Incidence of Tardive Dyskinesia in First-Episode Psychosis Patients Treated With Low-Dose Haloperidol

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Background: Previous studies suggest that the risk of tardive dyskinesia is increased with higher doses of conventional antipsychotics. This study evaluates the 12-month incidence of tardive dyskinesia in subjects with first-episode psychosis who were treated with very low doses of haloperidol.

Method: Fifty-seven subjects with first-episode psychosis and a DSM-IV diagnosis of schizophreniform disorder, schizophrenia, or schizoaffective disorder were treated according to a fixed protocol with a mean dose of haloperidol of 1.68 mg/day and prospectively studied for 12 months. Subjects were assessed for extrapyramidal symptoms and psychiatric symptoms at 3-month intervals. Data were gathered from 1999 to 2001.

Results: Twelve-month incidence of probable or persistent tardive dyskinesia according to Schooler and Kane criteria was 12.3% (N = 7). Subjects with tardive dyskinesia did not differ from the rest of the sample regarding gender, race, duration of untreated psychosis, or baseline clinical characteristics. Subjects with tardive dyskinesia were older compared with subjects without tardive dyskinesia (37.14 ± 9.23 vs. 27.30 ± 8.09 years, respectively; t = –2.77, df = 30, p = .01) and received higher mean doses of haloperidol at 12 months (2.80 ± 1.64 vs. 1.39 ± 0.69 mg/day, respectively; t = –3.13, df = 25, p = .004). Cox regression analysis revealed that age at inclusion (p = .031), percentage change in negative symptoms (p = .028), and dose of haloperidol at 12 months (p = .016) were significant predictors of risk for tardive dyskinesia.

Conclusion: Incidence of tardive dyskinesia was at least as high as in other samples treated with standard doses of conventional antipsychotics. Subjects at risk for tardive dyskinesia could not be identified on the basis of initial clinical features or acute treatment response. Risk of tardive dyskinesia was related to age, antipsychotic dose, and worsening of negative, depressive, and parkinsonian symptoms.

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While a variety of motor symptoms similar to tardive dyskinesia occur in schizophrenia patients who have never been treated with antipsychotic medication,[1,2] antipsychotic drug exposure is, by definition, a necessary pathogenic factor in tardive dyskinesia.[3] Particularly, conventional antipsychotics have been associated with tardive dyskinesia. Prevalence rates of tardive dyskinesia in patients treated with conventional antipsychotics are reported to be around 23%.[4] Incidence studies report figures of approximately 5% per year of treatment with conventional antipsychotics.[3] A similar figure of 4.8% has been reported for the first year in a first-episode psychosis cohort, with figures increasing to about 16% after 4 years.[5]

Tardive dyskinesia is a major clinical problem, insofar as it is common and resistant to treatment. While the majority of cases are mild and not distressing, tardive dyskinesia contributes to social and vocational impairment, as well as to the further stigmatization of patients. A minority of patients develop severe symptoms, which can be extremely distressing and disabling and may even be life-threatening.[5] Treatment of tardive dyskinesia is difficult. Dose reduction or discontinuation of antipsychotic medication may, paradoxically, exacerbate tardive dyskinesia symptoms[6,7] and also poses the risk of precipitating a psychotic relapse. With the exception of clozapine[6,7] and possibly vitamin E[8] and vitamin B,[6,9] scant evidence exists to suggest efficacy for any treatment modality for tardive dyskinesia. Strategies for preventing tardive dyskinesia are therefore important, and the atypical antipsychotics may be effective in this regard. Clozapine was the first antipsychotic associated with a reduced risk of developing tardive dyskinesia.[7] The more recently introduced

atypical antipsychotics all have reduced propensity for inducing acute extrapyramidal symptoms (EPS), and their risk for causing tardive dyskinesia is considered likely to be lower.[10,11] Indeed, a review of maintenance studies shows the risk of tardive dyskinesia to be substantially lower with olanzapine than with haloperidol.[12] However, others have argued that the evidence remains preliminary and inconclusive.[13] In any event, the high acquisition costs of the atypical antipsychotics mean that many patients worldwide will continue to be exposed to conventional antipsychotics, and tardive dyskinesia is likely to remain a major problem for the foreseeable future.

