

Expected Incidence of Tardive Dyskinesia Associated With Atypical Antipsychotics

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Given the problematic nature of tardive dyskinesia in persons taking conventional antipsychotics, evaluation of newer atypical antipsychotic agents should include a systematic assessment of tardive dyskinesia liability. Results of a prospective double-blind, randomized study of schizophrenic patients who participated in 3 preclinical olanzapine studies and were treated with 5 to 20 mg/day of olanzapine (N = 1192) or haloperidol (N = 522) recently indicated a significantly lower risk of development of tardive dyskinesia with olanzapine treatment than haloperidol treatment. This article discusses the known effects of atypical antipsychotic medications on tardive dyskinesia movements (both withdrawal and persistent) and the incidence rate of tardive dyskinesia among schizophrenic patients undergoing long-term treatment with olanzapine or haloperidol. (*J Clin Psychiatry* 2000;61[suppl 4]:21-26)

Tardive dyskinesia is an involuntary movement disorder characterized by choreiform movements, tics and grimaces of the orofacial muscles, and dyskinesia of the distal limbs, often the paraspinal muscles, and occasionally the diaphragm. The emergence of tardive dyskinesia during treatment with traditional antipsychotic agents represents a matter of continuing concern in psychiatric practice. While there is some evidence to suggest that tardive dyskinesia may be part of the schizophrenic disease process,^{1,2} the majority of cases of tardive dyskinesia are generally accepted to be iatrogenic in origin. Given the problematic nature of tardive dyskinesia, evaluation of newer atypical antipsychotic medications should include a systematic assessment of tardive dyskinesia liability. This article will discuss the known effects of atypical antipsychotic agents on tardive dyskinesia movements (both withdrawal and persistent) and the incidence rate of tardive dyskinesia among schizophrenic patients in a randomized, double-blind study during long-term treatment with olanzapine or haloperidol.

EFFECTS OF ATYPICAL ANTIPSYCHOTICS ON TARDIVE DYSKINESIA

Since the prototypic atypical antipsychotic clozapine was released in 1991, several studies have described the known effects of atypical antipsychotics on tardive

dyskinesia movements. Tardive dyskinesia has been observed to follow a course in which (1) withdrawal of conventional antipsychotic (neuroleptic) medications from some patients exacerbates their involuntary movements (withdrawal-exacerbated tardive dyskinesia), and (2) neuroleptic medication can suppress or mask tardive dyskinesia movements in many patients.³

Molindone Effect on Withdrawal Tardive Dyskinesia

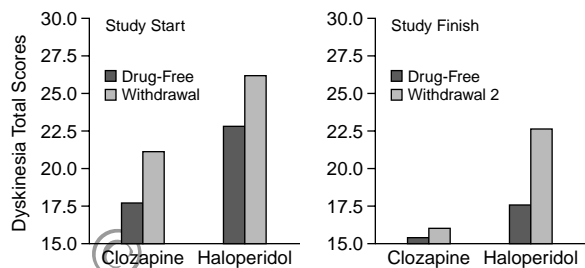
Early in this decade, an experimental method was utilized by Glazer and Hafez³ to compare the masking effects of the 2 neuroleptics molindone and haloperidol on 18 neuroleptic-treated schizophrenic patients who exhibited operationally defined withdrawal-exacerbated tardive dyskinesia. Molindone was selected because animal studies suggested that the agent had atypical properties that worked in a site-specific way, that is, on area A10. Thus, researchers hypothesized that molindone would be a less potent masker of withdrawal-exacerbated tardive dyskinesia than haloperidol. Patients taking typical antipsychotics were abruptly withdrawn from medication over a period of 3 weeks. Withdrawal tardive dyskinesia was measured by Abnormal Involuntary Movement Scale (AIMS) scores. A subgroup of patients who showed withdrawal tardive dyskinesia was randomly assigned to receive either molindone or haloperidol. After a week of taking the neuroleptics at a dose equivalent to 100% of the prestudy dose, molindone masked total AIMS scores by significantly less (12%) than haloperidol (27%). During the second week, when the dose of neuroleptics was equivalent to 200% of that of the prestudy dose, molindone similarly masked the total AIMS score significantly less (23%) than haloperidol (53%). Although several interpretations of the findings were submitted, this study offered a model for understanding pharmacologic differences among medications and

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Figure 1. Dyskinesia Scores Before and After Neuroleptic Withdrawal: Clozapine Versus Haloperidol^a



^aReprinted from Tamminga et al.,⁶ with permission. Before the blinded protocol, neuroleptic withdrawal produced an increase in dyskinetic movements of a similar degree in both groups. After 12 months of treatment, the haloperidol group still showed a significant increase in dyskinetic movements with neuroleptic withdrawal, but the clozapine group had lost this withdrawal-induced response.

suggested that some neuroleptics might have less dyskinesic potential than others.

