First-Episode Schizophrenia: The Importance of Early Intervention and Subjective Tolerability

Siegfried Kasper, M.D.

The majority of patients with schizophrenia are likely to experience multiple episodes. Furthermore, because schizophrenia may be a progressive encephalopathy, the longer patients experience symptoms, the more likely they are to suffer lasting impairment. Early identification and pharmacologic intervention to relieve symptoms and prevent relapse are likely to have a profound effect on the long-term clinical outcomes. The choice of antipsychotic can be critical in determining long-term treatment outcomes for first-episode patients who are often particularly sensitive to the potential side effects of treatment such as extrapyramidal symptoms (EPS). Atypical antipsychotics have proven efficacy against both the positive and negative symptoms of schizophrenia, have a lower propensity to cause EPS than conventional agents, and may also improve cognitive functioning. Their use is therefore recommended, particularly for those patients experiencing their first episode.

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Schizophrenia is a chronic, debilitating disorder and is generally regarded as the most devastating of all the mental illnesses with a lifetime prevalence rate between 0.5% and 1.0%. In addition to often severe functional impairment, the disorder is associated with significant morbidity and mortality; approximately 10% of schizophrenia patients will die by suicide.[1] Clinically, schizophrenia is a heterogeneous disorder; individual patients present with a range of symptoms that may change over time. These symptoms include disturbances in thought, feeling, and action, including hallucinations, delusions, and thought disorders. Abnormalities in cognition are also common, including impairments in memory, attention, and perception, a topic which is discussed in further detail by Velligan and Miller in this supplement.[2]

Typically, schizophrenia emerges during adolescence or early adulthood and is, for the majority of patients, a lifelong condition resulting in significant social and economic impairment. Rates of employment, marriage, and independent living are significantly lower among schizophrenia patients compared with the general population, reflecting the functional impairments they experience.

The complexity of clinical presentation, course, and severity of schizophrenia makes its treatment and long-term management particularly challenging. For patients presenting with their first episode of schizophrenia, prompt diagnosis and intervention may be critical in optimizing long-term outcomes in terms of symptom remission, time to psychotic relapse, and prevention of psychosocial deterioration. This article will provide an overview of the key clinical issues in the treatment of first-episode schizophrenia and will highlight, with reference to case material, the particular advantages in treatment offered by an effective and well-tolerated antipsychotic such as quetiapine.

THE COURSE OF SCHIZOPHRENIA

Just as the clinical presentation of schizophrenia is heterogeneous, so is the long-term course of the disorder. Schizophrenia was originally regarded as a progressive encephalopathy with patients experiencing an almost inevitable decline to states of severe cognitive and functional impairment and requiring long-term, intensive supervision. While the majority of patients are likely to have multiple episodes, often with increasing impairment, between one quarter and one third of patients will have a single episode or multiple episodes with little or no residual symptomatology.[3]

In 1993, Lieberman[4] suggested that schizophrenia could be regarded as a progressive encephalopathy, such that the longer patients experience the symptoms of schizophrenia the more likely they are to suffer lasting impairment. Indeed, McGlashan and Fenton[5] suggested that the processes that make schizophrenia a lifelong disorder may be most active during the early stages of the illness. A number of prospective studies in which patients were followed for up to 11 years after the initial onset of their ill-

From the University of Vienna, Vienna, Austria.

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Reprint requests to: Professor S. Kasper, University of Vienna, Department of General Psychiatry, Wahringer Gurtel 18-20, A-1090 Vienna, Austria.

The Use of Quetiapine in First-Episode Schizophrenia: A Case Study

Hugh Jones, M.R.C.Psych.

We report the successful treatment with quetiapine of a 21-year-old white woman (Ms. C) who first presented to Psychiatric Services at an Accident and Emergency Department over 10 months ago. The main symptoms at presentation were hearing voices commenting on her in the third person, fixed beliefs that her family and others communicated about her using a secret code, and a fixed belief that her thoughts were broadcast aloud. Ms. C was easily distracted and was often unable to give coherent responses to questions.

Case report. Following the development of symptoms, Ms. C had to give up her college course (she was training to become a nurse). She became argumentative with her family and spent her days alone at home. At this time, symptom rating using the Scale for the Assessment of Positive Symptoms (SAPS) was 77, the Scale for the Assessment of Negative Symptoms (SANS) was 81, and the Montgomery-Asberg Depression Rating Scale (MADRS) was 17, indicating a serious burden of schizophrenic symptomatology complicated by depressive symptoms.

