

# Assessment of EPS and Tardive Dyskinesia in Clinical Trials

## Collaborative Working Group on Clinical Trial Evaluations

The incidence of acute extrapyramidal symptoms (EPS)—akathisia, dystonia, and parkinsonism—associated with traditional antipsychotics varies, but most researchers agree that neuroleptic-induced EPS occur in 50% to 75% of patients who take conventional antipsychotics. Atypical antipsychotics were developed to widen the therapeutic index and to reduce EPS. Although the mechanisms are unclear, the risk of EPS is less with the novel antipsychotics than with conventional drugs, and agents that produce low levels of acute EPS are likely to produce less tardive dyskinesia. Nevertheless, clinicians should exercise caution when comparing data from investigations of the novel antipsychotics and, until long-term data become available, should administer the new drugs at doses below the EPS-producing level.  
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Extrapyramidal symptoms (EPS) have long been recognized as a cardinal feature of neuroleptic drugs; one of the main purposes for developing the atypical antipsychotics was to reduce EPS. Regardless of the side effect profiles of specific compounds, the entire class of conventional neuroleptics produces EPS. In fact, the antipsychotic effects and motor effects of neuroleptic drugs were formerly believed to be inextricably linked, and the ideal bioassay for defining the therapeutic antipsychotic dose—under the neuroleptic threshold concept—was to find the lowest dose that produced EPS. If the concept was carefully applied, the neuroleptic dose was titrated until the medication induced subtle EPS. In actual practice, however, the dosage was often increased until the EPS became intolerable, and the induction of toxic rather than subtle side effects became part of the neuroleptic profile. Most traditional neuroleptics have a narrow therapeutic index, which means that the separation between the dose that produces efficacy and the one that produces EPS and other adverse effects is narrow. Thus, researchers who developed the novel antipsychotic drugs set out to substantially widen the therapeutic index.

The relative lack of EPS is a major advantage for the atypical antipsychotics. However, it is important to clarify that when EPS rates are not significantly different from

those for placebo treatment, it does not necessarily mean absolutely no EPS for new antipsychotics. The issue is the research design. Patients who enter studies of the new antipsychotics may have been previously treated with traditional neuroleptics, and EPS may have persisted from this prior drug treatment. It usually takes a few weeks for previously administered neuroleptics to wash out and for the EPS effects of the old drug to resolve. Nevertheless, the EPS induced by prior treatment are rated in the new study because the research rules require that any EPS—even those occurring within the first weeks—be scored. Some of these patients may be randomly assigned to a placebo group. Therefore, the baseline of EPS in the placebo group is not zero, but some level above zero. Several recent clinical studies<sup>1–5</sup> of atypical antipsychotics have found that EPS were rated as present at least once in approximately 10% to 20% of patients taking placebo. Although some of these ratings occurred in the first few weeks of the study when the prior neuroleptic was washing out, the statistical effect is to raise the placebo-induced EPS rate. Thus, if a new drug does produce only minor EPS problems, these might not be detected in early research programs. Given this caveat, the new agents promise to be major advancements in solving the EPS problems of existing antipsychotic drug therapy.

With the evidence now available, 1 point that can be made with some certainty is that the risk of EPS is less with novel antipsychotics than with conventional drugs, although the mechanisms that account for the differences are unclear. When an appropriate antipsychotic is being considered for use, the emphasis, in some cases, on treatment of the negative symptoms of schizophrenia has overshadowed the importance of minimizing the risk of EPS. Clinicians should understand that the advantage of decreased EPS of the newer antipsychotics is a compelling reason to use them as first-line therapies.

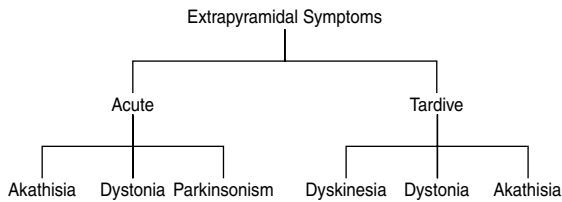
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Figure 1. Neuroleptic-Induced EPS\*



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Clinical trials may report rates of EPS differently, and caution should be used when comparing rates between trials. Some trials report EPS ratings, and others report rates of anticholinergic drug use.

