Partial Response to Antipsychotic Treatment: The Patient With Enduring Symptoms

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While approximately 70% of patients with schizophrenia and other psychotic disorders show a clear-cut reduction of symptoms in clinical trials, there is considerable variation in individual patient outcome, ranging from complete remission to absolute refractoriness. When additional indicators of treatment outcome are considered, such as cognitive and occupational and social functioning, it is clear that the overall outcome for schizophrenia is far from satisfactory. For many schizophrenic patients, treatment with conventional antipsychotic agents is not fully effective, and one approach has been to increase the administered dose. However, raising the dose increases the likelihood of side effects and may significantly compromise patient compliance. The availability of atypical antipsychotic agents represents a significant step forward for those patients who are nonresponsive to conventional antipsychotics, offering proven efficacy, a lower risk of extrapyramidal symptoms, and improved clinical outcomes. *(J Clin Psychiatry 1999;60[suppl 23]:10–13)*

Conventional antipsychotic agents have long been regarded as effective compounds in the treatment of schizophrenia and other psychotic disorders, with approximately 70% of patients showing clear-cut reduction of symptoms in short-term clinical trials.[1] However, considerable variation in individual patient outcome is observed, ranging from complete remission to absolute refractoriness. More recently, trials have been conducted over longer time periods, and multiple outcome criteria have been utilized to assess aspects such as cognitive functioning, occupational and social functioning, compliance, frequency of relapses, duration of hospitalization, and quality of life.[2] When treatment response is considered in these terms, it is clear that the overall outcome for schizophrenia is far from satisfactory.[3,4]

Effectiveness in practice may be substantially less than efficacy in clinical trials, due to patient heterogeneity, prescribing practices, and noncompliance.[5] For many patients with schizophrenia, treatment with conventional antipsychotics is not fully effective, and they continue to display clinically significant symptoms.[6,7] With respect to positive symptoms (hallucinations, delusions, feelings of persecution), studies indicate that in a "real world" setting, two thirds of first-episode patients continue to experience positive symptoms after 1 year, and about one third will continue to have them after 6 years.[8] In other words, the majority of patients with schizophrenia may best be regarded as partial responders.

CONSEQUENCES OF A PARTIAL RESPONSE TO TREATMENT

The persistence of positive symptoms may have important clinical ramifications. Partial response to treatment may increase the risk of relapse. Indeed, it has been estimated that as many as 50% of patients who receive conventional antipsychotic agents relapse within 2 years of initiating treatment.[9]

Ongoing hallucinations, delusions, or peculiar behavior contribute to the stigmatization of the illness and are demoralizing for the patient, his/her family, and the treating doctor. Furthermore, evidence exists suggesting that patients with a longer duration of positive symptoms prior to effective treatment have a poorer outcome.[10,11] Lieberman[12] has suggested that the presence of positive symptoms could be indicative of an active, ongoing, morbid process (i.e., a progressive encephalopathy), which, if not ameliorated by antipsychotic drug treatment, may result in lasting morbidity. In addition, it would appear that there is an evolution of resistance to treatment in the progression of the illness. According to Lieberman, if we can reduce the amount of time that schizophrenic individuals spend in an active psychotic phase of their illness, then we can reduce the lasting impairment that they may sustain. For this reason, effective intervention and treatment to remission are critical to the treatment outcome.

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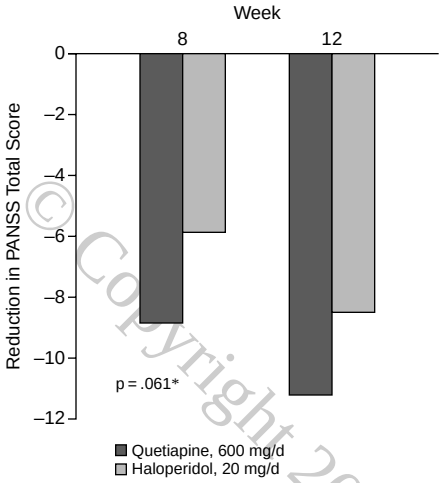
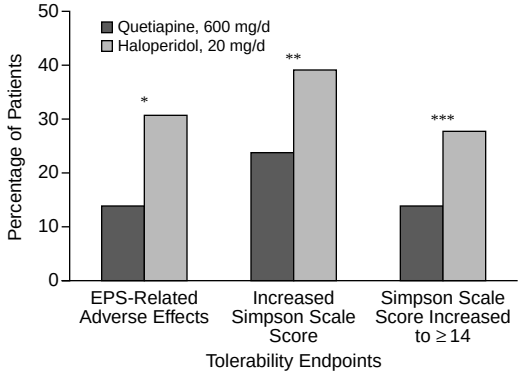
Figure 1. Reduction in PANSS Total Score for Patients After 4 and 8 Weeks of Randomized Treatment With Quetiapine or Haloperidol After a 4-Week Run-In Phase During Which All Patients Received Fluphenazine[a]



[a]Data from Emsley et al.[16]
*Between-treatment difference.