Laboratory investigations and a magnetic resonance imaging (MRI) brain scan revealed no abnormalities. A diagnosis of first-onset schizophrenia was made using ICD-10 criteria. Ms. C was prescribed quetiapine at a dose of 300 mg/day. She agreed to take this medication, although at the time she did not believe she had an illness. After 2 weeks, her family reported a mild improvement in her behavior but no change in her symptoms; the quetiapine dosage was increased to 400 mg/day. Ms. C reported only mild sedation and dry mouth as side effects, and these effects disappeared by 4 weeks of treatment.

The persecutory ideas about her family and other people lessened, and the auditory hallucinations reduced in intensity. The incomplete resolution of her symptoms led to a further increase in the quetiapine dosage to 600 mg/day. Notably, Ms. C did not experience any extrapyramidal side effects at any dose of quetiapine.

Symptomatic improvement with quetiapine for Ms. C was associated with the emergence of some depressive symptoms linked to her realization that she would probably not be able to return to nursing. However, she received intensive support from the care team and fortunately did not develop a formal depressive illness.

She began to attend both a structured program to prepare her for future work and support groups for people with mental illness. Following a family dispute, she decided that it may be more appropriate for her to move to independent accommodation.

Currently, her symptom ratings are SAPS 23, SANS 17, and MADRS 4, indicating a wide-ranging improvement. Her hallucinations, although still present, no longer affect her behavior or judgment. She has now started structured activity on a daily basis and is planning ahead. Ms. C accepts that she has schizophrenia and that she will not be able to return to nursing. She has reported no significant change in weight during her time on quetiapine.

This case report illustrates the efficacy of quetiapine in a 21-year-old woman with a first-onset of schizophrenia characterized by severe positive and negative symptoms and marked social and occupational impairment. For Ms. C, quetiapine has provided effective relief from both her positive and negative symptoms and has facilitated supportive and psychological therapy. She is now able to plan for the future and intends to start a college course in the autumn.

From the Section of Neurochemical Imaging, 1 Windsor Walk, Institute of Psychiatry, Denmark Hill, London, U.K.

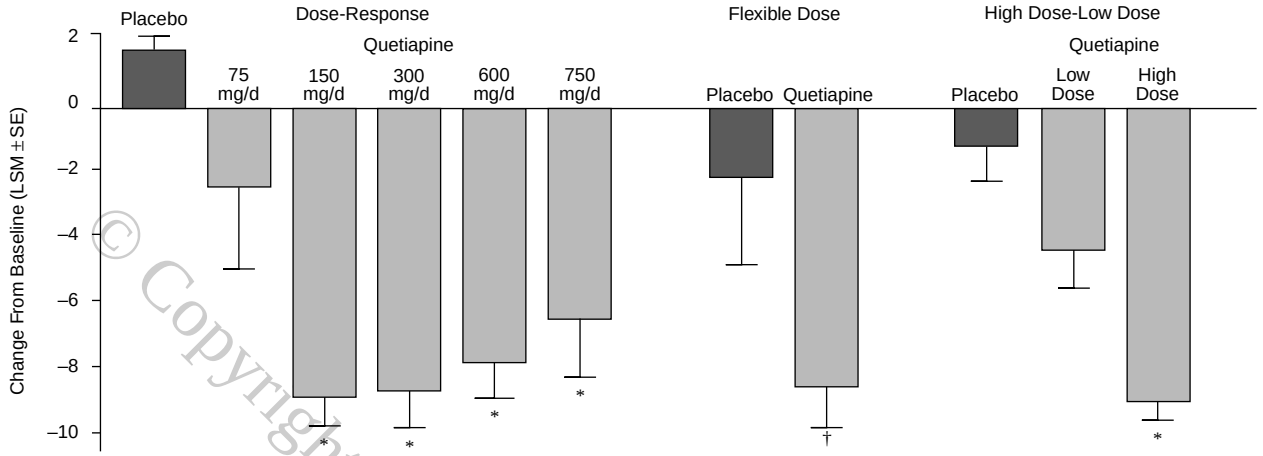
ness found that, after an initial phase of deterioration, patients tended to stabilize.[6–8] In fact, the majority of the deterioration is likely to take place in the early stages of their illness—during the first 5 to 10 years,[9] emphasizing the importance of early intervention.

