

The Continuing Problem of Extrapyrimal Symptoms: Strategies for Avoidance and Effective Treatment

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Antipsychotic agents remain the most effective treatment for both acute and chronic schizophrenia. However, conventional antipsychotic agents are frequently associated with significant side effects including, perhaps most notably, extrapyramidal symptoms (EPS). The emergence of EPS can significantly compromise patient compliance with treatment and can have profound effects on long-term treatment outcomes. Providing effective symptom relief with minimal side effects and without inducing EPS is, therefore, a primary goal in the treatment of schizophrenia. Atypical antipsychotic agents are now regarded as first-line therapies for the treatment of schizophrenia because of their lower propensity to induce EPS compared with conventional antipsychotics, and evidence exists that these agents are associated with a lower relapse rate, which perhaps reflects an improvement in patient compliance. *(J Clin Psychiatry 1999;60[suppl 23]:20-24)*

Antipsychotic agents remain the most effective treatment for acute and chronic schizophrenia. However, the association of the conventional agents with neurologic adverse effects—extrapyramidal symptoms (EPS)—can limit their usefulness. EPS are abnormalities in the coordination and integration of body movements and can be painful and disfiguring. Clinically, it may be useful to divide these symptoms into those which most often appear early during antipsychotic treatment (akathisia, dystonia, and parkinsonism) and the later (tardive) manifestations, notably tardive dyskinesia (TD).

Up to 75% of patients treated with conventional antipsychotic agents will experience some degree of EPS.¹ The emergence of EPS following the initiation of conventional antipsychotic therapy constitutes an additional burden on schizophrenic patients and can have serious implications for patient satisfaction and compliance with treatment. Furthermore, such effects may even counteract therapeutic efficacy and deter social integration, with serious implications for long-term outcomes.

While EPS are usually reversible at first, and may resolve on reduction or discontinuation of conventional antipsychotic therapy, in vulnerable patients they may progress to an irreversible stage and persist even after treatment discontinuation. Unfortunately, it is not possible to predict which patients will progress to the persistent forms of EPS, highlighting the need to avoid such effects when treating schizophrenia.

Providing effective symptom relief without inducing EPS is, therefore, a primary goal in the treatment of schizophrenia. The main characteristics of antipsychotic-associated EPS are outlined in this article, followed by a discussion of the place of the atypical antipsychotics (clozapine, risperidone, olanzapine, and quetiapine), with their generally lower propensity to induce EPS, in the treatment of schizophrenia.

EXTRAPYRAMIDAL SYMPTOMS

Akathisia

Akathisia is a subjective sense of inner restlessness, mental unease, irritability, and/or dysphoria and may even lead to an aggravation of psychotic symptoms. Akathisia is often evidenced by pacing, rocking, or shifting from foot to foot. Symptoms may appear within hours or days of initiating conventional antipsychotic therapy, and approximately 25% of patients will experience some level of akathisia, although some estimates are as high as 75%.²

Dystonia

Dystonia occurs most commonly within 12 to 48 hours of beginning or increasing the dose of conventional antipsychotic treatment and is characterized by involuntary muscle contractions. These are usually in the head (mouth and eyes) and neck regions, but can extend to the trunk and limbs. The prevalence of dystonia appears to be dependent on the presence of risk factors such as age and gender and occurs most often in young males.³ When dystonia becomes irreversible (tardive dystonia), it is one of the most disabling and untreatable adverse effects in psychiatry.

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Parkinsonism

Like the idiopathic disorder, tremor, bradykinesia, or akinesia (slowing or absence of movements), and sometimes rigidity, are all features of conventional antipsychotic-associated parkinsonism. In addition, mental aspects such as a slowing of thoughts (bradyphrenia) and cognitive impairments can be as disabling as the motor features of this syndrome, interfering with the activities of daily living. Approximately 50% of patients receiving conventional antipsychotics at modest doses will experience some level of parkinsonism, which usually develops within days or weeks of starting treatment. Women and elderly patients appear to be most at risk of developing parkinsonism.

