# Tardive Dyskinesia in Affective Disorders

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Soon after the introduction of antipsychotic drugs into clinical practice, these agents were observed to be capable of producing not only acute extrapyramidal ("parkinsonian") side effects, but also later occurring abnormal involuntary movements that came to be called tardive dyskinesia. Since antipsychotic drugs are used in a variety of conditions that include psychotic features, studies have attempted to determine whether specific diagnostic subgroups may experience different degrees of vulnerability to drug-induced movement disorders. This issue is important not only to inform clinical practice, but also to provide clues to pathophysiology. A number of studies suggest that patients with affective disorders are at greater risk for developing tardive dyskinesia (controlling, to the extent possible, for other relevant variables such as age, sex, length of treatment). Encouraging preliminary data with new antipsychotic drugs such as olanzapine suggest that the risk of tardive dyskinesia associated with long-term antipsychotic drug use may be substantially reduced. This would go a long way toward improving the benefit-to-risk ratio of antipsychotic drug treatment, particularly in patients with affective disorders.
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Antipsychotic drugs are widely used to treat not only schizophrenia, but also schizoaffective disorder, bipolar disorders, and major depression with psychotic features. Given the risk of tardive dyskinesia associated with long-term antipsychotic administration, determining the relative benefit-to-risk ratio of antipsychotic administration in affective disorders is important.

A series of findings have suggested that compared with patients with schizophrenia, patients with affective disorders may be at greater risk for developing tardive dyskinesia (assuming equivalent exposure to antipsychotic drugs). This report will provide an overview of research in this area and discuss the potential value of new-generation antipsychotic drugs in improving the benefit-to-risk ratio for patients with affective disorders.

Early reports suggesting an increased risk of tardive dyskinesia in affective disorder patients appeared in the mid-1970s. Davis et al.[1] reported that 9 of the first 14 patients with tardive dyskinesia interviewed met criteria for depression rather than schizophrenia. Rosenbaum et al.[2] reported a high incidence of primary affective disorder among tardive dyskinesia patients. Rush et al.[3] studied 11 patients with tardive dyskinesia and 8 non–tardive dyskinesia controls matched for age, sex, and age at first admission to a state hospital and found that tardive dyskinesia patients had significantly more affective symptoms at admission than non–tardive dyskinesia patients.

Hamra et al.[4] reported that patients with affective disorder were significantly overrepresented among their 17 patients with tardive dyskinesia as compared with a matched control group without tardive dyskinesia. Yassa and colleagues[5] reported a 41% prevalence of tardive dyskinesia in a sample of 83 patients with affective disorders, which was higher than many prevalence estimates in schizophrenia patients. In a larger sample of 328 patients, these investigators[6] found that a diagnosis of bipolar disorder was significantly associated with a higher prevalence of tardive dyskinesia.

Mukherjee et al.[7] studied 131 patients with bipolar disorder. Ninety-six had received antipsychotic drugs and 35 had not. Thirty-four cases of persistent tardive dyskinesia were found among the treated cases—a prevalence of 35%—whereas no cases were observed in the control group. Using multiple regression, 2 variables were found to predict the presence of persistent tardive dyskinesia: longer cumulative duration of maintenance antipsychotic treatment and shorter duration of previous lithium treatment.

Yassa et al.[8] conducted a 5-year study of elderly (65 years or older) patients who were admitted to a psychiatric hospital for the first time with no prior history of antipsychotic drug treatment. Of 99 patients who went on to receive antipsychotic drugs, 35% developed tardive dyskinesia. Significantly more patients with major depression (12

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[60%] of 20) as compared with patients with primary dementia or delusional psychosis (12 [25%] of 49) developed tardive dyskinesia, with no significant differences in length of antipsychotic drug treatment or total cumulative dose.

Glazer et al.[9] reported a statistically significant association between a schizoaffective or affective disorder diagnosis and the presence of orofacial dyskinesia in 228 outpatients with tardive dyskinesia. Cole et al.[10] studied 100 patients with recently developed dyskinesia and found both unipolar and bipolar patients to be more susceptible to developing tardive dyskinesia (in terms of shorter duration and lower cumulative dose of antipsychotic drug treatment) in comparison with patients with schizophrenia or schizoaffective disorder. Parepally et al.[11] did not find a difference in the prevalence of tardive dyskinesia between bipolar patients (44%) and patients with schizophrenia (43%).