**EPS**

The incidence of acute EPS (akathisia, dystonia, and parkinsonism) associated with traditional antipsychotics varies, but most researchers agree that neuroleptic-induced EPS occur in 50% to 75% of patients who take conventional antipsychotics.<sup>6</sup> There are both acute and tardive EPS (Figure 1).<sup>7</sup>

Neuroleptic-induced acute akathisia is characterized by subjective and/or objective feelings of restlessness that include a sense of anxiety, an inability to relax, jitteriness, pacing, rocking motions while sitting, and the rapid alteration of sitting with standing. Middle-aged women are at increased risk for akathisia, and its time course is similar to that of neuroleptic-induced parkinsonism.<sup>8</sup> Akathisia may occur at a lower rate with atypical antipsychotics than with conventional antipsychotics. The subjective rating of akathisia, which is generally rated on the Barnes Rating Scale for Drug-Induced Akathisia (BAS) can frequently be confused for partially-treated psychotic anxiety. Restlessness—which can be part of the clinical picture of psychosis—may occasionally be mistaken for akathisia. In general, the incidence of akathisia in schizophrenic patients is higher than the incidence of parkinsonism, and in relatively mild or borderline EPS, akathisia may be obvious while rigidity may not yet have surfaced. Acute dystonic reactions can occur within minutes to hours after the onset of neuroleptic treatment and can be potentially fatal, as in the case of acute laryngeal-pharyngeal dystonia. At the very least, acute dystonia is an extremely uncomfortable side effect that can adversely influence compliance. Acute dystonia has been reported in over 60% of patients undergoing acute treatment with haloperidol.<sup>7</sup> Parkinsonian motor symptoms of tremor, rigidity, and bradykinesia (slow movement) are also accompanied by the mental symptoms of bradyphrenia (slow thinking) and cognitive impairment.

The mental counterparts to EPS, which are less well-known, can be likened to the motoric side effects (Table 1).<sup>9</sup> Symptoms akin to parkinsonism and bradykinesia in-

Table 1. Motor and Mental Side Effects of Neuroleptic Drugs\*

Motor Side Effect	Mental Side Effect
Parkinsonism, bradykinesia	Bradyphrenia “mental parkinsonism” emotional indifference blunted affect anhedonia, no pleasure “social parkinsonism” reduced initiative, apathia reduced energy lack of social drive “cognitive parkinsonism” slow thought processes concentration problems
Dystonia	Anxiety
Objective akathisia	Subjective akathisia, restlessness, anxiety

\*Adapted from reference 9.

clude anhedonia and emotional indifference (“mental parkinsonism”); reduced energy and lack of social drive (“social parkinsonism”); and poor concentration (“cognitive parkinsonism”). Both dystonia and objective akathisia are linked to anxiety. Differentiating mental side effects from primary motor symptoms is often difficult, and these mental symptoms can masquerade as secondary or pseudonegative symptoms that restrict the clinical gains potentially available from traditional neuroleptics.

**TARDIVE DYSKINESIA**

The traditional neuroleptics appear to carry similar liability for tardive dyskinesia; cumulative incidence after 5 to 10 years of treatment is 30% to 50%.<sup>10</sup> These rates may be higher in middle-aged women and elderly patients (up to 60%) and may account for a high rate of noncompliance. This potentially irreversible side effect also has played a major role in stimulating research for novel antipsychotic drugs with a more favorable side effect profile. It has been hypothesized that conventional antipsychotics with a low incidence of EPS will also have low liability for tardive dyskinesia. Data supporting this proposal come from a prospective study<sup>11</sup> of elderly individuals taking neuroleptic drugs, which showed that those individuals in whom EPS developed had a substantially higher likelihood of tardive dyskinesia, whereas patients with low EPS also had a low risk for tardive dyskinesia. The accumulated evidence with clozapine also supports the hypothesis of the association between fewer EPS and less tardive dyskinesia. The early results with risperidone and olanzapine suggest that these agents will also have a low liability for tardive dyskinesia if used in doses that are unlikely to produce EPS.

