The Scourge of EPS: Have Atypical Antipsychotics Solved the Problem?

What Are EPS?

Treatment-emergent extrapyramidal symptoms (EPS) are frequent, distressing, and disabling complications of standard antipsychotics. They include, stated Professor Kasper in his introduction, akathisia, muscle spasms (dystonia), involuntary grinding or chewing movements (dyskinesia), and symptoms resembling Parkinson's disease (parkinsonism), e.g., tremor, rigidity, bradykinesia. All these types of movement disorder can manifest alone or in a mixed syndrome. Akathisia is a form of restlessness that can include both observed restlessness, manifesting as inability to sit still for any length of time, and a subtle sense of inner restlessness. It is an extremely debilitating side effect and has been linked to violence and suicide. Up to 90% of patients treated with standard antipsychotics develop EPS, and about 20% of them develop tardive dyskinesia (TD), which is 4 times higher than the prevalence of spontaneous dyskinesia in untreated individuals. It is postulated that antipsychotics with a high risk of EPS may predispose patients to develop TD through dopamine antagonistic action, inducing the gradual development of dopamine hypersensitivity as a maladaptive response.

Impact of EPS on Patients

Tardive dyskinesia, akathisia, and poor employment prospects for the patient, thereby reducing quality of life. In addition, the presence of EPS may have a negative impact on the overall outcome of treatment by causing significant noncompliance. For many, noncompliance with antipsychotic medication typically results in relapse, which may require extended hospitalizations or rehospitalization and place additional demands on health care resources and costs.

Professor Kasper described how clinicians have historically underestimated the damage that EPS inflicts on patient compliance, treatment outcome, and the therapeutic alliance between patient and psychiatrist. Hoge et al. investigated the reasons for noncompliance among 63 patients treated with antipsychotic medications and found that whereas the highest proportion of patients (37%) reported side effects to be the most frequent reason for noncompliance, only 7% of their clinicians recognized this association. Similarly, patients also highlighted “denial of illness” as a common reason for noncompliance; this reason was linked with the patients’ underlying intolerance and intense fear of the side effects of antipsychotics.

Implications of EPS in Special Patient Populations

The use of standard antipsychotics is hindered by an inherently high risk of EPS and TD in certain patient groups, including the elderly, adolescents, and neurologically impaired patients (for example, those who have dementia or any form of parkinsonism). Psychiatrists often attempt to lessen this risk by using low doses of...
standard antipsychotics. However, in practice, such doses are often subtherapeutic and remain associated with EPS, thus compromising effectiveness and resulting in poor treatment outcome. In his presentation, Dr. Juncos stated that approximately 50% of elderly patients receiving standard antipsychotics experience treatment-emergent EPS, and that the incidence of these side effects is correlated with the number of years of drug exposure. Dr. Kane also highlighted how the risk of TD in elderly patients (mean age = 77 years) receiving neuroleptics was 26% after 1 year and rose to 53% after 3 years (measured by Schooler-Kane criteria). These risks are much higher than those of TD in younger counterparts (mean age = 29 years), which were calculated to be 5% after the first year, 19% in the fourth year, and 26% after 6 years of treatment. Movement disorders tend to persist in the elderly, and patients may poorly tolerate the usual treatments for EPS (anticholinergics, β-blockers, or benzodiazepines).

Patients with Parkinson’s disease are the highest risk population for developing treatment-emergent EPS. Each year, approximately 10% of these patients will develop motor fluctuations and dyskinesias, either due to the progression of their Parkinson’s disease or as an adverse effect of treatment with levodopa. These effects and their progressive extrapyramidal disorder increase their risk of developing EPS while receiving antipsychotics.

As the potential for developing treatment-emergent EPS increases with long-term use of antipsychotics and because treatment may be lifelong, adolescent patients are at particular risk of the long-term consequences of EPS.

