AIMS assessment at 6 months. Subject attrition in this group was due to both discharge from

Table 3 Severity of Dyskinetic Movements (Sum of AIMS Items 1–7)

	Olanzapine (mean ± SD)	Conventional Antipsychotics (mean ± SD)	Test Statistic	p
Baseline	4.9 ± 4.2	5.6 ± 5.1	$t = 0.58$ $df = 61$	Not Significant
At 8 weeks	2.4 ± 3.8	4.9 ± 4.1	$t = 2.42$ $df = 55$	$p = 0.019$
At 6 months	2.5 ± 3.8[a]	6.9 ± 5.4*	$t = 2.8$ $df = 32$	$p = 0.008$

*Several patients were discharged in either group from the 8-week to the 6-month visit.

Table 4 Global Scores on AIMS Scale[a]

	Olanzapine (mean ± SD)	Conventional Antipsychotics (mean ± SD)	Test Statistic	p
Baseline	1.4 ± 0.98	1.4 ± 1.0	$t = 0.02$ $df = 61$	Not Significant
At 8 weeks	0.70 ± 0.92	1.5 ± 0.9	$t = 3.07$ $df = 55$	$p = 0.003$
At 6 months	0.65 ± 1.0	1.6 ± 0.8	$t = 3.01$ $df = 32$	$p = 0.004$

[a]Several patients were discharged in either group from the 8-week to the 6-month visit.
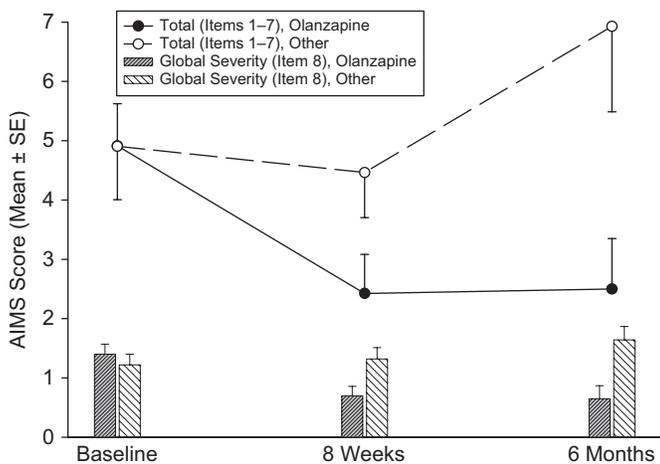
Figure 1 AIMS Scores in Patients Treated with Either Olanzapine or Conventional Antipsychotic Agents.

Table 5 Patients Meeting TD Criteria Among Completers

	Olanzapine(20)		Conventional Antipsychotics(14)	
	TD+	TD–	TD+	TD–
Baseline	8	12	8	6
8 Weeks	6	14	6	8
6 Months	4[a]	16	10[b]	4

TD+ = with tardive dyskinesia; TD– = no tardive dyskinesia.

[a]2 of 4 patients who met the TD criteria at 6 months also met the criteria at baseline; however, there were 2 new cases at 6 months.

[b]All patients who met the criteria at baseline (*n* = 8) also met the criteria at 6 months, and there were 2 new cases at 6 months.

the hospital as well as being switched from a conventional antipsychotic agent to an atypical antipsychotic agent.

In examining only those patients who were able to complete all the study assessments (completer analysis), trends similar to the intent-to-treat (with LOCF) analyses were observed. The number of patients meeting TD criteria among the completers in both groups is presented in Table 5. In the olanzapine group, of the 8 patients who met TD criteria at baseline, only 2 patients continued to meet the TD criteria at 6 months. The remaining 6 patients did not. Interestingly, the other 2 patients in the olanzapine group who met TD criteria at 6 months did not meet the criteria at baseline. In the comparator group (conventional agents), all the patients who met the TD criteria at baseline also met the criteria at 6 months. In fact, 2 additional patients in this group, who did not meet the TD criteria at baseline, now met the criteria.