In vitro binding profiles have been created for the atypical antipsychotics and compared with that of haloperidol.<sup>12,13</sup> The notion that relatively weak dopamine D<sub>2</sub> antagonism coupled with potent serotonergic effects, includ-

ing antagonism of the 5-HT<sub>2</sub> receptor subtype, is critical to atypicality—in terms of low EPS and high therapeutic efficacy—is the single most important influence in current antipsychotic drug development.<sup>14</sup> The favorable EPS clinical findings of the atypical agents are supported by a number of preclinical studies that have fostered their development. Serotonin 5-HT<sub>2</sub> receptor antagonism, purported to have a role in mitigating EPS, is a characteristic that is common to clozapine, risperidone, and olanzapine. Additionally, clozapine and olanzapine have been shown to have CNS site selectivity for differentially antagonistic limbic (antipsychotic) dopamine receptors but little antagonistic effect on the basal ganglia (EPS) dopamine receptors.<sup>6</sup> Recent studies of the development of EPS and tardive dyskinesia associated with the novel antipsychotics clozapine, risperidone, olanzapine, and quetiapine will be reviewed in this article.

## NOVEL ANTIPSYCHOTICS

### Clozapine

The first of the novel antipsychotics, clozapine, is noted for its low liability for producing EPS and tardive dyskinesia, but because of the serious side effect of agranulocytosis, it is indicated only for management of moderately or severely ill schizophrenic patients who fail to respond adequately to standard antipsychotic drug treatment or who are neuroleptic-intolerant. In the early trials, Kane et al.<sup>15</sup> found that clozapine-treated patients showed improvement in EPS through a 6-week study. Long-term experience with clozapine has shown that the agent has a motor and mental side effect profile that is distinct from classical neuroleptics. It may produce a parkinsonian-like bradykinesia and mild akathisia, but rigidity and tremors are rare. In patients who have tardive dyskinesia induced from other neuroleptics, dyskinesia disappears after clozapine starts in about half the cases. Tardive dyskinesia in clozapine-treated patients is most likely due to previous treatment with classical neuroleptics.

Some schizophrenic patients have dyskinetic movements when they begin antipsychotic treatment. In contrast with typical antipsychotics, which tend to rapidly mask symptoms of tardive dyskinesia after treatment starts or the dose is reduced, tardive dyskinesia symptoms tend to diminish more gradually after clozapine is begun.<sup>14</sup> Although it is unknown whether clozapine produces lasting improvement in tardive dyskinesia, the drug undoubtedly has a low risk for inducing tardive dyskinesia and is also beneficial, in low doses, in the treatment of levodopa-induced dyskinesia and psychosis in Parkinson's disease.<sup>16</sup>

### Risperidone

At low doses, risperidone, which was released in 1993, produces fewer EPS than traditional antipsychotics and lacks many of the serious side effects of clozapine. Risperidone

usually produces few EPS in the recommended dose range of 2 to 6 mg/day, but may cause dose-related EPS within and certainly above this range.<sup>6</sup> Although there was a dose-related increase in EPS associated with risperidone treatment in the clinical trials of risperidone, the proportion of patients taking risperidone at its most efficacious dose of 6 mg/day who required antiparkinson medications was no greater than the proportion in those taking placebo.<sup>3,17</sup>