What does the newer generation of atypical antipsychotics offer to address treatment-emergent EPS? The “Atypical Revolution”: Providing an EPS Advantage

The need to treat the multifaceted symptoms of schizophrenia more effectively while reducing the incidence of EPS has fueled the development of a new class of antipsychotics, the atypicals, most of which became available in the 1990s. The underlying characteristic of atypicality is a reduced propensity to induce motor system disturbance compared with standard antipsychotics such as haloperidol.

There is justifiable enthusiasm, said Dr. Tandon, about the benefits of the atypical antipsychotics. They are at least as effective as standard agents in treating the positive symptoms of schizophrenia and are more effective at improving negative symptoms. A study in schizophrenia patients, comparing the effects of the atypical agent sertindole with 3 different doses of the standard antipsychotic haloperidol, showed that even the lowest dose of haloperidol (4 mg/day) was associated with a significantly higher number of reports of EPS than any dose of sertindole (12, 20, and 24 mg/day) (p < .05). During the trial, there was little change from baseline in EPS and involuntary movements as assessed by the Simpson-Angus Scale (SAS) (total score, p < .001) and the Abnormal Involuntary Movement Scale (AIMS), which suggested that patients should improve compliance with treatment and provide a lower risk of relapse.

Atypicals in EPS-Vulnerable Patients

Although first-line prescription of atypical agents should benefit all relevant patient groups, their preferred use over standard antipsychotics is especially appropriate in patients who are vulnerable to treatment-emergent EPS. Long-term use of quetiapine in the elderly is associated with a low incidence of EPS. In a population of elderly patients (mean age = 76 years) receiving quetiapine (up to 800 mg/day, median daily dose = 138 mg) for 52 weeks, only 13% experienced EPS. Similarly, no patient developed TD during the study. The number of patients still taking quetiapine at the end of the study (48%) was higher than the retention rate normally expected in this population, which, Dr. Juncos concluded, suggests that quetiapine is a well-tolerated drug for the treatment of psychosis in the elderly.

In a study of Parkinson’s disease patients (N = 40) treated with quetiapine, there was no worsening in Parkinsonism motor symptoms or disability throughout 52 weeks of treatment at a median dose of 75 mg/day. Indeed, an improvement in motor signs and disability was noted at 12 weeks, as measured by the Unified Parkinson’s Disease Rating Scale (UPDRS) (total score, p < .001) and the Modified Schwab and England Activities of Daily Living Scale (p < .05). During the trial, there was little change from baseline in EPS and involuntary movements as assessed by the Simpson-Angus Scale (SAS) and the Abnormal Involuntary Movement Scale (AIMS), which suggested there were no treatment-emergent EPS or TD. Although part of the observed benefit in baseline EPS may have been attributed to a washout effect from stopping all other previous antipsychotics at baseline, these data show that, in this particularly vulnerable patient population, no significant treatment-emergent EPS were associated with quetiapine.

The management of psychosis in patients with Lewy body dementia is particularly difficult due to the severe EPS sensitivity in this patient population. Dementia with Lewy bodies is the second most common cause of dementia in the elderly, and it can oc-
cur in both Parkinson’s and Alzheimer’s disease.\textsuperscript{28–30}

A pilot trial\textsuperscript{31} of quetiapine (25–300 mg/day) in elderly patients suffering from dementia, parkinsonism, and psychosis has suggested that quetiapine may be appropriate for controlling psychosis in this EPS-susceptible population without inducing or exacerbating motor abnormalities. During the 24-week open trial, the 9 patients experienced no worsening of motor function (as measured by their total SAS and UPDRS scores), and by study end, motor function had improved in 6 patients.\textsuperscript{31}

Clozapine, like quetiapine, can be used to effectively treat drug-induced psychosis in Parkinson’s disease patients without worsening their parkinsonism. Data from the Parkinson Study Group\textsuperscript{32} suggest low-dose clozapine (≤ 50 mg/day) is an effective treatment for drug-induced psychosis in Parkinson’s disease that will not worsen parkinsonism. Additionally, clozapine helped parkinsonism tremor as evidenced in the UPDRS tremor subscore (p = .02).