DISCUSSION

Among patients treated with olanzapine there was a statistically significant improvement in pre-existing tardive

dyskinesia. One obvious explanation for this improvement in pre-existing TD is the removal of the older antipsychotic agents, which may have been responsible for TD in the first place, and secondly, the lack of induction of TD olanzapine treatment. However, 6 months is too short a time to definitively state this about olanzapine treatment. Another limitation of this study is the lack of random assignment, and it might be argued that physician choice biased the groups at baseline. However, this is unlikely to be the case, as both groups had similar rates of TD at baseline. An alternative explanation is that olanzapine might have ameliorated the pre-existing TD, similar to clozapine (11, 12). However, as olanzapine was neither withdrawn nor was the dosage reduced, it is possible that olanzapine was masking pre-existing TD. We did not obtain data relating to other risk and prognostic factors, namely, smoking habits, history of diabetes mellitus, or head injury or the chronicity of TD, all of which could account for the observed differences between groups. However, in a sample of patients with schizophrenia or schizoaffective disorder drawn from the same state hospital, we have observed high rates of diabetes mellitus that could account for the higher prevalence of TD in our study sample (28).

Several mechanisms have been proposed to explain the therapeutic effect of olanzapine on TD. In contrast to conventional antipsychotic agents, olanzapine is loosely bound to dopamine receptors and also dissociates more rapidly from it (29). These effects reduce dopamine receptor supersensitivity resulting in a restoration of motor control. The effects of olanzapine on other neurotransmitter systems, namely GABAergic, glutamatergic, and cholinergic may also explain its efficacy in reducing motor symptoms, but these mechanisms remain speculative (30, 31, 32). Furthermore, preliminary evidence suggests that olanzapine may reverse neurodegenerative changes related to the development of TD by increasing superoxide dimutase, an antioxidant enzyme that reduces free radical damage, and by decreasing the expression nerve growth factor involved in apoptosis (33).

Randomized controlled trials comparing the effects of olanzapine with conventional antipsychotics on pre-existing TD have shown significantly greater improvements in dyskinetic movements in association with olanzapine treatment. In a naturalistic randomized trial, Mari and colleagues (34) found that the relative risk of having TD according to the Schooler and Kane criteria (1982) after 9 months of treatment with conventional antipsychotics was four-fold higher than the risk ratio in patients treated with olanzapine for the same duration of time (*RR* = 4.1, 95% CI 1.1–14.9, *p* < 0.002). In the only randomized controlled trial in which patients underwent blinded dose reduction periods, a significant improvement in mean AIMS score was associated with olanzapine as early as after one week of treatment (35). After 8 months of treatment, approximately 70% of patients no longer met the Schooler and Kane criteria (27) for persistent TD. In this study, patients underwent one or two blinded dose reduction periods. Neither period was associated with a rebound worsening of TD. The prevalence of TD

for the 2 medication groups, olanzapine or conventional antipsychotics, was similar at baseline for both randomized controlled trials.

Re-analyses of previously reported prospective olanzapine studies revealed an annual incidence of TD around 0.5% compared to 7.5% incidence in the haloperidol-treated group (2, 3). Even in vulnerable populations, olanzapine-treated patients are less likely to develop TD (36). The patients who remained in the state hospital at the 6-month assessment probably represent a more treatment resistant or refractory chronic patient population, i.e., enriched for negative prognostic factors. This would perhaps explain why 2 patients on olanzapine, who did not meet the TD criteria at baseline, met the criteria by the end of the study period. Controlled studies of second-generation antipsychotics in vulnerable populations, which involve blinded reductions in dosage utilizing longer treatment duration designs, are more likely to provide the answers to such questions as: Does a second-generation antipsychotic actually ameliorate tardive dyskinesia or does it simply mask it? Furthermore, as second-generation antipsychotics are the standard of treatment for psychotic illnesses, future long-term studies with first-episode patients must be carried out to compare the relative efficacies of various agents in reducing the incidence of TD. Meanwhile, it appears that in patients with treatment-resistant psychoses who also have TD, olanzapine may be a useful treatment option.

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