Another suggested strategy to minimize the risk of tardive dyskinesia is the use of lower doses of conventional antipsychotics.[14] Greater severity and persistence of tardive dyskinesia has been associated with increased antipsychotic drug exposure,[3,14] and antipsychotic drug dose has been identified as a significant predictor of time to onset of tardive dyskinesia in subjects with first-episode psychosis who were followed for up to 8½ years.[5] It was calculated that each 100-mg chlorpromazine equivalent increment increased the risk of developing tardive dyskinesia by 5%.[5]

The primary aim of our study was to investigate whether the use of the lowest possible dose of haloperidol would protect against the development of tardive dyskinesia, by prospectively determining the incidence of tardive dyskinesia in patients with a first episode of psychosis who were treated with haloperidol over a 12-month period. In addition, other demographic and clinical factors that have been associated with tardive dyskinesia were examined. These factors include poor treatment response[5]; medication-free intervals[15]; being of African descent[16]; mood disorders, particularly depression[17]; increasing age[3,6]; female gender[6]; and the development of EPS during the acute treatment phase.[18]

METHOD

Subjects

The patient sample comprised 57 participants in a prospective study of first-episode psychosis admissions to the Stikland-Tygerberg academic hospital complex in Cape Town, South Africa. All subjects admitted with a first episode of psychosis are referred to the first-episode clinic and were considered for inclusion. Those who met inclusion criteria comprised inpatients or outpatients aged 16 to 55 years meeting DSM-IV diagnostic criteria for schizophreniform disorder, schizophrenia, or schizoaffective disorder who had been exposed to < 4 weeks of antipsychotic treatment. Subjects included in the study therefore did not have to be completely neuroleptic naive, but were considered for inclusion if they had less than 4 weeks of cumulative exposure to neuroleptics. This information was verified as far as possible through the history obtained from the subjects and collateral sources, which was extensive.

Exclusion criteria were DSM-IV Axis I diagnosis other than schizophreniform disorder, schizophrenia, or schizoaffective disorder; alcohol or drug dependence; depot neuroleptic treatment; significant general medical condition; and mental retardation. The study protocol and patient information and consent procedures were approved by the Institutional Review Board of the University of Stellenbosch (Cape Town, South Africa). Subjects and/or their guardians provided written informed consent. Data were gathered from 1999 to 2001. Patients' mean age was 28.2 ± 8.6 years, and 29 (50.8%) were female. Thirty-nine patients (68%) were followed for the full 12 months. Of the 57 subjects included, 11 were Caucasian and 46 were of mixed African-Caucasian origin.

Assessments

Subjects were assessed at baseline by means of the Structured Clinical Interview for DSM-IV,[19] and a full physical examination was performed. Dyskinesia was assessed by means of the Abnormal Involuntary Movement Scale (AIMS),[20] and tardive dyskinesia was diagnosed according to DSM-IV and Schooler and Kane criteria.[21] To meet these criteria, subjects must have had (1) a history of at least 3 months of cumulative antipsychotic exposure; (2) the presence of at least moderate abnormal, involuntary movements in 1 or more body areas or at least mild movements in 2 or more body areas; and (3) an absence of other conditions that might produce abnormal involuntary movements. For those patients in whom movements were rated as "minimal" or "mild" in only 1 body area, the examination was repeated within 1 week to confirm the presence of the movements. Other EPS were assessed by means of the Barnes Akathisia Scale (BAS)[22] and the Simpson-Angus Scale.[23] Symptoms of psychosis were measured with the Positive and Negative Syndrome Scale (PANSS).[24] Investigators were experienced psychiatrists who participated in regular interrater reliability training sessions. A high rate of interrater reliability was maintained throughout the study, with concordance coefficients for PANSS, AIMS, and Simpson-Angus Scale of greater than 0.8. Assessments were repeated at 3-month intervals.