In the Canadian Multicenter Risperidone Study, patients showed significantly ( $p < .05$ ) lower total dyskinetic scores on the Extrapyramidal Symptom Rating Scale (ESRS) than those patients who received placebo, which suggested that risperidone had a potent antidyskinetic effect.<sup>18</sup> To explore the beneficial antidyskinetic effect of risperidone, a post hoc analysis<sup>10</sup> was performed on a group of patients ( $N = 48$ ) who met the Schooler and Kane research diagnostic criteria for tardive dyskinesia at baseline or during double-blind treatment and had a Clinical Global Impressions (CGI) severity of dyskinesia score of 5 or greater (moderately severe) at baseline. This additional analysis revealed a greater antidyskinetic effect of risperidone than previously noted. Patients with tardive dyskinesia treated with risperidone (6 and 10 mg/day) had significantly lower ESRS dyskinetic symptom scores ( $p < .05$ ) compared with those of patients given placebo. Additionally, risperidone-treated (6 mg/day) patients with moderately severe tardive dyskinesia experienced a mean 1.2-point decrease in the total ESRS dyskinesia score from baseline to their worst score on double-blind treatment; this effect was statistically significant compared with placebo ( $p < .01$ ) and haloperidol ( $p < .05$ ). The greatest beneficial effect on dyskinetic symptoms was observed in patients with severe tardive dyskinesia, with risperidone-treated (6 and 10 mg/day) patients having significantly lower CGI severity of dyskinesia and total dyskinetic symptom scores compared with those of patients given placebo ( $p < .05$ ). The difference on the total dyskinesia score was also significant for the risperidone (6 mg/day) group compared with the haloperidol group.

The prevalence of EPS in first-episode patients before, during, and after treatment with risperidone has also been studied. Studying first-episode patients has the advantages of assessing signs and symptoms of illness before potentially confounding effects of treatment occur that ultimately become difficult to distinguish from the progression of illness. Kopala et al.<sup>19</sup> found that distinct EPS were present in 3 (14%) of 22 first-episode, drug-naive patients, but all were free of EPS after 7 weeks of risperidone treatment. Given the maximum dose (5–8 mg/day) of risperidone, 32% ( $N = 7$ ) of the total sample developed mild drug-induced akathisia or very mild parkinsonian rigidity, both of which diminished with a reduction in dosage. No EPS were observed in patients treated with 2 to 4 mg/day of risperidone.

A recently published open-label study of the first 3 years of general risperidone use in 1100 patients, 503 of whom had taken risperidone for at least 1 year, has been reported by Gutierrez-Esteinou and Grebb.<sup>20</sup> The authors reported an annual incidence of tardive dyskinesia of 0.3% in patients taking 7.6 to 9.4 mg/day of risperidone, compared with the historical data of an annual incidence of 5% to 10% in patients taking conventional neuroleptics. The low liability of risperidone for EPS also suggested that patients were more likely to be compliant. A double-blind comparison of olanzapine versus risperidone<sup>21</sup> in the treatment of schizophrenia and other psychotic disorders suggested that the incidence of EPS was statistically significantly lower in olanzapine-treated patients than in risperidone-treated patients but a mean modal risperidone dose of  $7.2 \pm 2.7$  mg/day was used, which is probably higher than necessary for efficacy. Risperidone, when used in an adequate dose range, and olanzapine both produce fewer EPS as compared with haloperidol. The databases of both risperidone and olanzapine suggest a lower risk of tardive dyskinesia than with conventional neuroleptics, but data are incomplete and long-term studies are awaited.

### Olanzapine

Olanzapine, which was released in 1996, also causes fewer EPS than traditional antipsychotics.<sup>6</sup> However, olanzapine, which has anticholinergic effects, was associated with akathisia in 5% of the patients enrolled in the short-term clinical trials.<sup>22</sup> In a double-blind, acute phase study, Beasley et al.<sup>2</sup> reported that no acute dystonia was observed with olanzapine. Treatment-emergent parkinsonism, assessed by the Simpson-Angus Neurologic Rating Scale, occurred in olanzapine-treated patients (12.5–17.5 mg/day) at approximately one third the rate of haloperidol-treated patients. Akathisia, assessed by the Barnes Akathisia Scale, occurred in olanzapine-treated patients (12.5–17.5 mg/day) at approximately one half the rate of haloperidol-treated patients. In another study, Tran et al.<sup>23</sup> analyzed the EPS data of 1796 patients treated with 5 to 20 mg/day of olanzapine and 810 patients treated with the same dose of haloperidol. Olanzapine was statistically ( $p < .02$ ) superior to haloperidol in 4 analyses related to emergence of EPS and in 2 analyses related to outcome. Data suggested that olanzapine exhibited a statistically significantly lower EPS profile than haloperidol at comparably effective antipsychotic doses. Fewer olanzapine-treated patients than haloperidol-treated patients discontinued treatment because of EPS, which provides additional evidence that atypical antipsychotics are linked with better compliance than are conventional neuroleptics.