TREATING THE FIRST EPISODE OF SCHIZOPHRENIA

The evidence is increasing to support the hypothesis that the long-term outcome of schizophrenia depends upon early identification and pharmacologic intervention to relieve symptoms and prevent psychotic relapse.[10–13] Thus, intervention at an early stage, sometimes referred to as the "critical period," should reduce progression of the disorder and maintain a better level of functioning and quality of life. Studies in which early intervention networks—consisting of psychiatrists and general practitioners—were established found that early detection, even before the frank onset of the disorder, appeared to prevent onset, reduce the incidence of schizophrenia, and improve treatment.[14,15] Thus, the early—even prodromal—phases of schizophrenia, as well as being the phases during which patients are likely to experience the most deterioration, can also be regarded as the critical period during which treatment intervention may be most influential in determining long-term outcomes.[16]

It has been suggested that the duration of psychotic symptoms prior to therapeutic intervention consistently strongly influences long-term outcomes. In a study of 118 first-episode patients, Lieberman and colleagues[17] also found that the duration of psychotic symptoms prior to the initiation of antipsychotic therapy was a strong predictor of treatment outcome. The authors also concluded that the

Figure 1. Summary of the Mean Change in Brief Psychiatric Rating Scale (BPRS) Total Scores From Baseline to Study End in 6-Week Clinical Trials Comparing the Efficacy of Quetiapine (up to 750 mg/day) With Placebo[a]



[a]Data from Arvanitis et al.,[25] Small et al.,[27] and Borison et al.[33]
*p < .05 vs. placebo.
†p > .05 and < .10 vs. placebo.

earlier the intervention, the more favorable the outcome. When psychoses have remained untreated for over 1 year, patients are more likely to experience delays in symptom remission, a longer time to recovery, and more psychotic relapses.[10,18]

With appropriate treatment, the majority of patients will recover fully from a first episode of schizophrenia.[18] However, there is evidence that with each successive episode the time to remission following the initiation of conventional antipsychotic therapy increases, the response to treatment may decrease, and symptoms may persist.[19]

Antipsychotic agents remain the mainstay of the treatment of schizophrenia. By relieving the acute symptoms of the disorder, they also facilitate psychosocial interventions that, in addition to direct therapeutic benefits, can maximize patient compliance with treatment. Effective sharing of information between the physician, the patient, and the family or caregivers regarding the nature and prognosis of the disorder, available treatments, and the likely benefits, risks, and/or side effects has been shown to improve compliance.[20]

Selecting an Antipsychotic

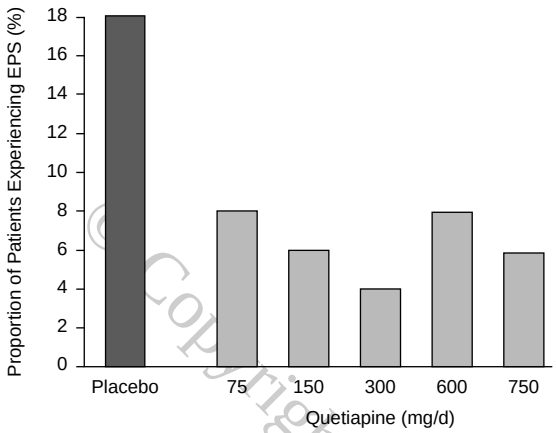
Since the introduction of antipsychotic agents for the treatment of schizophrenia in the 1950s, the long-term outcomes for this disorder have changed.[21] However, while conventional antipsychotic agents are undoubtedly effective in relieving the positive symptoms of schizophrenia, not all patients respond adequately. Indeed, after 5 years, as many as 50% of patients can be expected to have enduring symptoms despite antipsychotic treatment (see reference 3 and also articles by Hellewell[22] and Emsley,[23] this supplement), and a continuing pattern of relapse and increasing functional impairment is common. Moreover, the efficacy of conventional antipsychotic agents in relieving the negative symptoms, cognitive impairment, and mood disturbances associated with schizophrenia has been questioned. Furthermore, as many as 50% of patients who receive conventional antipsychotics will relapse within 2 years of starting treatment.[24]

Atypical antipsychotics such as quetiapine have proven efficacy against the positive and negative symptoms of schizophrenia, and there is some suggestion that they may offer cognitive improvements and are at least as effective as conventional agents in the treatment of schizophrenia. Quetiapine is effective in relieving both the positive and the negative symptoms of schizophrenia at dosages ranging from 150 to 750 mg/day[25] and is more effective than placebo (Figure 1), and at least as effective as the conventional antipsychotic agents haloperidol and chlorpromazine.[25–28]

The high relapse rates associated with conventional antipsychotic therapy, combined with the preliminary evidence of the positive effects of atypical antipsychotic agents on the negative symptoms of schizophrenia as well as on cognitive function (see the article by Velligan and Miller,[2] this supplement), support the use of the newer atypical antipsychotic agents as first-line treatments for patients experiencing their first episode of schizophrenia.