Treatment

Subjects were treated with very low doses of haloperidol in an open-label design according to a fixed protocol that has been described fully.[25] In brief, doses were restricted to 1 mg/day for the first 4 weeks. For nonresponders (≤ 20% reduction in PANSS total score), the dose was increased to 2 mg/day for 3 weeks, followed by weekly increments of 1 mg/day until (1) a response was achieved, (2) intolerable side effects developed, or

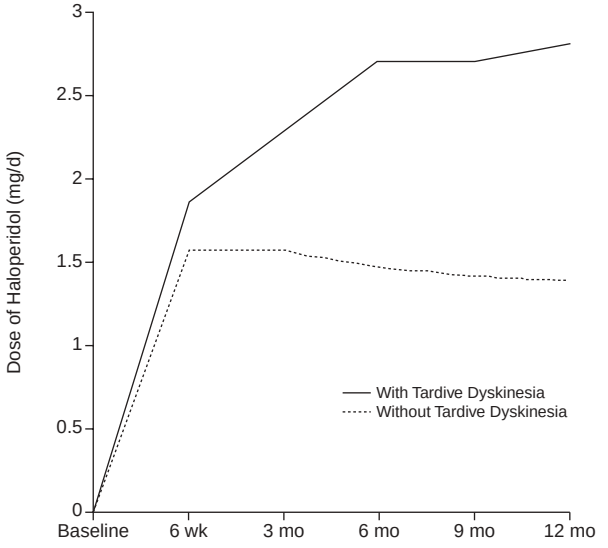
(3) a maximum dose of 10 mg of haloperidol per day was reached. Any nonresponders at this stage were switched to thioridazine, up to a maximum of 600 mg/day. Patients who were nonresponders after 3 weeks of thioridazine at maximum dose were switched to treatment with clozapine. Downward titration of haloperidol was permitted at any point if side effects emerged. Lorazepam was permitted for sedation, and orphenadrine and trihexyphenidyl were prescribed for treatment of EPS. Subjects were rated at weekly intervals for the first 9 weeks or until stabilized. Thereafter, rating took place at 3-month intervals, with additional unscheduled assessments as often as needed.

Table 1. Demographic and Clinical Data for 7 Patients Who Developed Tardive Dyskinesia on Treatment With Low-Dose Haloperidol

Patient	Age (y)	Sex	Schooler/Kane Classification	AIMS Score			
				Baseline	6 Months[a]	9 Months	12 Months
1	49	F	Persistent	0	4	4	5
2	42	F	Probable	0	0	0	2[b]
3	47	F	Persistent	0	3	3	8
4	30	F	Persistent	0	4	3	4
5	37	M	Probable	0	0	0	2[b]
6	30	M	Persistent	0	5	3	3
7	25	M	Probable	0	0	0	2[b]

[a]No subjects developed involuntary movements before the 6-month rating.
[b]Ratings were reconfirmed within 1 week.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, F = female, M = male.

Figure 1. Haloperidol Dose in Tardive Dyskinesia Subjects (N = 7) and Non–Tardive Dyskinesia Subjects (N = 25)



Statistical Analyses

An intent-to-treat design was used, with the last observation carried forward. The tardive dyskinesia group comprised those subjects with either "probable" or "persistent" tardive dyskinesia according to Schooler and Kane criteria.[21] In the initial analysis, we used chi-square and t tests to compare the tardive dyskinesia and non–tardive dyskinesia groups with respect to categorical and continuous variables, respectively. The relationship between the duration of antipsychotic exposure (dependent variable) and age, gender, race, antipsychotic dose at 12 months, depression factor scores at 6 and 9 months, and symptoms of parkinsonism (Simpson-Angus Scale total scores) (independent variables) was examined using the Cox proportional hazard model.