A study reported by Tollefson et al.<sup>24</sup> analyzed data from 3 actively controlled and blind long-term responder studies of subjects with schizophrenia, schizophreniform disorder, or schizoaffective disorder. The subjects had no evidence of tardive dyskinesia at baseline and were treated

with olanzapine or haloperidol at dosages up to 20 mg/day. The incidence of newly emergent tardive dyskinesia at any visit after baseline, at the final visit, and at the final 2 clinical assessments was statistically significantly lower among olanzapine-treated patients than among haloperidol-treated patients. At the final 2 AIMS assessments, 7 (1.0%) of the olanzapine treatment group ( $N = 707$ ) compared with 9 (4.6%) of the haloperidol treatment group ( $N = 197$ ) exhibited a new onset of tardive dyskinesia. This is more evidence that agents with low EPS potential are also likely to have low tardive dyskinesia potential.

### Quetiapine

Quetiapine was approved for use in 1997. It is an atypical antipsychotic with greater affinity for 5-HT<sub>2</sub> receptors than for D<sub>2</sub> dopamine receptors. In a multicenter, double-blind, placebo-controlled trial,<sup>25</sup> EPS were assessed by the Simpson-Angus Neurologic Rating Scale, the BAS, and the AIMS. Analyses of Simpson-Angus Scale total scores and BAS scores, the similar incidences of motor system adverse events across quetiapine and placebo treatment groups, and the limited need for anticholinergic medications suggest a minimal liability of EPS with quetiapine. In a double-blind, placebo-controlled, 6-week trial from 26 North American centers,<sup>26</sup> the incidence of EPS in quetiapine-treated patients was no different from placebo across the dose range studied. The drug has been on the market for only a short period of time, and more studies are needed to determine if treatment-emergent tardive dyskinesia will be a problem.

### ABRUPT DISCONTINUATION OF A DRUG

Abruptly discontinuing an antipsychotic can lead to a number of autonomic effects, including nausea, vomiting, and diarrhea, which probably result from cholinergic hyperactivity that occurs due to the release of anticholinergic effects of the antipsychotic.<sup>27</sup> Clinicians who have changed patients from drugs associated with a high incidence of EPS, such as haloperidol or fluphenazine, to those associated with a lower incidence of EPS, such as risperidone or clozapine, have often been disappointed by a lack of improvement or even worsening in side effects, but it is possible that some of the worsening could be attributed to withdrawal from the original drug. In older clinical studies, patients who were switched from an antipsychotic to placebo sometimes experienced a persistence of parkinsonism and a worsening of restlessness. These effects are more likely when the patient's antiparkinson medications are discontinued at the same time that treatment with the atypical drug is started. The observations of increased side effects and worsening of psychosis suggest that the switch from one antipsychotic to another should usually be done gradually and antiparkinson medications removed slowly.

## CONCLUSION

A drug that produces low levels of EPS is likely to produce less tardive dyskinesia, but clinicians should be wary of comparing data from different investigations. Because long-term data are incomplete on the potential for EPS and tardive dyskinesia suppression among the various atypical antipsychotics, the wisest course for practitioners is to use the new drugs at doses that are below the EPS-producing level.

*Drug names:* clozapine (Clozaril), fluphenazine (Prolixin and generic brands), haloperidol (Haldol and generic brands), levodopa (Larodopa), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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## DISCLOSURE OF OFF-LABEL USAGE

The authors of this article have determined that, to the best of their clinical estimations, no investigational or off-label information about pharmaceutical agents has been presented that is outside Food and Drug Administration-approved labeling.