Gardos and Cole[12] pointed out that although affective disorders in general appear to be associated with increased risk of tardive dyskinesia, the relative risk associated with bipolar versus unipolar versus schizoaffective disorder remains far from clear. Cole et al.[10] analyzed duration of antipsychotic treatment prior to the development of dyskinesia and found it to be a mean of 70 months in patients with schizophrenia (N = 77) and 78 months in those with schizoaffective disorder (N = 57), in contrast to 33 months in bipolar patients (N = 30) and 38 months in unipolar subjects (N = 40).

In our prospective study of the development of tardive dyskinesia at Hillside Hospital,[13,14] we have followed patients with a variety of psychiatric diagnoses in order to determine the incidence of tardive dyskinesia as well as relevant risk factors. Of 819 patients in our core sample, 110 (13%) were classified as having schizoaffective disorder, 88 (11%) major depressive disorder, and 120 (15%) bipolar disorder. The mean ± SD age at study entry was 28 ± 10 years. The overall hazard rate for the development of tardive dyskinesia among patients treated with (conventional) antipsychotics was 5.3% per year. The primary method employed to study risk factors was the Cox proportional hazards analysis with time-dependent covariates.

Patients classified as having major depressive disorder developed tardive dyskinesia at a higher rate than patients with other diagnoses. The 1-year hazard rate (based on 6-year data) was 13.5% for unipolar depressions compared with 5.3% for the rest of the sample, reflecting a hazard ratio of 2.7 (95% confidence interval of 1.8 to 4.0). While unipolar patients are high on some other risk factors (e.g., older age), the higher tardive dyskinesia rate is not accounted for by these variables. We did not find a significantly increased hazard rate in bipolar or schizoaffective patients. Interestingly, lithium treatment was associated with lower hazard rates, given patients' similar exposure to antipsychotic drugs, in all diagnostic categories. (This was statistically significant among schizophrenia, schizoaffective, and bipolar subgroups, but not among unipolar patients, who, in general, are less likely to receive lithium treatment.)

This apparent effect of lithium is of interest in view of animal studies suggesting that administration of lithium concurrently with antipsychotics can reduce the dopamine receptor hypersensitivity associated with chronic dopamine receptor antagonism.[15,16] In addition, as mentioned previously in a retrospective review, Mukherjee et al.[7] found that shorter duration of lithium exposure was associated with greater risk of persistent tardive dyskinesia in bipolar patients.

A number of additional factors may complicate the assessment of tardive dyskinesia risk in patients with affective disorder. In addition to lithium, many patients receive other drugs, antidepressants, and now anticonvulsants. The interactions of these compounds in this context are not well understood; however, we have no substantive data at this point suggesting a significant influence on risk (in either direction). Antidepressants are capable of producing parkinsonian side effects in some vulnerable patients, and there are occasional reports of dyskinesias associated with antidepressants,[17] although these are rarely persistent once the drug is discontinued.

Carbamazepine and valproic acid have been widely used in recent years in the treatment of affective and schizoaffective disorders. Some reports have implicated carbamazepine in the production of abnormal involuntary movements,[18,19] but these are also very infrequent and reversible. Carbamazepine is also capable of reducing blood levels of concurrently administered antipsychotics, adding another potential confound. Valproate treatment can be associated with tremor in the upper extremities in some patients, but has not been associated with movements resembling tardive dyskinesia.

There have also been reports suggesting that mood state may play a role in the presence or severity of abnormal involuntary movements. Cutler and Post[20] were the first to describe increased dyskinesias during a depressed state and a reduction in dyskinetic movements during mania; however, others[21] have suggested that this phenomenon is not seen in most bipolar patients with tardive dyskinesia.

## THE ROLE OF NEW DRUGS

With the introduction of clozapine into clinical practice,[22] it became clear that it was possible to separate antipsychotic effects from the extrapyramidal side effects. Clozapine appears to cause little if any tardive dyskinesia.[23] A number of compounds have now been developed with the hope of significantly reducing these adverse effects.