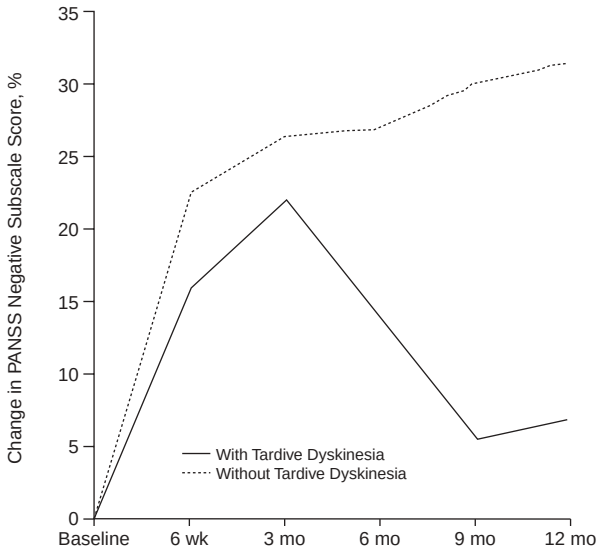
RESULTS

Of the initial 57 subjects, 37 (64.9%) were still on active treatment at the end of the 12-month period. Thirty (81.1%) of the 37 were still taking haloperidol, at a mean ± SD daily dose of 1.68 ± 1.02 mg/day. Fifteen (50.0%) of these were stabilized on 1 mg/day or less. Generally, the treatment was effective and well tolerated.[25]

None of the patients displayed signs of spontaneous dyskinesia at baseline, and acute EPS were minimal (there were no significant changes from baseline in Simpson-Angus Scale, AIMS, or BAS scores at 3, 9, and 12 weeks). However, 7 subjects (12.3%) met Schooler and Kane criteria for tardive dyskinesia at 12 months (Table 1). Three of the subjects did not meet the time qualifier of 3 months for "persistent" tardive dyskinesia, as they first manifested tardive dyskinesia at the end of the study period (12 months). They were therefore labeled as having "probable" tardive dyskinesia. In each of these cases of "probable tardive dyskinesia," the presence of abnormal movements was confirmed 1 week after the diagnosis was made.

Subjects with tardive dyskinesia were compared with the rest of the sample, and no significant differences were found with regard to gender (Fisher exact p = .12), race (Fisher exact p = .63), or duration of untreated psychosis (p = .50). There were, however, differences between the tardive dyskinesia and non–tardive dyskinesia groups in age at entry into the study (37.14 ± 9.23 vs. 27.30 ± 8.09 years, respectively; t = –2.77, df = 30, p = .01) and dose of haloperidol at 6 months (2.70 ± 1.79 vs. 1.57 ± 1.06 mg/day, respectively; t = –2.11, df = 48, p = .04) and 12 months (2.80 ± 1.64 vs. 1.39 ± 0.69 mg/day, respectively; t = –3.13, df = 25, p = .004) (Figure 1). While mood symptoms (as measured by the depression factor of the PANSS[26]) were initially similar in the 2 groups, the subjects who were to later develop tardive dyskinesia manifested significantly higher scores (7.43 ± 3.21 vs. 5.38 ± 1.69; t = –2.28, df = 29, p = .03) at 6 months

Figure 2. Change in PANSS Negative Subscale Scores for Patients With Tardive Dyskinesia (N = 7) and Without Tardive Dyskinesia (N = 25)



Abbreviation: PANSS = Positive and Negative Syndrome Scale.