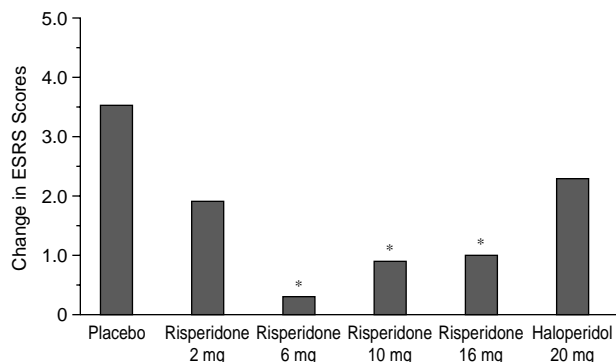
Clozapine Effect on Persistent Tardive Dyskinesia

Kane et al.⁴ and Lieberman et al.⁵ have reviewed several published studies that described the effects of clozapine on tardive dyskinesia, and the authors found that tardive dyskinesia movements were dramatically reduced with clozapine therapy compared with 2 different doses of chlorpromazine.

Tamminga et al.⁶ observed the severity of withdrawal tardive dyskinesia before and after a 12-month blinded treatment with clozapine or haloperidol (Figure 1). The mean \pm SD drug dose at study end was 28.5 ± 23.8 mg/day of haloperidol or 293.8 ± 171.9 mg/day of clozapine. In comparing the 2 drugs, clozapine produced significantly greater benefit for motor symptoms after 12 months of treatment than did haloperidol ($p < .001$). Moreover, the dyskinesia rebound that occurred equally in both drug groups at the beginning of the study was sustained in the haloperidol group but lost in the clozapine-treated patients. These data suggest that patients with dyskinesia lose their symptoms of tardive dyskinesia along with dopaminergic hypersensitivity when taking long-term clozapine treatment.

A retrospective chart review of 13 patients by Dalack et al.⁷ compared tardive dyskinesia and symptom rating scales between groups (with and without tardive dyskinesia) at baseline and between individuals (self as own control) in the tardive dyskinesia group at baseline and at the end of the follow-up period. In patients with tardive dyskinesia at baseline, mean \pm SD AIMS scores decreased by 85% over 10.3 ± 5.5 months at a mean \pm SD clozapine dose of 358 ± 196 mg/day. The authors concluded that these data and other literature supported the striking utility of clozapine for chronically psychotic patients, especially those with tardive dyskinesia.

Figure 2. Effect of Risperidone on Persistent Tardive Dyskinesia^a



^aReprinted from Chouinard et al.,⁸ with permission. Mean change scores from baseline to worst scores for ERSR total dyskinesia. Abbreviation: ERSR = Extrapyramidal Symptom Rating Scale. * $p < .05$ in comparison to placebo.

Risperidone Effect on Persistent Tardive Dyskinesia

In a Canadian multicenter placebo-controlled study⁸ of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients, risperidone—at the optimal therapeutic dose of 6 mg/day—produced significant improvement in both positive and negative symptoms and with a significant beneficial effect on tardive dyskinesia (Figure 2). In the treatment of 10 schizophrenic patients with tardive dyskinesia taking chronic neuroleptic medications, Meco et al.⁹ reported no effect of risperidone compared with placebo; this finding may represent a masking effect similar to that of clozapine.

Olanzapine Effect on Persistent Tardive Dyskinesia

Kinon et al.¹⁰ suggest that atypical antipsychotic drugs may offer beneficial treatment for tardive dyskinesia since clozapine⁵ as well as olanzapine¹¹⁻¹³ have been reported to cause a reduction of tardive dyskinesia symptoms over weeks to months. A retrospective analysis of 129 patients with presumptive tardive dyskinesia who entered 1 of 3 olanzapine clinical trials demonstrated a significant reduction of mean AIMS total scores. There were mean reductions of total AIMS scores of 55% and 71% noted at weeks 6 and 30, respectively. The marked and persistent effect for up to at least 30 weeks suggests that olanzapine may contribute to the improvement of tardive dyskinesia through a mechanism other than neuroleptic masking of symptoms.

DO ATYPICAL ANTIPSYCHOTIC AGENTS CAUSE TARDIVE DYSKINESIA?

