Extrapyramidal Side Effects, Tardive Dyskinesia, and the Concept of Atypicality

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The most frequent problems associated with the older generation of antipsychotic agents are extrapyramidal side effects (EPS) and tardive dyskinesia. Neuroleptic-induced EPS are thought to be caused by blockade of nigrostriatal dopamine tracts resulting in a relative increase in cholinergic activity; tardive dyskinesia is less well understood but is thought to be a supersensitivity response to chronic dopamine blockade. The leading hypothesis for the mechanism of action of the newer generation of atypical antipsychotics is the presence of a high serotonin-to-dopamine receptor blockade ratio in the brain. When serotonergic activity is blocked—as is the case with atypical antipsychotics—dopamine release increases and balances out the dopamine blockade effect at postsynaptic receptor sites, which results in few or no EPS. Prospective data indicate that the risk of tardive dyskinesia in patients taking atypical antipsychotics is less than that for those taking typical antipsychotics. This article reviews the mechanisms of neuroleptic-induced EPS and tardive dyskinesia and discusses the relationship between these movement disorders and atypical antipsychotic agents.

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The most frequent problems associated with the older generation of antipsychotic agents are extrapyramidal side effects (EPS) and tardive dyskinesia, and few remedies have been found for these neuroleptic-induced movement disorders. The Nithsdale schizophrenia survey,[1] which followed 271 individuals with schizophrenia over a 10-year period, reported a point prevalence of 27% for parkinsonism, 29% for tardive dyskinesia, and 23% for akathisia or pseudoakathisia; only 44% of the patients surveyed had no movement disorder. In the Yale Tardive Dyskinesia Study,[2] my colleagues and I estimated the risk of persistent tardive dyskinesia in a prospective cohort of 362 chronic psychiatric outpatients who were free of tardive dyskinesia at baseline and were followed for 5 years while taking typical neuroleptic medications. On the basis of the 5-year follow-up using retrospective medication histories, we were able to estimate the cumulative incidence of tardive dyskinesia for up to 25 years of neuroleptic exposure. The years of neuroleptic exposure and estimated risks for tardive dyskinesia were: 0 to 5 years, 31.8%; 5 to 10 years, 49.4%; 10 to 15 years, 56.7%; 15 to 20 years, 64.7%; and 20 to 25 years, 68.4% as shown in Table 1. These findings suggest that tardive dyskinesia is a public health problem and a source of great concern to the psychiatric community as well.

It should come as no surprise that EPS and tardive dyskinesia are prevalent in patients taking traditional antipsychotics when one considers the manner in which these agents and their effects have been identified. In the past, researchers commonly used behavioral measures that involved movements in animals to define compounds with antipsychotic properties. Similarly, clinicians commonly used movement disorders in patients as indicators of antipsychotic effects. The serendipitous discovery of clozapine—which causes few EPS and little tardive dyskinesia—has provided a means to utilize neuroscientific methods to identify the atypical properties of clozapine and hopefully to create new agents that will avoid unwanted adverse effects. This article will review the mechanisms of neuroleptic-induced EPS and tardive dyskinesia and discuss the relationship between these movement disorders and the new generation of atypical antipsychotic agents.

ATYPICAL ANTIPSYCHOTIC AGENTS AND EPS

Neuroleptic-induced EPS are thought to be caused by the blockade of nigrostriatal dopamine tracts resulting in a relative increase in cholinergic activity.[3] Drugs that block cholinergic activity (e.g., antiparkinsonian agents) or drugs that increase striatal dopamine function (e.g., various atypical antipsychotics) correct the biochemical imbalance caused by postsynaptic striatal dopamine blockade.

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Positron emission tomography (PET) and selective radioligands have been used to determine dopamine receptor occupancy induced by neuroleptics in the basal ganglia of drug-treated schizophrenic patients. These studies show that dopamine D_2 occupancy in the basal ganglia is 70% to 90% in patients treated with typical antipsychotic agents at clinically effective doses and that EPS occur with 80% or greater occupancy of the D_2 receptors[4]; less than 60% D_2 blockade may be insufficient to induce a satisfactory antipsychotic response.[5] Monitoring of antiparkinsonian medications administered during neuroleptic treatment of schizophrenic patients is another method for assessing EPS. In a multicenter double-blind placebo-controlled study evaluating the efficacy and safety of sertindole and haloperidol in 497 hospitalized schizophrenic patients, there was a clear dose-response relationship between increasing doses of haloperidol and the use of antiparkinsonian agents.[6]