(i.e., in the postpsychotic phase). These higher depressive symptom scores did not persist at 9 and 12 months. The tardive dyskinesia group also developed significantly more symptoms of parkinsonism (Simpson-Angus Scale total score) at 9 months (12.00 ± 1.83 vs. 10.32 ± 0.63; t = –3.97, df = 30, p = .0004) and at 12 months (11.86 ± 1.95 vs. 10.20 ± 0.65; t = –3.70, df = 30, p = .0009). Our initial analysis revealed no significant differences between the 2 groups in terms of symptom severity as rated on the PANSS, although the percentage change in negative symptoms (p = .083) (Figure 2) and PANSS total scores (p = .081) approached significance.

In the Cox regression analysis, investigation of the effects of different predictor variables revealed that parkinsonism ratings and mood symptoms were no longer significant predictors of risk for tardive dyskinesia. However, 3 variables that were found to be significant were age at inclusion (p = .031), percentage change in negative symptoms (p = .028), and dose of medication at 12 months (p = .016).

DISCUSSION

The incidence of tardive dyskinesia in this study was considerably higher than expected. Given the previous finding that lower dosing strategies afford some protection against tardive dyskinesia,[14] we would have anticipated a rate below the ± 5% per year reported with standard doses of conventional antipsychotics.[3,5] Also, the very low incidence of acute EPS observed in this sample led us to expect a reduced incidence of tardive dyskinesia. Even if the cases of "probable" tardive dyskinesia are disregarded, the 12-month incidence of "persistent" tardive dyskinesia of 7% in the present sample is similar to that previously reported in samples receiving standard doses.[3,5] Thus, while lower doses of conventional antipsychotics have a low risk of inducing acute EPS,[25,27,28] this does not appear to translate into a reduced risk of tardive dyskinesia in the case of haloperidol. While for many people with schizophrenia treated with antipsychotics tardive dyskinesia develops after many years of treatment, there may be a subgroup of patients who develop tardive dyskinesia within a short period of time, even with low doses.

In the initial analysis, we did find a tentative relationship between parkinsonism, dose, and tardive dyskinesia; however, in the proportional hazards model, this was not the case. It is unclear at this time whether our data therefore support an acute EPS–tardive dyskinesia link.

Our findings support a relationship between the dose of haloperidol, a first-generation antipsychotic, and the risk of developing tardive dyskinesia within the first year of starting treatment.[5] Clearly, if lowering the dose of haloperidol is to be employed as a strategy to prevent acute EPS and tardive dyskinesia, our data seem to suggest that such a dose would need to be around 2 mg/day or less. While it was possible, in the majority of cases, to adjust the dose of haloperidol so that the patient could remain within the therapeutic window in which antipsychotic efficacy could be achieved without acute EPS,[27,29] this dosing did not achieve the expected reduction in risk for tardive dyskinesia. This finding may imply that the therapeutic index for tardive dyskinesia is different from that for acute EPS or that it involves a completely different mechanism.

Other possibilities should, however, also be considered. The causative relationship between higher dose of haloperidol and tardive dyskinesia may theoretically be the inverse of what has been proposed; i.e., an alternative explanation for the previously reported association between dose and risk of tardive dyskinesia [3,5,14] is that the accompanying negative and depressive symptoms are interpreted by clinicians as a deterioration or poor response in the patient's condition, with consequent increase of the antipsychotic dose. This would explain our finding of a significant association between tardive dyskinesia and drug dose only later in the study. Furthermore, the increase in parkinsonism scores that we found at 6 and 12 months could be explained on this basis, i.e., the higher scores could be a consequence of increased antipsychotic dose.

Nonetheless, these findings have important implications that may extend beyond the use of conventional antipsychotic agents, insofar as a strategy known to reduce acute EPS appears to have failed to reduce the rate of tardive dyskinesia. The inability of this low-dosing

strategy to protect against the neurotoxic effects of haloperidol therefore also calls into question earlier proposals by us[25] and others[13] that the use of low doses of this conventional antipsychotic may be a reasonable alternative to the atypical antipsychotics. For many patients, finding the therapeutic window may be an impossible task.