Preliminary data suggest that Parkinson’s disease patients may be particularly sensitive to the EPS effects of olanzapine.\textsuperscript{33,34} In these patients, EPS emerge at lower doses (2.5–5 mg/day) than those capable of inducing EPS in patients without Parkinson’s disease.\textsuperscript{35} Furthermore, the limited data from these studies suggest that the incidence of EPS with olanzapine is likely to be higher in patients with Parkinson’s disease, especially those with complex parkinsonism syndromes (such as Lewy body dementia and progressive supranuclear palsy) than in other elderly and psychotic patients.\textsuperscript{33,34}

Dr. Juncos also discussed preliminary data from a subset of elderly patients (N = 78) with Alzheimer’s disease\textsuperscript{36} receiving quetiapine (up to 800 mg/day) for 52 weeks in an open-label trial. Significant improvements in baseline EPS were reported, as measured by the SAS, at weeks 12 and 52 (p = .0006 and p = .0061 [last observation carried forward], respectively). There was no apparent change in mean AIMS score during the trial, which suggested that there was no evidence of treatment-emergent TD. These data further support the notion that quetiapine is unlikely to cause treatment-emergent EPS in this population. Data from a 12-week evaluation of 3 fixed daily doses of risperidone (0.5 mg, 1.0 mg, and 2.0 mg) versus placebo in elderly patients with dementia suggest that the incidence of treatment-emergent EPS with risperidone is dose-related (6.7%, 12.8%, and 21.2%, respectively, vs. placebo, 7.4%).\textsuperscript{37}

Preliminary data from a small group of adolescents (N = 10, mean age = 13.1 years) with psychotic disorders who received quetiapine for 21 days showed that preexisting EPS improved consistently during the trial, with significant improvements from baseline in SAS and Barnes Akathisia Scale scores on day 20 (p ≤ .05).\textsuperscript{38} However, further long-term studies are needed to fully evaluate the use of the atypical antipsychotics in this younger population.

**Are All Atypical Antipsychotics the Same?**

Dr. Tandon questioned whether all atypicals provide the same EPS advantage. Although as a class, atypicals are associated with a lower risk of treatment-emergent EPS than typical antipsychotics, data are emerging to suggest that the ease and consistency with which atypicals achieve this EPS benefit vary. Such variations are linked to each drug’s unique pharmacology, and differences in their EPS profiles have been demonstrated both preclinically and clinically. In the general schizophrenia patient population, clozapine and quetiapine have a low risk of EPS across their entire clinical dosage range, whereas the incidence of EPS for risperidone and olanzapine is dose related.

**Preclinical Differences**

The risk of EPS with an antipsychotic is related to its ratio of serotonin-2A (5-HT\textsubscript{2A}) to striatal dopamine-2 (D\textsubscript{2}) receptor occupancy rates.\textsuperscript{39} Although high occupancy of striatal D\textsubscript{2} receptors (> 80%) by antipsychotics will induce treatment-emergent EPS in most patients,\textsuperscript{40} in theory, a coincident blockade of a sufficiently high population of 5-HT\textsubscript{2A} receptors could mitigate this effect. However, in practice, whether mechanisms involved in the development of EPS can be negated completely by 5-HT\textsubscript{2A} receptor blockade depends on the balance of 5-HT\textsubscript{2A}/striatal D\textsubscript{2} receptor occupancy. Within the antipsychotic class, the lowest risk of EPS is associated with the atypical antipsychotics and appears to be related to their high 5-HT\textsubscript{2A}/low D\textsubscript{2} receptor occupancy ratio.\textsuperscript{40}