Clozapine

Even after almost 10 years, there are few data on the liability of clozapine for causing tardive dyskinesia. In an at-

tempt by Kane et al.¹⁴ to determine if chronic exposure to clozapine caused tardive dyskinesia, a total of 28 schizophrenic or schizoaffective patients with no prior history of definite tardive dyskinesia were treated with clozapine for at least 1 year and monitored with the Simpson Dyskinesia Scale every 3 months. These data were compared with those of another group of similarly diagnosed patients who were treated with typical antipsychotics for at least 1 year. Two patients in the clozapine-treated group—both of whom had previously taken neuroleptics and had ratings of questionable tardive dyskinesia at baseline—were later rated by the Simpson Dyskinesia Scale as having mild tardive dyskinesia. Although there was uncertainty about whether clozapine definitely caused tardive dyskinesia in the 2 patients, a survival analysis showed a lower risk of tardive dyskinesia in the clozapine-treated group. Nevertheless, the authors were unable to definitely conclude whether clozapine causes tardive dyskinesia.

Risperidone

Although isolated cases of tardive dyskinesia have been reported with risperidone treatment,¹⁸⁻¹⁹ there are few data with which to determine the relative risk of tardive dyskinesia associated with risperidone treatment. In this supplement, Jeste et al.²⁰ discussed a recent longitudinal prospective study²¹ in which the 9-month cumulative incidence of tardive dyskinesia was evaluated in 61 risperidone-treated outpatients matched for age, diagnosis, and length of neuroleptic exposure at study entry with 61 haloperidol-treated patients. Life-table analysis revealed that tardive dyskinesia was significantly more likely to develop in haloperidol-treated than in risperidone-treated patients ($p < .05$, Peto-Prentice).

A recent case report²² described an adolescent taking risperidone, 6 mg/day, who had mild hand-dangling movement and tongue protrusion noted on the initial visit by the author. Although the risperidone dose was decreased, the patient had pronounced involuntary oral-buccal twitches, right-to-left spillover of the hands with rapid alternating movements, and stiffness of the legs noted 8 months after the initial visit. Soon afterward, risperidone was discontinued and the movement disorder resolved by 16 months. The authors believe that tardive dyskinesia and choreiform movements in this patient may have been a side effect of risperidone, since a thorough workup provided no alternative diagnosis.

Quetiapine

Tardive dyskinesia in a patient taking quetiapine has been reported,²³ but prospective data are lacking.

Comparison of the Incidence of Tardive Dyskinesia in Patients Treated With Olanzapine Versus Haloperidol

Olanzapine shares several pharmacologic properties with clozapine without the disadvantage of causing

agranulocytosis. Receptor binding studies²⁴ have shown olanzapine to have affinity for a broad range of receptors including serotonin 5-HT_{2A/2C}, 5-HT₃, 5-HT₆, dopamine D₄/D₃/D₁/D₂, and muscarinic cholinergic (M₁-M₅), α_1 -adrenergic, and histamine H₁ receptors. Like clozapine, olanzapine demonstrates greater affinity for serotonergic receptors than for dopaminergic receptors.

The development of tardive dyskinesia was recently evaluated in a prospective double-blind, randomized study²⁵ of schizophrenic patients treated with 5 to 20 mg/day of olanzapine (N = 1192) or haloperidol (N = 522) for up to 2.6 years. This study is a further extension of a previously reported study²⁶ of the incidence of tardive dyskinesia in patients entering long-term extensions of 3 double-blind randomized studies of olanzapine. Analysis of the rate of development (number of cases per patient time) of tardive dyskinesia and the potential influence of risk factors has been emphasized in the study presented here.²⁵ The study population consisted of patients who participated in 3 separate preclinical studies with different designs:

- Study 1²⁷ (N = 335) compared dose ranges of olanzapine (5 \pm 2.5, 10 \pm 2.5, 15 \pm 2.5 mg/day), placebo, and one dose range of haloperidol (15 \pm 5 mg/day). Randomized double-blind acute treatment continued for 6 weeks. Patients responding to acute treatment continued double-blind treatment for up to 32 months more. Olanzapine patients completing the double-blind extension entered an open-label extension.
- Study 2²⁸ (N = 431) was identical to Study 1 except that a very low dose of olanzapine (1 mg/day) replaced placebo.
- Study 3²⁹ (N = 1996) compared 5 to 20 mg/day of olanzapine with the same dose of haloperidol. Randomized double-blind acute treatment continued for 6 weeks. Patients responding to acute treatment continued double-blind treatment for up to 19 months more. Patients not responding to double-blind treatment entered the open-label olanzapine extension at week 4, 5, or 6. Olanzapine patients completing the double-blind extension entered an open-label extension.