### Risperidone

Risperidone was developed with the intention of combining dopamine $D_2$ receptor and serotonin 5-$HT_2$ receptor blocking properties. Its efficacy was established in several

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well-designed and well-controlled clinical trials.[24] At doses of 4 to 6 mg/day, risperidone produced no more extrapyramidal side effects than were seen in a placebo-control group, while producing significantly fewer side effects than those seen with patients receiving haloperidol at doses of 10 or 20 mg/day. As the dose of risperidone is increased to 8, 10, or 12 mg/day, the incidence of extrapyramidal side effects increases, but continues to remain below that associated with equivalent doses of haloperidol. Although some cases of tardive dyskinesia have now been reported with risperidone,[25–27] there are no data currently published with which to determine the relative risk of tardive dyskinesia associated with risperidone. Brecher[28] reported preliminary data on 882 patients treated with risperidone for at least 12 weeks, representing 902 patient-years of exposure. The incidence of new cases of tardive dyskinesia was 0.3% in comparison with 2.7% among 73 patients (representing 50 patient-years) treated with haloperidol. As yet, no specific data relating to patients with affective disorders are available.

## Olanzapine

Olanzapine is a chemical with a structure similar to that of clozapine. There are some shared pharmacologic properties between olanzapine and clozapine; however, their clinical actions are not identical. Olanzapine has antagonist effects at $D_1$ and $D_2$ dopamine receptors, as well as at several serotonin receptors and the $\alpha_1$-adrenergic, muscarinic $M_1$, and histaminic $H_1$ receptors. Its affinity for these sites is high. In addition, olanzapine also has affinity for the dopamine $D_4$ receptor as well as 5-$HT_{2A}$, 5-$HT_{2C}$, and 5-$HT_6$, but no affinity for 5-$HT_1$ receptors.[29]

Olanzapine has been studied in a number of large-scale, well-designed, well-controlled trials.[30] The results of these studies suggest that olanzapine in doses of 10 mg/day produces no more motor side effects (extrapyramidal side effects) than those seen in the placebo-control groups. As doses of olanzapine are increased to 16 or 20 mg/day, more extrapyramidal side effects are observed along with a higher use of anticholinergic, antiparkinsonian medication; however, these rates are still well below those associated with 15 to 20 mg of haloperidol per day.

A recent report[31] provides encouraging results that olanzapine may be associated with a lower incidence of tardive dyskinesia than that observed with haloperidol. This study involved patients who continued into double-blind maintenance treatment after completing a short-term controlled trial for acute treatment. To be eligible for the continuation trial, patients had to have responded to the acute phase treatment with a decrease of 40% or more in total score on the Brief Psychiatric Rating Scale or a final score of 18 or less. In addition, they had to be outpatients at the last acute phase visit.

The age, sex, diagnosis, and other characteristics of the 707 olanzapine-treated patients and the 197 haloperidol-treated patients are presented in Table 1. The length of drug treatment was a median of 237 days (range, 42–964 days) for olanzapine and 203 days (range, 42–540 days) for haloperidol. Changes in total Abnormal Involuntary Movement Scale (AIMS) are presented in Table 2 and showed highly significant differences favoring olanzapine on both baseline to endpoint change and baseline to maximum score change.

**Table 1. Characteristics of Patients With Schizophrenia Who Participated in Blind, Controlled, Long-Term Studies of Treatment With Olanzapine or Haloperidol[a]**