Tardive Dyskinesia

TD involves involuntary, repetitive movements, usually of the mouth and face, such as chewing and tongue protrusion. Between 15% and 20% of patients receiving conventional antipsychotics experience some degree of TD; in certain high-risk patient groups such as the elderly, prevalence rates may be as high as 70%.⁴ The precise etiology of TD remains unclear, but may be a direct result of the long-term effects of conventional antipsychotics on the central nervous system. Alternatively, TD may be the result of the disease process of the psychotic illness or an effect of advancing age, or, indeed, a combination of these variables. Comorbid conditions such as affective disorders and diabetes mellitus are also risk factors for the development of TD, although the etiologic basis for this is unclear. TD can result in serious physical and psychosocial complications, since it may affect both mobility and physical appearance.

EPS AND CONVENTIONAL ANTIPSYCHOTICS

Despite the widespread awareness of EPS, it appears that clinicians may seriously underestimate the prevalence of these syndromes. A recent survey found that while almost 90% of patients reported EPS arising from antipsychotic treatment, approximately 60% of psychiatrists and just 20% of nurses reported that their patients had experienced EPS.⁵ This discrepancy may arise because certain EPS (for example, bradykinesia) are not apparent unless the patient is observed when standing, walking, or performing simple voluntary movements. For example, abnormal finger position or finger dyskinesia and akathisia may not be seen until the patient has stood for a short while.⁶ When a patient is using conventional antipsychotics, regular and specific assessments for EPS are important and should include observation of the patient while seated and walking, checking of the arms and

Quetiapine in the Management of Treatment-Emergent Tardive Dyskinesia and Parkinsonian Side Effects: A Case Report

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Antipsychotic agents remain the most effective treatment for schizophrenia. However, their association with extrapyramidal symptoms (EPS) and tardive dyskinesia (TD) can compromise patient compliance. This case study illustrates the utility of the atypical antipsychotic agent quetiapine in a schizophrenic patient with drug-induced parkinsonism and TD.

Case report. Mr. R (age 35 years) was first seen by a consultant psychiatrist at a local police station following an attack by local youths. He displayed poor self-care, auditory hallucinations, and disordered thoughts and subsequently received a diagnosis of paranoid schizophrenia (DSM-IV). Although Mr. R admitted that the voices had been persistent over the past 2 years, he lacked insight and felt he did not require treatment. He was admitted to an acute psychiatric ward under Section 2 of the 1983 (U.K.) Mental Health Act.

Mr. R initially received an intramuscular depot injection of flupenthixol in an attempt to ensure treatment delivery following discharge. The auditory hallucinations subsided slowly over the next 3 to 4 weeks, although marked poverty of thought was noted. Parkinsonian side effects (mask-like face and tremor) were treated with oral procyclidine that had to be prescribed over the duration of the depot treatment. He was discharged after 2 months on treatment with a depot injection every 2 weeks.

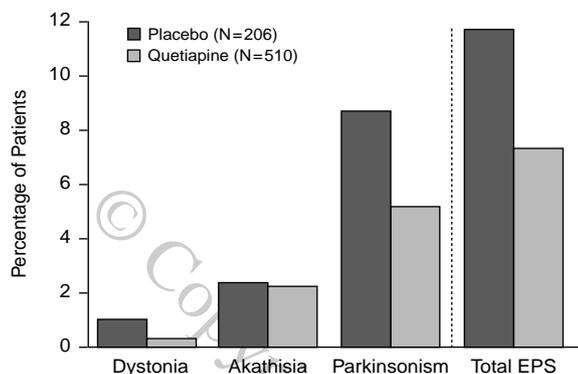
Mr. R was seen in the clinic several times following discharge and on each occasion he was noted to have quite marked tremor. Four months after discharge, Mr. R developed TD of the wrists and upper limbs, and there was profound cogwheel rigidity. He also had a mask-like face, blunted affect, and poverty of thought, and he complained of occasional breakthroughs of voices. Mr. R was switched to oral quetiapine, and his other medications were discontinued. The quetiapine dosage was titrated from 50 mg twice daily to a maximum of 150 mg twice daily over 7 days.

