

Efficacy, Safety, and Tolerability of Quetiapine in Patients With Schizophrenia

Henry A. Nasrallah, M.D., and Rajiv Tandon, M.D.

Schizophrenia is a serious and disabling psychiatric disorder affecting approximately 1% of the world's population, with its economic cost in the United States alone estimated to exceed that of all cancers combined. The new generation of atypical antipsychotics introduced over the past decade have comparable or greater efficacy than traditional antipsychotics in treating the psychotic symptoms of schizophrenia and a much improved neurologic side effect profile. Quetiapine, the fourth atypical antipsychotic marketed in the United States, was approved by the U.S. Food and Drug Administration in September 1997 and is also currently approved in over 70 countries worldwide for the treatment of psychosis associated with schizophrenia. This article will review the clinical trials examining the efficacy, safety, and tolerability of quetiapine in the treatment of patients with schizophrenia. (*J Clin Psychiatry* 2002;63[suppl 13]:12–20)

Schizophrenia is a neuropsychiatric syndrome that affects approximately 1% of the world's population.¹ Because its symptoms can begin early in life and persist for decades, the economic cost of the disease in the United States is large and estimated to exceed that of all cancers combined.¹ Treatment of the disease was revolutionized with the discovery of first-generation—also known as conventional or typical—antipsychotics in the 1950s. Because of medically serious side effects, particularly movement disorders including acute extrapyramidal symptoms (EPS) and tardive dyskinesia, associated with the use of these drugs, researchers sought to develop compounds with equivalent antipsychotic activity but without a propensity for producing EPS (i.e., atypical drugs). Quetiapine, the fourth atypical antipsychotic marketed in the United States, was approved in September 1997 by the U.S. Food and Drug Administration (FDA) for the treatment of schizo-

phrenia. It is also approved in over 70 countries around the world.

Treating patients with drugs that have a decreased likelihood of producing side effects is important for a number of reasons. Long-term treatment is necessary, and significant adverse effects contribute to patient noncompliance with medication, leading to relapse.^{2–4} Another reason is that early and consistent treatment of psychotic symptoms may improve the long-term prognosis of patients.^{5,6} Furthermore, prophylactic treatment in the prodromal stage of schizophrenia has been proposed as a strategy to limit deterioration, and this ethically requires drugs with minimal adverse effects.^{7,8} Adverse effects of antipsychotic agents can also negatively impact different symptom domains in schizophrenia, thereby limiting their spectrum of efficacy.^{9,10} This article will review the pivotal trials (Table 1) and additional trials examining the efficacy, safety, and tolerability of quetiapine in the treatment of patients with schizophrenia; this comprehensive body of data demonstrates a favorable overall profile.

CLINICAL TRIALS

The key placebo-controlled clinical trials of quetiapine include 3 randomized, double-blind, controlled, 6-week trials of moderately to severely ill hospitalized patients with schizophrenia.^{11–13} In the study by Borison et al.,¹¹ flexible dosing of quetiapine (up to a maximum of 750 mg/day) was compared with placebo. In the study by Arvanitis and Miller,¹² 5 fixed doses of quetiapine (75, 150, 300, 600, and 750 mg/day) were compared with haloperidol (12 mg/day) and placebo. Finally, in the study by Small et al.,¹³ patients were titrated to a lower-dose (250 mg/day) or higher-dose

From the Department of Psychiatry, University of Mississippi Medical Center, Jackson, Miss. (Dr. Nasrallah), and the Department of Psychiatry, University of Michigan Medical Center, Ann Arbor, Mich. (Dr. Tandon).

Supported by AstraZeneca Pharmaceuticals, L.P.

Dr. Nasrallah has been a consultant for Abbott, AstraZeneca, Bristol-Myers, Janssen, and Pfizer; has received grant/research support from AstraZeneca, Janssen, and Pfizer; has received honoraria from AstraZeneca, Abbott, Bristol-Myers, Janssen, and Pfizer; and has served on the speakers or advisory boards for Abbott, AstraZeneca, Bristol-Myers, Janssen, and Pfizer. Dr. Tandon has served on the speakers or advisory boards for AstraZeneca, Bristol-Myers, Lilly, Janssen, and Pfizer.

Corresponding author and reprints: Henry A. Nasrallah, M.D., University of Cincinnati Medical Center, 231 Albert Sabin Way, P.O. Box 670559, Cincinnati, OH 45267 (e-mail: hnasra2905@aol.com).