**Striatal D\textsubscript{2} receptor occupancy rates.** Pharmacodynamic investigations of antipsychotics have suggested that a striatal D\textsubscript{2} occupancy rate of below 70% is not associated with EPS side effects. However, it has been suggested that an occupancy rate of 70% to 80% increases the risk of inducing treatment-emergent EPS and that at occupancy rates > 80%, EPS could be anticipated in most patients.\textsuperscript{40} Data from single photon emission computed tomography (SPECT) and positron emission tomography suggest clozapine and the standard antipsychotic haloperidol are positioned at 2 extremes with regard to risk of EPS because of their respective low and high striatal D\textsubscript{2} occu-
Professor Kasper presented collated data from studies using SPECT (Figure 1), which suggest that clozapine, 475 mg/day, because of its low D₂ receptor occupancy rate (26%), has a small attendant risk of EPS, whereas haloperidol, 13 mg/day, is correlated with a high risk of EPS because of a high striatal D₂ receptor occupancy rate (88%). From Figure 1, quetiapine, 600 mg/day, is the only atypical antipsychotic with a striatal D₂ receptor occupancy similar to clozapine, 475 mg/day, which suggests that it should also be associated with less EPS. In contrast, evidence of high striatal D₂ receptor occupancy rates was provided for risperidone, 8 mg/day (75%); olanzapine, 18 mg/day (73%); and zotepine, 225 mg/day (73%), suggesting that at these doses, these atypicals would be associated with a greater risk of EPS than clozapine, 475 mg/day, or quetiapine, 600 mg/day (Figure 1). The striatal D₂ receptor occupancy rate for 3 mg/day of risperidone (64%) is lower than that for 8 mg/day (75%) and is consistent with the dose-related increases of EPS seen with risperidone in clinical trials⁴¹ (Figure 1). This rationale may also explain the dose-related increases of EPS reported with olanzapine in clinical trials⁴³ (Figure 3).

5-HT₂A receptor occupancy rates. Professor Kasper explained how the degree of 5-HT₂A receptor blockade is an important feature of an antipsychotic since it may mitigate the treatment-emergent EPS side effects caused by binding of the agent to the D₂ receptor. For the currently available atypical antipsychotics, data suggest that clozapine and quetiapine are the only agents to possess a low D₂ receptor occupancy rate coupled with a 5-HT₂A receptor occupancy rate⁴⁰ that appears to be of sufficient magnitude to provide low risk of EPS at any clinically used dose. Thus, both clozapine and quetiapine may be given at the therapeutic dose that meets an individual patient’s needs without the induction of EPS above placebo level.⁴³⁴⁴ Although olanzapine, risperidone, ziprasidone, and zotepine have high 5-HT₂A occupancy, they also have intermediate D₂ receptor occupancy that may result in appreciable EPS at higher doses.⁴⁰ In contrast, haloperidol has a low 5-HT₂A receptor occupancy rate coupled with a high D₂ receptor occupancy rate,⁴⁰ which correlates with its high risk of inducing EPS.

The high 5-HT₂A receptor occupancy of clozapine and quetiapine may explain their ability to mitigate EPS carryover from previously administered antipsychotics. This ameliorative effect has been recorded during a
placebo-controlled, dose-response study in which patients were switched from their previous antipsychotic medication to either quetiapine or haloperidol. For patients switched to quetiapine, the incidence of EPS with any dose of quetiapine was no different from that with placebo. This amelioration was also observed in the open-label study reported by Dr. Juncos in Parkinson’s disease patients, in which motor scores improved for 12 weeks following initiation of quetiapine and slowly drifted back to baseline by week 52.

Clinical Differences

**EPS response.** The tendency of antipsychotics to cause EPS can be predicted from the degree of separation between their efficacy and EPS dose-response curves (Figure 4). These data, obtained from animal models, show that EPS side effects of standard antipsychotics are closely related to their antipsychotic effect. In contrast, the atypicals as a class achieve a broader separation between the antipsychotic and EPS effects, Dr. Tandon explained. However, the degree of separation varies between the different atypical agents. Clozapine has the broadest degree of separation between efficacy and EPS, expressed clinically by its favorable EPS profile. Of the newer atypicals, quetiapine exhibits a broad degree of separation between efficacy and induction of EPS comparable to that of clozapine. Hence, like clozapine, quetiapine should be associated with a lower risk of EPS than the other atypicals. In contrast, risperidone, olanzapine, and ziprasidone have a narrower separation between antipsychotic effect and EPS. This supports the low frequency of EPS observed clinically at low doses of these drugs and the increasing rate of EPS observed at intermediate and higher doses.