Three months after starting quetiapine treatment, Mr. R was completely free of psychotic symptoms. He was more animated and made better eye contact. His conversation, although relatively sparse, was no longer monosyllabic, and he had taken up swimming again and was shopping 3 times a week. The tremor and rigidity had gone and his TD, although still present to a mild degree, had improved markedly.

Treatment-emergent EPS, TD, and other side effects are frequently associated with antipsychotic therapy and can prove particularly troublesome to patients. This case study illustrates the significantly reduced burden in this respect of the atypical antipsychotic quetiapine. Although in this case, the maximum quetiapine dose was 300 mg/day, it is important to note that, even at the highest recommended doses, quetiapine is associated with only placebo-equivalent levels of EPS, thus allowing the clinician the valuable opportunity to titrate dose against ongoing symptoms.

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Figure 1. Percentage of Patients Developing Acute Extrapyrarnidal Symptoms (EPS) and EPS-Related Dystonia, Akathisia, and Parkinsonism While Receiving Either Quetiapine or Placebo in Placebo-Controlled Clinical Trials^a



^aAdapted from Yeung et al.¹⁷ Patients may have experienced more than 1 EPS adverse event.

wrists for rigidity, and observation during simple voluntary movements.

The treatment of schizophrenia often involves a process of risk-benefit analysis. While conventional antipsychotic treatment is generally effective in relieving the positive symptoms of schizophrenia, the emergence of EPS and other adverse effects can compromise patient compliance and thereby eventual outcome. The long-term nature of schizophrenia means that maintaining compliance is a significant clinical challenge, particularly if the treatment is causing the patient considerable distress or discomfort.

Most conventional antipsychotics have a narrow therapeutic window between efficacy and emergence of EPS. Lower dosages, or less potent conventional antipsychotics, are generally associated with less severe EPS. As dosage or potency of conventional agents increases, so does the severity of the symptoms. When using conventional agents, achieving a dosage regimen that provides optimal symptom relief with minimal EPS and other adverse effects can be a long and distressing process.

The introduction of additional pharmacologic agents for the treatment of adverse effects may permit the maintenance of therapeutic doses of the conventional antipsychotic, although the risk of tardive EPS remains. β -Blockers may relieve the symptoms of akathisia, and anticholinergic agents may relieve dystonia and parkinsonism. However, the introduction of additional pharmacologic agents can themselves add to the adverse-event burden. For example, anticholinergic agents can induce delirium or memory deficits and even a worsening of psychotic symptoms. Therefore, the prophylactic use of anticholinergic agents is not recommended.⁷ In addition, increasingly complex medication regimens may further compromise patient compliance with treatment.

ATYPICAL ANTIPSYCHOTICS IN THE MANAGEMENT OF EPS

Atypical antipsychotics are now regarded as first-line therapies for the treatment of schizophrenia because of their lower EPS and adverse-event burden compared with that of conventional antipsychotics.⁸ Comparative studies have shown considerably lower relapse rates with atypicals, suggesting increased patient compliance, which in turn is likely to be the result of the more benign adverse event and EPS profiles.

A range of atypical antipsychotic agents are available for the treatment of schizophrenia, including clozapine, risperidone, olanzapine, and quetiapine. As a group, the atypical antipsychotics are at least as effective in the treatment of schizophrenia as the conventional agents, more effective in certain patient groups, and have a far lower propensity to induce clinically significant EPS.