| Characteristic | Patients Treated With Olanzapine (N = 707) | | Patients Treated With Haloperidol (N = 197) | | | | |
|---|---|---|---|---|---|---|---|
| | N | % | N | % | p Value[b] | | |
| Sex | | | | | .68 | | |
| Male | 450 | 63.6 | 129 | 65.5 | | | |
| Female | 257 | 36.4 | 68 | 34.5 | | | |
| Origin | | | | | .83 | | |
| White | 594 | 84.0 | 164 | 83.2 | | | |
| African descent | 60 | 8.5 | 17 | 8.6 | | | |
| East or Southeast Asian | 10 | 1.4 | 3 | 1.5 | | | |
| Western Asian | 5 | 0.7 | 2 | 1.0 | | | |
| Hispanic | 25 | 3.5 | 5 | 2.5 | | | |
| Other origin | 13 | 1.8 | 6 | 3.0 | | | |
| Diagnosis type | | | | | .37 | | |
| Schizophrenia | 612 | 86.6 | 175 | 88.8 | | | |
| Schizoaffective | 75 | 10.6 | 20 | 10.2 | | | |
| Schizophreniform | 20 | 2.8 | 2 | 1.0 | | | |
| | Mean | SD | Mean | SD | F | df | p |
| Age (y) | 37.1 | 11.0 | 36.4 | 10.3 | 0.76 | 1,898 | .38 |
| Age at onset of psychosis (y)[c] | 24.5 | 7.8 | 22.9 | 6.4 | 2.35 | 1,895 | .13 |
| Duration of illness (y)[c] | 12.6 | 9.6 | 13.6 | 9.2 | 0.05 | 1,895 | .82 |
| Length of current episode (d)[d] | 470.3 | 1167.3 | 873.0 | 1956.3 | 1.12 | 1,759 | .29 |

[a]From reference 31, with permission.
[b]p values for analyses of categorical variables are from a 2-tailed Fisher exact test; p values for analyses of continuous variables are from an analysis of variance (ANOVA) model containing the terms *treatment*, *protocol*, and *treatment-by-protocol interaction*.
[c]N = 705 for olanzapine-treated patients; N = 196 for haloperidol-treated patients.
[d]N = 603 for olanzapine-treated patients; N = 162 for haloperidol-treated patients.

When patients were categorized by Schooler and Kane criteria,[32] significant differences favoring olanzapine were observed using all 3 measures: any AIMS assessment during the trial, the final 2 AIMS assessments, and the final AIMS assessment (Table 3).

These results are very encouraging in suggesting a lower risk of tardive dyskinesia with olanzapine; however, additional data will be necessary before this is established conclusively. With regard to affective disorders, a total of 95 patients with a diagnosis of schizoaffective disorder participated in these trials. Of the 75 patients receiving olanzapine, none developed tardive dyskinesia and 1 case (5%) was observed among the 20 haloperidol-treated

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Table 2. Change in Abnormal Involuntary Movement Scale (AIMS) Total Score for Patients With Schizophrenia Without Current or Historical Dyskinesia at Baseline Who Participated in Blind, Controlled, Long-Term Studies of Treatment With Olanzapine or Haloperidol[a]

| | Change in Total Score on Abnormal Involuntary Movement Scale | | | | | | |
|---|---|---|---|---|---|---|---|
| | Patients Treated With Olanzapine (N = 707) | | Patients Treated With Haloperidol (N = 197) | | Analysis[b] | | |
| Period | Mean | SD | Mean | SD | F | df | p |
| Baseline to endpoint | –0.13 | 1.59 | 0.36 | 2.04 | 9.02 | 1,898 | .003 |
| Baseline to maximum score (any visit) | 0.80 | 1.93 | 1.52 | 2.52 | 7.92 | 1,898 | .005 |

[a]From reference 31, with permission.
[b]Test of treatment from an ANOVA model containing the terms *treatment*, *protocol*, and *treatment-by-protocol interaction*.

Table 3. Long-Term Treatment-Emergent Dyskinesia in Patients With Schizophrenia Who Participated in Blind, Controlled, Long-Term Studies of Treatment With Olanzapine or Haloperidol[a]

| | Patients With Tardive Dyskinesia[b] | | | | |
|---|---|---|---|---|---|
| | Patients Treated With Olanzapine (N =707) | | Patients Treated With Haloperidol (N=197) | | |
| Time | N | % | N | % | p[c] |
| Any assessment after baseline | 50 | 7.1 | 32 | 16.2 | < .001 |
| Final AIMS assessment | 16 | 2.3 | 15 | 7.6 | .001 |
| Final 2 AIMS assessments | 7 | 1.0 | 9 | 4.6 | .003 |

[a]From reference 31, with permission.
[b]Tardive dyskinesia was defined according to Research Diagnostic Criteria for tardive dyskinesia[32] as a score of 3 or greater on any 1 of the AIMS categorical items 1 through 7 or a score of 2 or greater on any two of the categorical items that were not present at baseline. The median exposure to olanzapine was 237 days (range, 42–964 days) and the median exposure to haloperidol was 203 days (range, 42–540 days).
[c]Two-tailed Fisher exact test.