Baseline tardive dyskinesia was assessed by AIMS scores and the modified research diagnostic criteria for tardive dyskinesia (modified RD-TD) of Morgenstern and Glazer³⁰; that is, a score of ≥ 3 on any 1 of AIMS categorical items 1 through 7 or ≥ 2 on 1 of the categorical items and ≥ 1 on another of the categorical items. The researchers chose this modified narrower definition of tardive dyskinesia in order to identify more baseline cases. AIMS examinations were performed weekly to twice monthly during the 6-week acute phase and monthly during the indefinite extension phase. Patients meeting the criteria for

Table 1. Incidence of Tardive Dyskinesia: Double-Blind Therapy Period^a

Patient Population/Therapy	Patients (N)	Tardive Dyskinesia (N)	Kaplan-Meier Estimated Risk % (95% CI) ^b	p Value ^c	Haloperidol-Olanzapine Proportional Hazards Ratio (95% CI)	Patient Years of Therapy	Incidence Rate/Year (95% CI)	Haloperidol-Olanzapine Incidence Rate Ratio (95% CI)	p Value ^d
Overall period									
Olanzapine	1192	24	2.59 (1.46–3.72)			471.92	0.051 (0.033–0.076)		
Haloperidol	522	24	8.02 (4.24–11.80)	<.001	2.66 (1.50–4.70)	127.72	0.188 (0.122–0.281)	3.69 (2.10–6.50)	<.001
Stratum 1: 0–6 wk									
Olanzapine	1192	20	...			119.74	0.167 (0.107–0.253)		
Haloperidol	522	15116	1.72 (0.88–3.36)	48.55	0.309 (0.181–0.496)	1.85 (0.95–3.61)	.067
Stratum 2: > 6 wk									
Olanzapine	513	2	0.52 (0–1.26)			328.38	0.006 (0–0.022)		
Haloperidol	114	5	7.45 (0–15.37)	.002	11.37 (2.21–58.60)	69.23	0.072 (0.027–0.166)	11.86 (2.30–61.13)	<.001

^aFrom Bymaster et al.,²⁴ with permission.

Abbreviations: CI = confidence interval. Symbol: ... = information missing.

^bThe values shown represent the estimated 1-year risk (Overall period) and 1-year risk after the initial 6 weeks of observation (Stratum 2), respectively.

^cp Value from exact log-rank test comparing survival curves.

^dp Value for test that haloperidol-olanzapine incidence rate ratio = 1.

either of 2 baseline AIMS assessments as well as patients with an historical diagnosis of tardive dyskinesia were excluded from the analysis of incidence of treatment-emergent tardive dyskinesia. Patients with fewer than 2 AIMS assessments were also excluded from the analysis because they did not have the opportunity to meet the modified RD-TD criteria for 2 consecutive visits. Patients were considered to have persistent treatment-emergent tardive dyskinesia if they met the Schooler and Kane RD-TD criteria³¹—that is, a score of ≥ 3 on any 1 of the AIMS categorical items 1 through 7 or ≥ 2 on any 2 of the categorical items—on 2 consecutive visits. Data analysis included Kaplan-Meier survival analysis and incidence rate analysis. The incidence rate of tardive dyskinesia was expressed as the number of cases of tardive dyskinesia per patient-year of exposure. The total patient-years of exposure were calculated by summing the exposure time until diagnosis with tardive dyskinesia or discontinuation for each patient across treatment groups.

The time of diagnosis was the first of 2 consecutive visits where criteria for tardive dyskinesia were met. Because the study designs allowed patients to continue on blinded therapy past 6 weeks only if they were responders to study medication, the analysis was stratified into 2 distinct time strata based on time observed in study. These strata were (1) patients observed through 6 weeks and (2) patients observed for longer than 6 weeks. Nonresponders in stratum 1 could not continue in stratum 2; therefore, stratum 2 was selective for responders to study medication. Cases of tardive dyskinesia that occurred prior to week 6 were felt to be preexisting withdrawal cases. Moreover, patients in stratum 1 were undergoing medication adjustments and

multiple AIMS evaluations—perhaps as many as 6 assessments during the first 6 weeks of the study—which increased the likelihood of early detection of tardive dyskinesia. Therefore, incident cases of tardive dyskinesia were defined as cases occurring after 6 weeks and by 52 weeks. Patients could contribute exposure information into both strata; however, once a patient was diagnosed with tardive dyskinesia in the first time stratum, he or she could not contribute exposure information in the second time stratum.