Clozapine was the first marketed atypical antipsychotic, and its efficacy compared with that of conventional agents, even in treatment-refractory patients, represented a significant breakthrough in the management of schizophrenia.⁹ However, clozapine is associated with a small risk of agranulocytosis, restricting its utilization. Even so, clozapine remains useful, especially for treatment-resistant patients. The incidence of EPS is significantly lower compared with conventional agents, and may be as low as 5%.¹⁰

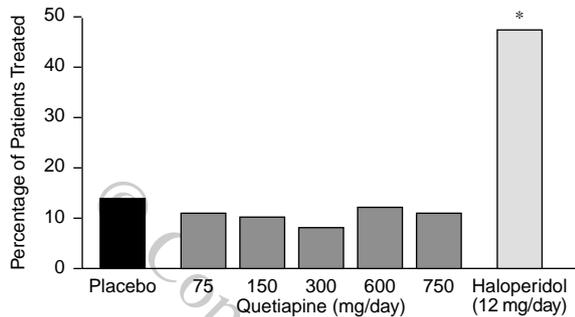
Unlike clozapine, neither risperidone nor olanzapine is associated with a significant risk of agranulocytosis, and, at lower doses, these atypicals have a more benign EPS profile than conventional antipsychotics. However, both agents are associated with EPS at higher doses.^{11,12} At dosages above 6 mg/day, risperidone is regarded as a more conventional agent, with EPS increasing as dosage increases.¹³ Also, olanzapine dosages of 10 to 20 mg/day may be associated with EPS,¹⁴ and the rate of akathisia increases as dosage increases, although it is associated with lower rates of TD compared with haloperidol.¹⁵

Quetiapine

Quetiapine is the latest addition to the atypical antipsychotics. Unlike risperidone and olanzapine, quetiapine has a low propensity to induce EPS that is maintained across all dosages (75–750 mg/day).¹⁶ In a pooled data analysis of 4 placebo-controlled studies, quetiapine (75–750 mg/day; N = 510) was associated with no more EPS than placebo (N = 206) (Figure 1).¹⁷

The proportion of patients who developed EPS was significantly lower with quetiapine than with haloperidol (40% vs. 8%), with statistically significant differences in favor of quetiapine for the incidence of dystonia, akathisia, and parkinsonism.¹⁸ In 1997, Peuskens and Link¹⁹ reported differences in favor of quetiapine versus chlorpromazine using the Barnes Global Clinical Assessment of

Figure 2. Percentage of Patients Requiring Anticholinergic Medication to Treat EPS During 6 Weeks of Treatment With Placebo, Quetiapine (75–750 mg/day), or Haloperidol (12 mg/day)^a



^aAdapted from Yeung et al.¹⁷
* $p < .001$ vs. quetiapine (1 study).

Akathisia item. These differences reached statistical significance in favor of quetiapine after 4 weeks of treatment.

The requirement for additional medication provides another indicator in the assessment of EPS. Meats¹⁸ reported that overall, only 8.6% (44/510) of patients treated with quetiapine required additional anticholinergic medication compared with 12.6% (26/206) of patients treated with placebo. In a placebo-controlled, multiple fixed-dose comparison with haloperidol, 12% or fewer patients treated with quetiapine at any dosage between 75 and 750 mg/day required biperiden, compared with 14% of those who received placebo and 48% of those who received haloperidol (Figure 2).¹⁷ In an additional double-blind study, 49% of patients who received haloperidol also required additional anticholinergic medication, compared with 13% of patients who received quetiapine ($p < .001$).²⁰ Withdrawal from treatment due to EPS may reflect the subjective response of patients and indicate likely treatment outcomes in the clinical setting. In a double-blind comparative study, no patients treated with quetiapine were withdrawn due to EPS, whereas 10 patients treated with haloperidol were withdrawn.²⁰

The low propensity for quetiapine to induce EPS and its overall relatively benign side effect profile would appear to translate into high levels of patient satisfaction and acceptability. Hellewell et al.²¹ evaluated the views of 129 patients who had been receiving quetiapine for at least 6 months (mean = 19.9 months; range, 6.1–47.2 months). Over 75% of patients were very or extremely satisfied with quetiapine. Seventy-four percent of patients reported no side effects; 23.3%, mild side effects; and 2.3%, moderate side effects over the previous month of treatment, and patients were able to identify improvements in their quality of life.