Table 1. Estimated Risk of Tardive Dyskinesia (TD) (and 95% Confidence Intervals)[a] by Net Years of Previous Neuroleptic Use (Without TD) and Additional Years Taking Neuroleptics: Results of the Yale TD Study, 1985–1990[b]

Years of Previous Neuroleptic Use	Additional Years Taking Neuroleptics				
	5	10	15	20	25
0	0.318 (0.225, 0.429)	0.494 (0.396, 0.592)	0.567 (0.468, 0.662)	0.647 (0.546, 0.736)	0.684 (0.579, 0.774)
5	0.258 (0.177, 0.360)	0.366 (0.266, 0.478)	0.482 (0.369, 0.598)	0.537 (0.411, 0.658)	
10	0.145 (0.072, 0.270)	0.302 (0.189, 0.445)	0.376 (0.241, 0.533)		
15	0.184 (0.092, 0.333)	0.270 (0.145, 0.446)			
20	0.106 (0.030, 0.315)				

[a]Risk estimates are based on the density method, conditional on the number of net years of previous use; confidence-limit estimates are based on a modification of Rothman's method.
[b]From reference 2, with permission.

The pathophysiology of tardive dyskinesia is less well understood but is thought to be a supersensitivity response to chronic dopamine blockade—i.e., the blockade of receptors in the nigrostriatal dopamine pathway causes a proliferation of dopamine receptors on the postsynaptic side of the nigrostriatal tract. It is thought that this state of chronic dopamine supersensitivity is manifested clinically as tardive dyskinesia.[7] Although the theory is inconclusive[8] and unsupported by research, it remains the leading explanation for the development of tardive dyskinesia and is heuristically useful.

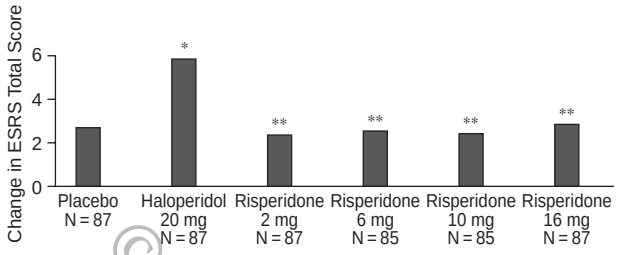
What is the mechanism of action of atypical antipsychotics? The leading hypothesis is the presence of a high serotonin-to-dopamine receptor blockade ratio in the brain[5]; while the various atypical antipsychotics differ in receptor activities, they all share in common a ratio of serotonin-to-dopamine blockade greater than 1. There is evidence for serotonin/dopamine interactions at the level of the basal ganglia in animal models, and serotonergic blockade is thought to play a role in the reduction of risk for EPS associated with atypical agents.[9] Under normal conditions, presynaptic blockade at the serotonin receptor site inhibits or curbs dopamine release. When serotonergic activity is blocked—as is the case with atypical antipsychotics—it is thought that dopamine release increases and balances out the dopamine blockade effect at postsynaptic receptor sites, resulting in few or no EPS. Thus, in essence, serotonin blockade brings the system into balance.

Risperidone and Clozapine

Simpson and Lindenmayer[10] analyzed data from both arms[11,12] of the North American multicenter comparison of risperidone (2 mg, 6 mg, 10 mg, or 16 mg/day), haloperidol (20 mg/day), or placebo for 8 weeks in 253 chronic schizophrenic patients. The severity of EPS was assessed by the Extrapyramidal Symptom Rating Scale (ESRS), and at the clinically most effective risperidone dose (6 mg/day) the mean ESRS change score was not significantly different from that of the placebo group. A significant linear relationship was noted between change scores and increasing risperidone doses on 4 of the 12 ESRS subscales; nevertheless, even at 16 mg/day, mean change scores were lower than in the haloperidol group (Figure 1). A linear relationship between an increasing risperidone dose and administration of antiparkinsonian medications was also apparent.