**Placebo-controlled trials.** Data from clinical trials in general schizophrenia patients have borne out the predictions that atypical antipsychotics have different propensities to cause EPS. Dr. Tandon described the results from an 8-week study of fixed doses of risperidone and haloperidol, which showed risperidone to be associated with a dose-related increase in EPS (see Figure 2). While low doses of risperidone (1 and 4 mg/day) were associated with the lowest levels of EPS, intermediate doses (8 and 12 mg/day) caused levels significantly greater than those observed at the low doses (p < .05). At the highest dose tested (16 mg/day), the level of EPS with risperidone was comparable to that observed with haloperidol, 10 mg/day. Similarly, clinical data with olanzapine show that EPS appeared to be dose depen-
dent\textsuperscript{15} (see Figure 3). In a placebo-controlled trial,\textsuperscript{16} no significant difference in EPS level was observed between low-dose olanzapine (2.5–7.5 mg/day) and placebo. However, significantly more akathisia was observed at the doses of olanzapine that are commonly used in clinical practice (> 7.5 mg/day). Furthermore, a trend toward a dose-related increase in parkinsonian effects was also observed within this dose range. Preliminary data also suggest that the frequency of EPS with ziprasidone may be dose related. In a 6-week placebo-controlled trial\textsuperscript{16} of 2 fixed doses of ziprasidone (80 and 160 mg/day), both doses resulted in about twice the rate of akathisia than observed with placebo. In contrast, a study\textsuperscript{16} of fixed doses of quetiapine, 75, 150, 300, 600, and 750 mg/day, failed to show any dose dependency for EPS, even at the highest recommended doses. Dr. Tandon and Professor Kasper both pointed out that the occurrence of total EPS events and the usage of medication required to treat EPS remained at or below placebo level throughout this dose range (reference 44 and J. Gavin, Ph.D., data on file, AstraZeneca) (Figure 5).

**Comparative trials.** Dr. Tandon outlined some comparative data to consolidate the differing propensities of atypical antipsychotics to cause EPS. A 16-week open study\textsuperscript{47} of risperidone (mean dose = 4.4 mg/day at 16 weeks) and quetiapine (mean dose = 253.9 mg/day at 16 weeks) reported that by study end, 4.5% of quetiapine patients required anticholinergics to treat EPS compared with 19.6% of patients in the risperidone group (Figure 6). In this study, the odds of having EPS that required adjustment of medication or addition of anti-EPS medication for a risperidone-treated patient were approximately 6 times greater than for a quetiapine-treated patient (p < .001).

**Tardive dyskinesia and akathisia.** Dr. Kane described how onset of treatment-emergent EPS increases the risk for TD.\textsuperscript{2,4} Patients consider TD, along with akathisia, to be the most debilitating of the EPS symptoms. Since all the atypical antipsychotics have less risk of EPS than standard agents, it may also be expected that they have a correspondingly lower risk of TD. Dr. Kane explained. However, risperidone, olanzapine, and ziprasidone have an increased association with EPS at higher doses, and consequently the risk of TD with these agents could follow the same pattern. In contrast, TD has been very rarely associated with clozapine treatment.\textsuperscript{52} Similarly, preliminary data from 301 patients aged between 18 and 65 years who received quetiapine for > 2 years suggest the incidence of TD with quetiapine is 0.4% per year (measured by Schooler-Kane criteria\textsuperscript{11}; J. Gavin, Ph.D., data on file, AstraZeneca). The risk of TD with quetiapine therefore seems to be lower than that seen with standard agents in relatively young popula-

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**Figure 5. Incidence of Patients With Extrapyramidal Symptoms (EPS) and Proportion of Total Patients Receiving Benztropine Mesylate During 6 Weeks of Treatment With Quetiapine**

![Figure 5](image1)

*J. Gavin, Ph.D., data on file, AstraZeneca.