Case Studies

The cases of Mr. R²² and Ms. B²³ illustrate many of the issues discussed in this article. Mr. R's case highlights the

Clinical Heterogeneity Between Atypical Antipsychotics in the Treatment of Schizophrenia: A Case Report

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This case study illustrates the clinical heterogeneity that exists between atypical antipsychotics used in the treatment of schizophrenia, particularly with regard to extrapyramidal symptoms (EPS) and other adverse effects.

Case report. Ms. B, a 31-year-old woman, first presented to the clinic (Caracas, Venezuela) in March 1998. Over the previous 8 months, she had begun to experience auditory hallucinations and delusions (visual hallucinations were suspected), which were becoming increasingly paranoid. Ms. B's social functioning was affected to the extent that she withdrew from her postgraduate university studies and isolated herself within the family home. It was established that Ms. B had a history of cannabis and cocaine abuse, although this was not felt to be sufficiently intense to account for the current symptoms. A diagnosis of schizophrenic disorder, paranoid subtype (F20.0/ICD-10) was made.

Risperidone was prescribed initially at 1 mg twice daily for 2 days, then titrated to 8 mg/day (4 mg twice daily). The clinical manifestations began to subside after 4 weeks. However, in the fifth week it was necessary to add 2 mg of biperiden to her treatment regimen owing to the appearance of EPS. After 2 months, Ms. B was free of symptoms, and the risperidone dose was titrated downward to 2 mg twice daily. Below this dose her delusions reappeared, and it was not possible to withdraw biperiden even at the lowest effective risperidone dosage. Ms. B remained nonpsychotic, although side effects such as sedation, rigidity, and amenorrhea proved problematic and threatened her compliance with treatment.

In August 1998, quetiapine treatment was initiated at 50 mg in the morning and 100 mg at night. This dose was reduced to 100 mg/day taken at night after the patient reported sedation and drowsiness. Within 7 days of treatment at the lower quetiapine dose, the patient reported, "I feel as if I have awakened after months of being asleep." Ms. B's symptoms were controlled, her menses resumed, and treatment-related side effects (sedation, drowsiness, EPS) were minimized. Such improvements were thought likely to ensure good compliance.

In September 1998, Ms. B resumed her university studies and was looking forward to resuming her social life. She will receive quetiapine for at least 2 years with 3 yearly clinic visits.

In summary, Ms. B's symptoms responded to risperidone treatment after several weeks, and she proved particularly sensitive to the side effects and EPS caused by this antipsychotic. Quetiapine treatment offered Ms. B rapid, effective symptom control without EPS, to which she appeared sensitive, and with minimal side effects, which is expected to ensure her continued compliance with treatment and a positive clinical outcome.

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fact that while conventional antipsychotics may be effective in the relief of the positive symptoms of schizophrenia, their propensity to induce EPS can have serious implications for quality of life and compliance with treatment. For Mr. R, a switch to quetiapine offered effective symptom control and a significantly reduced EPS burden. The case of Ms. B illustrates the clinical heterogeneity between the atypical antipsychotics. In this case, risperidone treatment led to the appearance of side effects and EPS that she found intolerable and that threatened her compliance with treatment. Again, treatment with quetiapine offered this patient effective relief from her symptoms without EPS.

SUMMARY

The atypical antipsychotics are associated with far fewer EPS than conventional agents. However, considerable differences remain in the side effect profiles of the various antipsychotics. Quetiapine is well tolerated and has a relatively low propensity to cause EPS, even when high dosages are needed for individualized optimal antipsychotic efficacy, during both acute and long-term treatment. In addition to its use as a first-line treatment for schizophrenia, quetiapine may also prove useful in patient groups particularly sensitive to EPS such as the young, the elderly, or patients experiencing their first episode.

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

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