Poor response to treatment is often due to noncompliance, which is a common problem with conventional antipsychotics; clinicians often resort to strategies such as depot injections of antipsychotics in the hope of ensuring compliance with treatment in the community setting. The

Figure 2. Proportion of Patients Developing Acute Extrapyramidal Symptoms (EPS) While Receiving Either Quetiapine (75–750 mg/day) or Placebo for 6 Weeks[a]



[a]Data from Arvanitis et al.[25] Patients may have experienced more than one EPS adverse event.

reasons for noncompliance can be complex, but the association of conventional antipsychotics with extrapyramidal symptoms (EPS) and other adverse effects is likely to be a major contributory factor. Patients receiving treatment for a first episode of schizophrenia appear to be especially sensitive to the EPS associated with antipsychotic therapy. Such sensitivity can significantly undermine the patients' confidence in—and willingness to comply with—treatment. Ultimately, noncompliance with treatment will, for the majority of patients, result in relapse and, potentially, further deterioration in health. Therefore, when treating patients in the first episode, the avoidance of EPS is of vital importance in ensuring continued compliance and optimal long-term treatment outcomes. Atypical agents are associated with fewer EPS compared with the conventional antipsychotics. Indeed, quetiapine is associated with a level of EPS no different than placebo (see the article by Gerlach,[29] this supplement) across all doses (Figure 2), with important implications for compliance with treatment. This lack of EPS is supported by the brain imaging findings which indicate that quetiapine has the lowest dopamine D_2-receptor occupancy within the new atypical antipsychotics.[30]

Case Studies

The cases of Ms. C (Jones,[31] this supplement) and Mrs. A (Lee,[32] this supplement) illustrate the value of prompt diagnosis and pharmacologic intervention for patients experiencing their first episode of schizophrenia. Ms. C was first seen by psychiatric services following a referral from an Accident and Emergency department. The severity of her symptoms meant that she had become increasingly paranoid, withdrawn, and argumentative and was often unable to respond coherently to questions. In contrast, on

Rapid Relief From the Symptoms of Schizophrenia With Quetiapine: A Case Study

Kevin M. S. Lee, M.B., M.R.C.G.P.

The prompt diagnosis of schizophrenia and timely pharmacologic intervention may improve long-term treatment outcomes. Reported here is the case of a 46-year-old, married woman (Mrs. A) who experienced her first acute episode of schizophrenia and showed a rapid and dramatic relief from her symptoms following treatment with quetiapine.

Case report. Mrs. A had no history of psychiatric illness until 1994 when her husband became concerned that his wife was hearing voices and was becoming increasingly paranoid. Following an outpatient appointment, she was admitted to the hospital and reported having heard voices for the past 7 years, but these were now becoming more frequent. She was diagnosed with an acute exacerbation of chronic undifferentiated schizophrenia per DSM-IV.

Treatment with quetiapine was initiated at a dosage of 300 mg/day (100 mg in the morning and 200 mg at night). Within 2 weeks, Mrs. A reported feeling much better, her auditory hallucinations had subsided, and she was no longer experiencing paranoid thoughts.

Mrs. A is now fully integrated back into normal life. Her husband is the only family member aware of her diagnosis and her problem. In the past year, her mother-in-law has moved to stay with them and, despite sharing the same house and living in such close proximity, she neither knows nor suspects that her daughter-in-law suffers from a chronic psychiatric illness.

Reports of prodromal symptomatology for some time prior to formal diagnosis are not uncommon. Indeed, it is not until such symptoms become intrusive or increase in severity that a formal diagnosis of schizophrenia is likely to be made. This case illustrates that quetiapine is an effective and well-tolerated first-line treatment for the symptoms of schizophrenia. Mrs. A has experienced no side effects over the 5 years of treatment and is happy to continue with quetiapine.

From the Scott Practice, Balby, Doncaster, U.K.

assessment, it emerged that Mrs. A had experienced prodromal symptoms (auditory hallucinations) for a number of years. She was admitted to the hospital following an outpatient appointment when her husband became concerned about her symptoms.

Treatment with quetiapine, 300 mg/day, was initiated for both patients. For Mrs. A, this proved sufficient. She reported an improvement in her condition within 2 weeks, and she did not experience any adverse effects. In the 5 years since her initial diagnosis, Mrs. A has not experienced a relapse of her symptoms and remains happy to

continue with her treatment. Ms. C required a dose increase to 600 mg/day to ensure complete resolution of her symptoms. As the dosage of quetiapine was increased, some sedation and dry mouth emerged. However, these effects resolved without intervention within 4 weeks, and Ms. C did not experience EPS at any dose. Treatment with quetiapine facilitated supportive and psychological therapies, and Ms. C has been able to gain an insight into her disorder and is once again able to plan for the future.

CONCLUSIONS

Early diagnosis and pharmacologic intervention can dramatically improve the long-term prognosis for first-episode schizophrenia patients. The combination of proven efficacy and a low propensity to induce EPS offered by the newer agents, together with potential improvements in cognitive impairment, means that the use of atypical agents such as quetiapine is recommended.

Drug names: chlorpromazine (Thorazine and others), haloperidol (Haldol and others), quetiapine (Seroquel).

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