Figure 2. Incidence of EPS During 8 Weeks of Treatment With Either Quetiapine or Haloperidol Immediately After a 4-Week Run-In Phase During Which All Patients Received Fluphenazine[a]



[a]Data from Emsley et al.[16]
*p < .001. **p = .005. ***p = .002.

APPROACHES TO TREATMENT

Patients with persistent positive symptoms need to be carefully reassessed in order to rule out other possible causes, such as general medical conditions and substance-related psychotic symptoms in particular. Also, compliance needs to be carefully assessed.

Conventional Antipsychotic Agents

One strategy in treating patients with persistent symptoms has been to increase the dose of the conventional antipsychotic drug above the standard therapeutic dose the patient has been receiving. This is sometimes successful, since there are individual differences in the dose that patients require, and there may be a few patients who require such doses in order to block their dopamine receptors satisfactorily. However, the evidence for efficacy in high doses is limited, and high doses are likely to cause an increase in side effects.[13]

Atypical Antipsychotic Agents

Another option in treating patients who are nonresponsive to conventional antipsychotic agents is the use of clozapine and perhaps the newer atypical antipsychotics.[14] However, while considerable work has been conducted with nonresponders, less attention has been focused on partial responders.

It is not clear whether the results of trials involving nonresponders are applicable to the heterogeneous patient population seen in clinical practice, as most studies have investigated nonresponders according to strictly defined criteria, thus excluding a significant number of patients. An exception is a study involving a small sample of partial responders to conventional antipsychotics, who had failed to respond to a 6-week prospective trial of fluphenazine.[15] In these patients, clozapine was found to be superior to haloperidol in terms of reducing positive and negative symptoms, suggesting that it has utility for a broad spectrum of patients with schizophrenia beyond the most severely ill. Although the concept is not well established, the authors referred to this population of patients as "partial responders."

A more recent study[16] suggests that quetiapine, a novel atypical antipsychotic, has advantages in terms of both efficacy and safety in patients who only partially respond to conventional antipsychotics. This international, multicenter, double-blind study compared the efficacy and tolerability of 8-week treatment of quetiapine, 600 mg/day, with haloperidol, 20 mg/day. Two hundred eighty-eight patients diagnosed with schizophrenia, with a history of partial response to conventional antipsychotics, who displayed a partial or no response (defined as < 30% reduction in the Positive and Negative Syndrome Scale [PANSS][17] total score and a PANSS positive score ≥ 15) to 4 weeks of treatment with fluphenazine (20 mg/day) were recruited. Significantly more patients ($p < .05$) receiving quetiapine (52%) than haloperidol (38%) achieved a clinical response (defined as ≥ 20% reduction in PANSS total score). Patients who received quetiapine also tended to have a greater improvement in the mean PANSS score after 4 weeks of treatment and at the end of the study than those who received haloperidol (Figure 1).

Similarly, there was a trend for quetiapine-treated patients to demonstrate greater improvements in other secondary efficacy measures (Clinical Global Impressions, PANSS subscale, and Brief Psychiatric Rating Scale

Symptom Relief and Improved Social Functioning Following Treatment With Quetiapine in a Schizophrenic Patient With a History of Poor Response to Antipsychotics

Edward B. Freeman, Sr., M.D.

This case report describes the symptom relief achieved by a 69-year-old Hispanic man with a diagnosis of schizophrenia and a long history of poor response to antipsychotics following treatment with quetiapine.

Case report. Mr. A began exhibiting symptoms of mental illness around 1977. Following a long history of psychiatric problems including an attempted suicide, a diagnosis of bipolar affective disorder with mania, and repeated hospitalizations, Mr. A was diagnosed with DSM-IV chronic paranoid schizophrenia in 1988. Since 1988, Mr. A has been treated with a range of antipsychotic agents including haloperidol, fluphenazine, and risperidone; however, his physical and mental condition continued to deteriorate. Isolation; inappropriate behavior; poor regard for health, hygiene, and grooming; and resistance to physical activity have characterized Mr. A's illness and have led to a steady deterioration in Mr. A's physical health including obesity, insulin-dependent diabetes, and cerebrovascular disease.

When Mr. A first presented to the clinic in 1998, poor hygiene and grooming and urinary incontinence were marked. He was barely able to walk, and his thought processes were poor. Mr. A was hospitalized in November 1998, and quetiapine treatment at 25 mg twice daily was initiated in addition to existing treatment with lithium (300–600 mg/day) and lorazepam (5–7 mg/day); thiothixene treatment was stopped. In addition, behavioral modifications were instituted, and Mr. A was encouraged to stay out of his room, attend group meetings, use his walker, and attend to his own personal hygiene. Quetiapine was titrated to 100 mg/day by day 5, and by day 6 Mr. A began to show less resistance to activity, attended groups with minimal encouragement, and began to mobilize well.