The finding of a relationship between the onset of dyskinesia and a worsening of negative symptoms, depressive symptoms, and parkinsonism scores is of interest. While an association between tardive dyskinesia and negative symptoms is well documented,[30,31] the temporal relationship has not been elucidated. Although subjects with mood disorders per se are at greater risk for tardive dyskinesia,[17] we are not aware of a previously reported association between depressive symptoms in schizophrenia and tardive dyskinesia. Whereas most depressive symptoms occur in the acute phase of schizophrenia, and resolve as psychosis remits,[32] persistent or emergent depressive symptoms in the postpsychotic phase[33] appear to be associated with poor social and vocational functioning,[34,35] increased risk of relapse,[36] and suicide.[37] It was postpsychotic depressive symptoms that were associated with tardive dyskinesia in our sample.

Our study confirms that baseline clinical features are not significant predictors of tardive dyskinesia[5] and further suggests that the acute response to antipsychotic treatment is similar in both tardive dyskinesia and non–tardive dyskinesia subjects. Some undefined event then appears to trigger the onset of tardive dyskinesia in certain individuals, with the simultaneous emergence of negative and depressive symptoms, as well as features of parkinsonism (one should keep in mind, however, that mood, negative, and parkinsonian symptoms are difficult to distinguish from one another and may overlap on the assessment scales).

It has been proposed that subjects who are more severely ill and less responsive to treatment have increased vulnerability to tardive dyskinesia, either due to an intrinsic aspect of the disease process or due to greater antipsychotic drug exposure.[5] However, the fact that the tardive dyskinesia subjects did not differ from non–tardive dyskinesia subjects in terms of baseline psychopathology and acute treatment response argues against this proposal. Also, the tardive dyskinesia subjects did not have more persistent psychotic symptoms, as would be expected in a more severe form of schizophrenia. It would appear, rather, that the onset of tardive dyskinesia coincides with the emergence of negative, depressive, and parkinsonian symptoms in subjects with no prior distinguishing characteristics.

As was the case in a number of previous studies,[3,4,6,38] we found an association between age and tardive dyskinesia. This finding was somewhat surprising given the youthful age and limited age range of our sample and indicates that advanced age as an independent risk factor for tardive dyskinesia is not limited to elderly samples. Our failure to identify gender, race, and acute EPS as risk factors for tardive dyskinesia is in keeping with the findings in a similar cohort of first-episode schizophrenia patients.[5] However, the incidence of acute EPS was extremely low in our sample, so comparisons were difficult.

Limitations of this study include the lack of a control group (either higher-dose haloperidol or an atypical antipsychotic), the relatively brief period of follow-up, and the small number of cases of persistent and probable tardive dyskinesia. Excluding subjects with substance dependence, as well as using fairly strict inclusion criteria in terms of previous neuroleptic treatment, also limited the size of the sample. Also, our findings may not generalize to all ethnic groups. Previous work suggests that patients of African descent may be at particular risk for developing tardive dyskinesia,[16] and we have reported significant racial differences in treatment response to antipsychotics,[39] suggesting that some groups may be more sensitive to the effects of these agents. Lastly, this study did not take into account the effects of the use of antiparkinsonian medication on the development of tardive dyskinesia. Future studies may benefit from the inclusion of this variable in the analysis.

Tardive dyskinesia is likely to remain a focus of attention in the management of psychosis for a long time. Our failure to reduce the risk of tardive dyskinesia by using very low doses of haloperidol argues strongly against use of haloperidol as a first-line treatment in psychosis if a choice of agents is available.

CONCLUSION

Our study indicates that tardive dyskinesia remains a serious adverse effect of haloperidol, even when used in low doses. Negative and depressive symptoms may be additional clinical manifestations of the underlying morbid process responsible for tardive dyskinesia.

Drug names: chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril and others), haloperidol (Haldol and others), lorazepam (Ativan and others), olanzapine (Zyprexa), orphenadrine (Norflex and others), thioridazine (Mellaril and others), trihexyphenidyl (Artane and others).

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