No significant differences were noted with respect to age, gender, or ethnic origin between the olanzapine and haloperidol treatment groups. The population was approximately two thirds male, and the mean \pm SD age was 36.6 ± 10.6 years. The majority of patients were of the paranoid schizophrenic subtype (chronic course) or were chronic patients of the same subtype with acute exacerbation. The treatment groups were also comparable with respect to age at onset of psychosis, duration of illness, and length of current episodes. Patients were evaluated for baseline severity of illness during the screening visit using the Brief Psychiatric Rating Scale (BPRS) total scores; baseline severity of illness was comparable between the 2 treatment groups for all BPRS subscales. Baseline severity of illness and EPS were evaluated using Simpson-Angus Scale total scores and Barnes Akathisia Scale global scores.

The overall relative risk for developing tardive dyskinesia at 1 year was 2.59% for olanzapine and 8.02% for haloperidol with a proportional hazards rate ratio of 2.66 (95% CI = 1.50 to 4.70) (Table 1). This high overall risk may reflect the withdrawal tardive dyskinesia cases within the first 6 weeks of the study and the multiple examina-

tions performed within that time period. In stratum 2, in which withdrawal cases were probably excluded, the relative risk of developing tardive dyskinesia at 1 year was 0.52% for olanzapine and 7.45% for haloperidol with a proportional hazards rate ratio of 11.37 (95% CI = 2.21 to 58.60). During the overall time period of 52 weeks, the incidence rate of tardive dyskinesia was 0.188 for haloperidol and 0.051 for olanzapine with a haloperidol-olanzapine incidence rate ratio of 3.69 ($p < .001$). When evaluating stratum 1 only, the incidence rate was 0.309 for haloperidol and 0.167 for olanzapine with a haloperidol-olanzapine rate ratio of 1.85 ($p = .067$). When stratum 2 was examined, the incidence rate was 0.072 for haloperidol and 0.006 for olanzapine, with a haloperidol-olanzapine incidence rate ratio of 11.86—or almost a 12-fold reduction in the risk of developing tardive dyskinesia with olanzapine treatment.

The clinical implications of this study include the following considerations. During 1 year of treatment, the risk of developing tardive dyskinesia may be less than one tenth for olanzapine-treated patients than for haloperidol-treated patients. Furthermore, over an observation period of at least 3 years, the estimated annual risk of tardive dyskinesia occurring during olanzapine treatment may be less than 1% per year. Finally, more clinically significant dyskinesic symptoms—possibly transient or due to medication changes—were diagnosed more often than expected during the intensive assessments of the first 6 weeks of observation. The limitations of this study include the following considerations. It is difficult to compare these results with other analyses because of the frequent assessments for tardive dyskinesia in this study. Moreover, the number of olanzapine-treated patients dropped off rapidly after 3 years of treatment, which limited the estimation of the rate of development of tardive dyskinesia. Additionally, since virtually every patient in the study population had received prior antipsychotic treatment, the contribution (or lack thereof) of olanzapine treatment to the development of tardive dyskinesia in a D_2 -antagonist-naïve population is still uncertain. Nonetheless, multiple assessments of the incidence of tardive dyskinesia in these studies among patients with a long duration of illness and previous antipsychotic treatment indicate a substantially lower risk of development of tardive dyskinesia with olanzapine treatment than with haloperidol treatment.

CONCLUSION

Studies of the new antipsychotic medications point to a lower risk for development of tardive dyskinesia. A recently published double-blind, randomized study of schizophrenic patients who participated in 3 preclinical olanzapine trials showed a significantly lower risk of development of tardive dyskinesia in olanzapine- than haloperidol-treated patients. After the first 6 weeks of

the study, during which patients underwent medication changes and frequent AIMS assessments, the 1-year risk of development of tardive dyskinesia was 0.52% with olanzapine treatment and 7.45% with haloperidol treatment. The relative risk throughout this follow-up period was 11.37 (95% CI = 2.21 to 58.60). If these results are supported by findings of other prospective studies—especially in drug-naïve patients—consideration should be given to replacing conventional antipsychotic treatment with the newer atypical agents.

Drug names: clozapine (Clozaril and others), haloperidol (Haldol and others), molindone (Moban), olanzapine (Zyprexa), risperidone (Risperdal).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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