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patients (G. D. Tollefson, M.D., Ph.D., personal communication, March 1998). These numbers are too small to draw meaningful conclusions, and we must await the availability of additional data specifically on patients with affective disorders. However, there is no reason to assume that a reduced risk among patients with schizophrenia would not also be generalizable to patients with affective disorders.

### Quetiapine

Quetiapine is a novel dibenzothiazepine agent that binds to a wide variety of neurotransmitter sites including dopamine $D_1$ and $D_2$, serotonin 5-$HT_{2A}$ and 5-$HT_{1A}$, and adrenergic $\alpha_1$ and $\alpha_2$ receptor sites. Quetiapine has a considerably higher affinity for serotonin 5-$HT_2$ receptors relative to dopamine $D_2$ receptors. Quetiapine has fewer muscarinic and somewhat fewer $\alpha_1$ receptor blocking properties than observed with clozapine.[33]

A number of large-scale clinical trials have been conducted in the United States and abroad, demonstrating the safety and efficacy of quetiapine. In general, the incidence of extrapyramidal side effects was no different between quetiapine and placebo with respect to rating scale scores or the use of antiparkinsonian medication.[34]

### Ziprasidone

Ziprasidone is chemically unrelated to any other antipsychotic drug currently under development. This is the next new antipsychotic likely to be marketed in the United States. It has potent 5-$HT_{2A}$ antagonism, as well as 5-$HT_{1A}$ and 5-$HT_{1D}$ antagonism. It has very high affinity for the 5-$HT_{2C}$ receptor and is also a potent $D_2$ antagonist. Ziprasidone displays a moderate inhibition of serotonin and norepinephrine reuptake, which distinguishes it from most other antipsychotic agents.[35]

This drug has also been evaluated in a number of clinical trials and has been demonstrated to be effective and well tolerated. Ziprasidone has also been shown to be relatively free of clinically significant extrapyramidal side effects at the dosages studied.[36]

### Sertindole

Sertindole has been marketed in some countries, but is not yet available in the United States. This compound has high affinity for 5-$HT_2$, $D_2$, and $\alpha_1$ receptors; somewhat lower affinity for $D_1$ receptors; and minimal activity at $\alpha_2$, $H_1$, and $M_1$ receptors.[37]

This drug has demonstrated a very low propensity to produce extrapyramidal side effects, even in comparison to only 4 mg of haloperidol.[38] As yet, there are no published reports of tardive dyskinesia with sertindole; however, further long-term experience is necessary.

## CONCLUSION

Clearly, a new generation of antipsychotic drugs is becoming available, and so far they appear to have an advantage over conventional drugs in the area of neurologic side effects. As yet, it is difficult to draw conclusions regarding the relative merits of the new drugs in comparison with each other, because few direct head-to-head trials have been conducted, and dose equivalency considerations will also need to be resolved before drawing firm conclusions.

With regard to tardive dyskinesia, data from our prospective trials[14,39] suggest that patients exhibiting early-occurring extrapyramidal side effects are at substantially greater risk of subsequently developing tardive dyskinesia. This suggests, but by no means establishes, the possibility that those drugs with lower propensity to produce extrapyramidal side effects might also produce less tardive dyskinesia. The early results with olanzapine are encouraging, but large-scale prospectively collected databases will be necessary to establish relative risk.

*Drug names:* carbamazepine (Tegretol and others), clozapine (Clozaril), haloperidol (Haldol and others), quetiapine (Seroquel), olanzapine (Zyprexa), risperidone (Risperdal), valproic acid (Depakene and others).

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## DISCLOSURE OF OFF-LABEL USAGE

The following agents mentioned in this article are *not* indicated for treatment of affective disorder: carbamazepine, valproic acid.

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