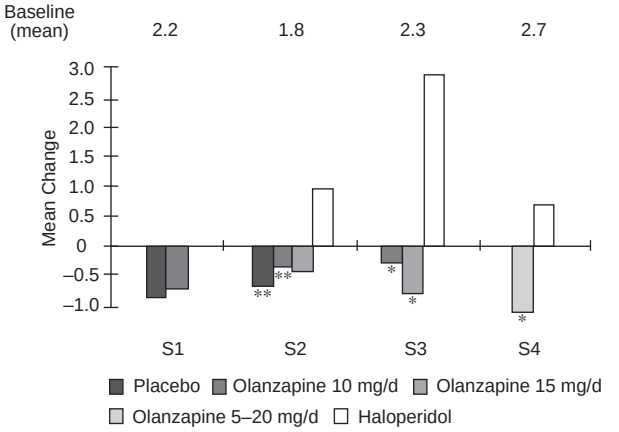
In a PET analysis of central dopamine receptor occupancy in patients treated with traditional antipsychotics and clozapine,[4] a total of 22 schizophrenic patients treated with conventional doses of various classical neuroleptics demonstrated D_2 occupancy of 70% to 80% in the basal ganglia; patients with acute EPS had a higher D_2 occupancy than patients without EPS. In 5 patients treated with clinically effective doses of clozapine, a lower D_2 occupancy of 38% to 63% was observed, and this finding was thought to correlate with the atypicality of the drug and the low frequency of EPS. A PET study of 9 risperidone-treated patients[13] showed that the mean level of D_2 receptor occupancy per drug dose was 66% at 2 mg/day, 73% at 4 mg/day, and 79% at 6 mg/day. Three patients with the highest receptor occupancies exhibited mild EPS although none required antiparkinsonian medications. The emergence of EPS at higher levels of D_2 receptor occupancy suggests that the high 5-HT_2 affinity of risperidone provides a relative protection only from EPS; once the D_2 occupancy exceeds a certain threshold, that protection may be lost. The implication of these clinical studies and PET data point to a ceiling dose for risperidone, perhaps at 6 mg/day.

Figure 1. ESRS for Placebo, Risperidone, and Haloperidol (change in total score)[a]



[a]Data from reference 10. Abbreviation: ESRS = Extrapyramidal Symptom Rating Scale.
*p < .001 vs. placebo.
**p < .001 vs. haloperidol.

Figure 2. Simpson-Angus Scale Changes in Acute Extrapyramidal Symptoms in 4 Olanzapine Studies[a]



[a]From reference 14, with permission. Last observation carried forward.
*p < .001 vs. haloperidol.
**p < .05 vs. haloperidol.

Olanzapine

Beasley et al.[14] summarized the data on the clinical safety of olanzapine from 4 studies of schizophrenia involving 2500 olanzapine-treated patients, 810 haloperidol-treated patients, and 236 placebo patients. Figure 2 shows the mean change in Simpson-Angus Scale (SAS) scores for acute EPS occurring in patients who participated in the studies. In all 4 trials, there was an improvement over baseline in the SAS analysis for EPS in both mid- and high-dose groups of olanzapine-treated patients compared with haloperidol-treated patients. In study 2,[15] the 5- and 10-mg/day olanzapine doses were significantly less associated with EPS than the 10- and 20-mg/day haloperidol doses. Also in study 2, baseline SAS scores in the 15-mg/day olanzapine-treated patients were not statistically significantly different from those of haloperidol-treated patients, but the patients taking olanzapine showed improvement in EPS while patients taking haloperidol showed worsening of symptoms.

A recent PET study by Kapur et al.[5] investigated the binding characteristics of olanzapine to 5-HT_2 and D_2 receptors in 15 schizophrenic patients. Imaging of randomly-assigned patients showed that the D_2 striatal occupancy increased with dose; 12 patients taking olanzapine, 5 mg/day to 20 mg/day, showed 43% to 80% D_2 occupancy while 3 patients taking 30 mg/day to 40 mg/day showed 83% to 88% occupancy. The authors concluded that olanzapine is a potent 5-HT_2 blocker and shows a higher 5-HT_2 than D_2 occupancy at all doses; the D_2 occupancy of olanzapine is higher than that of clozapine and similar to that of risperidone. In the usual clinical dose range (10–20 mg/day) of olanzapine, the D_2 occupancy varies from 71% to 80%, which may account for the freedom from EPS in patients who take this agent.

Clinicians should be forewarned that studies involving PET scans may fail to accurately define patients' clinical status because of the following circumstances: (1) medications are usually administered for a few days only prior to scans, (2) there may be interpatient variability of blood levels per drug dose, and (3) studying the striatum may reflect EPS but not efficacy. Therefore, it is difficult to draw firm conclusions about the relationship of dose, blood levels, and clinical response in PET studies. Thus far, the implication of clinical studies and PET data is that the ceiling dose of olanzapine is less clear than risperidone; additional studies of high dose ranges of olanzapine are needed.