The patient was discharged from the hospital after 8 days, although he remained incontinent of urine and continued to receive quetiapine (50 mg twice daily). Mr. A was seen in the doctor's office 3 weeks after discharge from the hospital. At this time, his affect was brighter and he was able to articulate clear and concise thoughts, although some mild disorganization remained. He was continent of urine, was maintaining his personal hygiene, and continued to ambulate well. Mr. A had also lost 15 pounds in weight attributed to his increased activity and was also reported to have a decrease in the sliding scale of insulin due to better control of his diabetes. Mr. A reported feeling stronger.

This report shows that, despite a long history of poor or partial response to antipsychotic therapy, treatment with atypical antipsychotic agents, such as quetiapine, can offer significant benefits in terms of symptom relief and general health and well-being.

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scores), but the difference between treatments did not reach statistical significance. Patients receiving quetiapine required less anticholinergic medication, showed greater reduction in preexisting extrapyramidal symptoms (EPS), and experienced fewer treatment-emergent EPS-related adverse events compared with those in the haloperidol group (Figure 2). In the quetiapine group, the elevated serum prolactin concentrations returned to the normal range between weeks 4 and 12, whereas high prolactin levels were sustained in the haloperidol group, the difference between the 2 treatment groups reaching statistical significance ($p < .001$). These results suggest that quetiapine is a useful drug in patients with a history of partial response to conventional antipsychotics.

Case Studies

The efficacy of quetiapine in the treatment of patients with a history of poor or partial response to antipsychotic therapy is illustrated by the case studies reported by Freeman[18] and Koziupa.[19] Both patients had experienced persistent symptoms for much of their adult lives and had responded poorly to antipsychotic therapy. For Mr. A,[18] his persistent symptoms and comorbid psychiatric illnesses had meant repeated hospitalizations and poor self-care; while for Ms. B,[19] her persistent hallucinations interfered with her ability to interact appropriately with others. The introduction of quetiapine offered both patients rapid symptom relief. Mr. A's emotional state was brighter and his self-care and general health improved. The character and content of Ms. B's hallucinations have changed so that she is now better able to cope with them, allowing her to develop positive interpersonal skills.

CONCLUSIONS

For many schizophrenic patients, treatment with conventional antipsychotics is not fully effective; indeed, "partial responders" may represent the majority of patients seen in clinical practice. The development of new atypical antipsychotic agents, such as quetiapine, represents a significant step forward for patients who respond poorly to conventional antipsychotics, offering proven efficacy, a

The Efficacy of Quetiapine in Relieving Persistent Symptoms in a Patient With Poor Response to Both Conventional and Atypical Antipsychotic Therapy

Diana M. Koziupa, M.D.

I report here the successful treatment with quetiapine of a 34-year-old woman with a well-documented history of poor or partial response to a range of antipsychotics, including atypicals at therapeutic doses. Ms. B has been diagnosed with hypothyroidism for which she has been treated successfully for the past 6 years.

Case report. Ms. B was diagnosed with DSM-III-R schizophrenia (paranoid type) at age 21. She had a history of mental illness since age 15 and hallucinations from the age of 19. Since the age of 19, persistent auditory hallucinations, which Ms. B perceived as threatening and negative both toward herself and those around her, had been distressing and interfered with her ability to interact appropriately with others. Numerous antipsychotic medications, including the atypicals risperidone and clozapine at therapeutic doses, had been tried, none of which gave significant relief from her symptoms.

On entering a partial hospital program, Ms. B was receiving olanzapine, 15 mg h.s. (initiated in March 1997), and lithium carbonate, 300 mg 3 times daily (since 1994). Ms. B's hallucinations had increased in intensity and severity, leading to her suspension from the day treatment program due to her loud, argumentative dialogue with the hallucinations. For this reason, quetiapine treatment, in addition to her existing medication, was initiated at 25 mg twice daily, and her dose was titrated to 500 mg daily (100 mg in the morning and 400 mg at night). Within 2 weeks of this dose increase, the character of her hallucinations changed dramatically. The voices were no longer threatening or recriminatory, and her interpersonal interactions improved as she began to engage in appropriate conversation with others. In addition, Ms. B has been better able to participate in therapeutic activities.

While Ms. B's auditory hallucinations persist, the addition of quetiapine has changed the character and content of the hallucinations to allow her to function at a higher interpersonal level. It appears that quetiapine had the greatest impact on the affective component of her hallucinations, such that the affective tone of the hallucinations shifted from being threatening and recriminatory to supportive. Her response to them, in turn, has changed from anger and paranoia to acceptance, allowing her to focus on developing positive interpersonal skills.

This case report illustrates the efficacy of quetiapine in a patient who had not responded well to other antipsychotic agents, including other atypicals.

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lower risk of EPS and other adverse effects, and improved clinical outcomes. The significant improvement seen with quetiapine over other agents in the absence of dose-related EPS at the higher doses not only offers an attractive option, but may also change the paradigm that higher doses are not likely to be effective. In fact, such limitations appear to apply only to the conventional antipsychotic agents.

Drug names: clozapine (Clozaril and others), haloperidol (Haldol and others), quetiapine (Seroquel).

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