**Figure 6. Comparison of the Cumulative Percentage of Patients Requiring Concomitant Antiepileptic Symptoms Medication During 16 Weeks of Treatment With Risperidone or Quetiapine**

![Figure 6](image2)

*Data from Mullen et al.\textsuperscript{47}
tions. Since the incidence of EPS with quetiapine, like that with clozapine, remains at placebo level across its entire dose range (references 43 and 44 and J. Gavin, Ph.D., data on file, AstraZeneca; see Figure 5), it would be anticipated that any reduced risk of TD would also apply to all its recommended doses.

Although atypical agents are perceived to have a lower risk of akathisia compared with standard agents, again there are differences within the atypical class. A summary analysis of the frequency of akathisia reported in quetiapine phase 2/3 controlled clinical trials showed that quetiapine was associated with a placebo-level occurrence of akathisia (3.2% and 2.4%, respectively), whereas the corresponding frequency with risperidone (15.4%) was similar to that reported for haloperidol (20.0%) (J. Gavin, Ph.D., data on file, AstraZeneca).

Conclusion: Implications for Clinical Practice

Compliance with antipsychotic medication is fundamental to a successful treatment outcome, which fosters and maintains the therapeutic alliance between the psychiatrist and the patient. The recently introduced atypical antipsychotics have a substantially lower risk of EPS than standard antipsychotics, which is likely to lead to improved patient acceptability and compliance with long-term treatment, thus minimizing the risk of relapse. Ultimately these benefits should help in the successful management of patients with schizophrenia, something not as readily achievable with the standard agents.

However, the degree of separation between efficacy and risk of EPS is different among all the atypicals. Dose-response studies in animals and clinical evidence suggest that there are 2 discrete types of atypicals. In one subgroup (risperidone, olanzapine, and potentially ziprasidone), EPS effects are masked at low doses, whereas in the second subgroup (clozapine and quetiapine), minimal EPS effects are unaffected by dose. Dose-response curves predict that risperidone and olanzapine should have a closer association between efficacy and EPS than clozapine and quetiapine. This translates into an increasing risk of EPS as the dose rises, as has been reported with risperidone and olanzapine in clinical trials. Data from clinical trials also suggest that EPS with ziprasidone may be dose dependent. In contrast, clozapine and quetiapine are associated with placebo-level EPS across their entire dose ranges, suggesting that these may be the “cleanest” atypicals with respect to EPS avoidance.

 Emerging data suggest that the features of the atypicals demonstrated in the general schizophrenic population may also apply to patients at particular risk of EPS. These data show quetiapine to be associated with a low incidence of EPS, and thus potentially a low risk of TD, in elderly and adolescent populations and in patients with Alzheimer’s or Parkinson’s disease. The results in patients with Parkinson’s disease are particularly interesting since their underlying extrapyramidal disorder makes them highly susceptible to treatment-emergent EPS. In addition, the lack of significant EPS in patients with Lewy body dementia treated with quetiapine suggests that the likelihood of any other population developing EPS while taking quetiapine should be very low.

Quetiapine appears to be a suitable atypical antipsychotic for both the general and EPS-vulnerable patient populations because it allows for doses to be individualized to patients’ needs without the induction of treatment-emergent EPS above placebo level. Although clozapine, like quetiapine, has very low risk of treatment-emergent EPS in both patient populations, its use in clinical practice is limited because of its potential to cause agranulocytosis. Similarly, the dose-related EPS seen with risperidone and olanzapine at higher doses may restrict the usage of these drugs in certain patients. For example, use of olanzapine in patients with Parkinson’s disease may be limited by the apparent sensitivity of these patients to the drug’s EPS effects.

It is important for psychiatrists to recognize the differences between the atypical antipsychotics, i.e., the degree of separation between EPS and efficacy, in terms of each agent’s specific pharmacologic profile. Understanding these differences should guide the use of atypical antipsychotics in clinical practice, utilizing their full therapeutic benefit in individual patients and improving quality of life for both patients and caregivers.

References

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