Olanzapine Versus Risperidone

Olanzapine and risperidone, both second-generation atypical antipsychotics, differ by virtue of their chemical structure, spectrum of receptor binding affinities, animal neuropharmacology, pharmacokinetics, and in vivo neuroimaging profile. Thus, it was hypothesized that the 2 compounds would show distinct safety and/or efficacy characteristics. To test this hypothesis, an international multicenter double-blind, 28-week prospective study was conducted involving 339 patients who met DSM-IV criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder.[16] Treatment-emergent EPS—assessed by the SAS and the Barnes Akathisia Scale—were fewer in olanzapine-treated patients (mean dose = 17 mg/day) than in risperidone-treated patients (mean dose = 7 mg/day); these findings also coincided with greater use of anticholinergic medications in risperidone-treated patients. The authors stated that a lower dose range of risperidone and a slower dose titration might have reduced the incidence of EPS in risperidone-treated patients. However, the question remains whether low doses of risperidone will maintain efficacy over time.

Most traditional neuroleptics have a narrow therapeutic-to-toxic index; that is, the separation between the dose that produces efficacy and the one that produces EPS and other

adverse effects is narrow.[17] Researchers who developed the novel antipsychotic drugs set out to substantially widen the distance between the dose that treats psychosis and the one that produces adverse effects.[18,19] Available data and clinical experience suggest that the therapeutic dose threshold for EPS may be wider for olanzapine than for risperidone. Multiple fixed-dose comparisons of the 2 drugs are needed to verify this preliminary impression.

Quetiapine

Arvanitis et al.[20] used 5 fixed doses (75, 150, 300, 600, or 750 mg/day) of the atypical antipsychotic quetiapine to delineate a dose-response relationship and to compare efficacy and tolerability opposite a fixed dose (12 mg/day) of haloperidol and placebo. A total of 361 patients from 26 North American centers with diagnoses of acute exacerbation of chronic schizophrenia per DSM-III-R criteria entered the double-blind, placebo-controlled trial. None of the quetiapine-treated patients—contrasted with 4 haloperidol-treated patients and 1 placebo patient—were withdrawn from the study because of EPS. Moreover, unadjusted mean changes from baseline to endpoint SAS total scores were negative, indicating improvement in EPS for all patient groups except the haloperidol group. Accordingly, the ceiling dose of quetiapine relative to EPS remains unclear.

ATYPICAL ANTIPSYCHOTIC AGENTS AND TARDIVE DYSKINESIA

Do Fewer EPS Predict Less Tardive Dyskinesia?

Clinicians and researchers have long been interested in the relationship between tardive dyskinesia and EPS. As stated above, neuroleptic-induced EPS are likely caused by blockade of nigrostriatal dopamine tracts,[3] and tardive dyskinesia is thought to be a supersensitivity response to chronic dopamine blockade.[7] The supersensitivity theory would predict that patients who develop early neuroleptic-induced EPS will develop tardive dyskinesia. As early as 1972, Crane[21] hypothesized that tardive dyskinesia is more likely to occur in patients who experience early EPS. The clinical logic underlying this hypothesis was that the appearance of EPS early in the course of exposure to neuroleptic medications was indicative of pathology that would eventually evolve into tardive dyskinesia. Direct support for this hypothesis can be found in various incidence studies.

Kane et al.[22] compared the incidence of tardive dyskinesia in 369 relatively young neuroleptic-treated patients who had no history of EPS with that of 52 neuroleptic-treated patients who exhibited severe EPS; patients in the latter group were 2.3 times more likely to develop tardive dyskinesia. The strongest data supporting the hypothesis were reported by Saltz et al.,[23] who investigated the incidence of tardive dyskinesia in elderly individuals just beginning treatment with antipsychotic drugs. Researchers found that the presence of EPS early in treatment was a predictor of tardive dyskinesia in a newly-exposed elderly population. These findings were replicated by Jeste et al.,[24] who studied 266 middle-aged and elderly outpatients with a median duration of 21 days of total lifetime neuroleptic exposure prior to study entry. Patients were treated with either a high- or low-potency neuroleptic and maintained at relatively low doses. The cumulative incidence of tardive dyskinesia was 26%, 52%, and 60% after 1, 2, and 3 years of treatment, respectively.

Two incidence studies found no evidence for support of the hypothesis. Chatterjee et al.[25] found no correlation in the prevalence of EPS and spontaneous dyskinesia in neuroleptic-naive, first-episode schizophrenic patients. However, the follow-up period may have been too short to identify enough incident cases of tardive dyskinesia to demonstrate a relationship between the 2 adverse movement disorders. Among long-term outpatients maintained with neuroleptic medications in the Yale Tardive Dyskinesia Study,[26] our group found no baseline relationship of tardive dyskinesia to antiparkinsonian drug use and no clinical findings of EPS or history of EPS. This study may have failed to identify such a relationship because the clinical history was retrospective and may not have accurately identified early EPS.

If an antipsychotic agent causes few EPS—and if few EPS early in treatment are prognostic of less tardive dyskinesia—will the antipsychotic cause less tardive dyskinesia? Prospective data indicate that the risk for tardive dyskinesia is less with administration of the atypical antipsychotic agents clozapine and olanzapine than for the neuroleptic haloperidol.

Clozapine

To determine if chronic exposure to clozapine could cause tardive dyskinesia, Kane et al.[27] utilized prospective data on abnormal involuntary movements derived from 28 at-risk schizophrenic or schizoaffective patients who had received clozapine for at least 1 year. The patients were monitored with the modified Simpson Dyskinesia Scale every 3 months, and findings were compared with another group of patients with similar diagnoses who were treated with a variety of typical neuroleptics for at least 1 year. Two patients in the clozapine-treated group—both of whom had ratings of questionable tardive dyskinesia at baseline—were rated as having mild tardive dyskinesia. A survival analysis comparing patients in the clozapine-treated group with those in the neuroleptic-treated group showed a lower risk of tardive dyskinesia developing in the clozapine-treated group; however, the authors were unable to definitely conclude whether chronic exposure to clozapine could cause tardive dyskinesia.

Olanzapine

In a recently-published, long-term, follow-up study, Beasley et al.[28] utilized data from a double-blind extension

Table 2. Incidence Rate/Year of Tardive Dyskinesia: Olanzapine Versus Haloperidol[a]

Treatment	N	N with TD	Incidence Rate/y
Olanzapine	513	2	0.006
Haloperidol	114	5	0.072

[a]Adapted from reference 28. Abbreviation: TD = tardive dyskinesia.

of 3 studies to compare incidence rates of tardive dyskinesia in 513 olanzapine-treated patients and 114 haloperidol-treated patients. Abnormal Involuntary Movement Scale examinations were performed twice weekly to weekly in the 6-week acute phase and every 2 weeks to every 2 months during the extension phase. Cases of tardive dyskinesia that occurred during the first 6 weeks were eliminated from the study, because researchers attributed them to either withdrawal cases or overlooked baseline cases. In doses of 5 mg to 20 mg/day, 2 olanzapine-treated patients—compared with 5 haloperidol-treated patients—developed tardive dyskinesia; thus, haloperidol-treated patients had an estimated tardive dyskinesia incidence rate/year 12 times higher than that of olanzapine-treated patients (Table 2). Patients included in this study had long histories of illness and treatment with antipsychotics, and incidence rates should ultimately be evaluated in prospective comparison studies among drug-naive patients. In summary, studies of the new antipsychotic medications point to a lower risk for development of tardive dyskinesia. If these studies are accurate, atypical antipsychotic agents will quickly replace the traditional agents.

CONCLUSION

What are the considerations for use of atypical antipsychotics as standard care in the treatment of schizophrenic patients in the present clinical environment? Definition of a patient's *stability* is changing because of evidence that atypical agents improve functioning and promote rehabilitation. Thus, the "stable" patient, i.e. the one who is staying out of the hospital, may now be able to function better. He or she should be able to move toward greater independence and maximal potential. At a minimum, patients should be informed about the option of taking atypical antipsychotics; if the risk of relapse from switching drugs is weighed by the physician and felt to be manageable, treatment with the new antipsychotics should be considered. In unstable or first-break schizophrenics or those who have been untreated for a long period of time, atypical antipsychotics are the drugs of choice.

Extrapyramidal symptoms and tardive dyskinesia are commonly associated with the use of traditional neuroleptics and are a source of great concern to the psychiatric community. The mechanism of neuroleptic-induced EPS is thought to be blockade of nigrostriatal dopamine tracts that results in an increase in cholinergic activity; tardive dyskinesia is thought to be the clinical manifestation of a supersensitivity response to chronic dopamine blockade. The new generation of atypical antipsychotics shares a common serotonin-to-dopamine blockade ratio that may play a role in reduction of risk of EPS. Early studies are showing a diminished risk of tardive dyskinesia with atypical in comparison to typical antipsychotics. While additional studies are indicated, these results should have a profound impact on clinical practice. Data and clinical studies are emerging that support the first-line use of atypical antipsychotics in patients with schizophrenia. In today's clinical environment, patients should be apprised of the advantages of the new agents and given the option of taking the medications if the attending physician believes the risk of switching drugs is manageable.

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

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

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