Table 1. Summary of Randomized Trials With Quetiapine in the Treatment of Patients With Schizophrenia^a

Clinical Trial	N	Dosing/ Duration	Maximum Dose of Quetiapine (mg/d)	Comparator and Dose	Overall Efficacy	Safety and Tolerability
Placebo Control						
Borison et al, 1996 ¹¹	109	Flexible/6 wk	750	Placebo	Quetiapine > placebo ^b	EPS and prolactin: quetiapine = placebo
Arvanitis and Miller, 1997 ¹²	361	Fixed/6 wk	75, 150, 300, 600, 750	Placebo, haloperidol, 12 mg/d	Quetiapine, 150–750 mg/d = haloperidol > placebo	EPS and prolactin: quetiapine, 150–750 mg/d = placebo
Small et al, 1997 ¹³	286	Flexible/6 wk	250 (lower dose) 750 (higher dose)	Placebo	Quetiapine, 250 mg/d = placebo Quetiapine, 750 mg/d > placebo	Quetiapine: no EPS or sustained elevations of prolactin
Active Control						
Peuskens and Link, 1997 ¹⁴	201	Flexible/6 wk	750	Chlorpromazine, ≤ 750 mg/d	Quetiapine = chlorpromazine	Adverse events: quetiapine < chlorpromazine
King et al, 1998 ¹⁵	618	Fixed/6 wk	225 bid 150 tid 25 bid	Quetiapine, 25 mg bid	Quetiapine, 225 mg bid = quetiapine, 150 mg tid > quetiapine, 25 mg bid	EPS: quetiapine, 225 mg bid = quetiapine, 150 mg tid, no sustained prolactin change
Copolov et al, 2000 ¹⁶	448	Fixed/6 wk	455	Haloperidol, 8 mg/d	Quetiapine = haloperidol	EPS and prolactin: quetiapine < haloperidol
Emsley et al, 2000 ¹⁷	288	Fixed/8 wk	600	Haloperidol, 20 mg/d	Quetiapine = haloperidol ^c	Prolactin: quetiapine < haloperidol
Goldstein et al, 2001 ¹⁸	95	Fixed/8 wk	600	Haloperidol, 20 mg/d	Quetiapine > haloperidol ^d	Prolactin: quetiapine < haloperidol
Velligan et al, 2001 ¹⁹	58	Fixed/24 wk	300, 600	Haloperidol, 12 mg/d	Cognition: quetiapine, 600 mg/d > haloperidol	EPS: quetiapine < haloperidol

^aAbbreviation: EPS = extrapyramidal symptoms. Symbols: >: significantly more effective than, =: not significantly different from, <: significantly less effective than.

^bStatistically significant differences between treatment groups ($p \leq .05$) in favor of quetiapine were observed at various times throughout the trial but not at endpoint ($p = .07$).

^cTrend toward greater improvement with quetiapine, but difference between treatments did not reach significance.

^dProportion of patients classified as treatment responders.

(750 mg/day) regimen of quetiapine, compared to treatment with placebo.

A number of other randomized, double-blind studies (6–24 weeks in duration) with an active control have been conducted. In a 6-week study by Peuskens and Link,¹⁴ flexible dosing of quetiapine (up to 750 mg/day) was compared with chlorpromazine (up to 750 mg/day). A 6-week, fixed-dosing study by King et al.¹⁵ compared the following dosages of quetiapine: 225 mg twice daily, 150 mg 3 times daily, and 25 mg twice daily. Copolov et al.¹⁶ compared the results of a mean dosage of quetiapine, 455 mg/day, with haloperidol at 8 mg/day in a 6-week study. In 8-week, fixed-dose studies, 600 mg/day of quetiapine was compared with 20 mg/day of haloperidol.^{17,18} Finally, in a 24-week study by Velligan et al.,¹⁹ dosages of quetiapine of 300 and 600 mg/day were compared with 12 mg/day of haloperidol.

EFFICACY

The efficacy of treatment with quetiapine in patients with schizophrenia has been assessed using a number of standardized clinical rating scales. The Brief Psychiatric Rating Scale (BPRS)²⁰ is an 18-item scale that measures major psychotic and nonpsychotic symptoms in patients with major psychiatric illness, particularly schizophrenia.

It is suitable for assessing baseline psychopathology, clinical course, and treatment response and is administered by psychiatrists, psychologists, or other trained raters. The BPRS is probably the most widely used scale in the treatment of schizophrenia and allows comparisons to be made among different studies. The BPRS positive symptoms cluster score (mean of conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is used to assess positive symptoms associated with schizophrenia.^{21,22} Conversely, the BPRS negative symptoms cluster (consisting of emotional withdrawal, motor retardation, and blunted affect) is sometimes used to assess negative symptoms of schizophrenia.^{21,22} The Positive and Negative Syndrome Scale (PANSS)²³ is a 30-item rating instrument that evaluates positive, negative, and other symptoms in patients with schizophrenia and is becoming the most frequently utilized scale in clinical trials. The Scale for the Assessment of Negative Symptoms (SANS)²⁴ assesses 5 symptom complexes to obtain clinical ratings of negative symptoms in patients with schizophrenia: affective blunting, avolition/apathy, anhedonia/asociality, and disturbance of attention. The Clinical Global Impressions (CGI) scale²⁵ is a 3-item scale that measures treatment response in psychiatric patients. This assessment is performed by a physician or

trained rater who assesses severity of illness, clinical progress, and therapeutic efficacy.

Global Symptoms

In the placebo-controlled clinical trials, significant differences occurred between higher doses of quetiapine and placebo for BPRS total scores.¹¹⁻¹³ In the clinical trials with active controls, quetiapine, 450 mg/day, was more effective than 50 mg/day in reducing BPRS total scores,¹⁵ and quetiapine, 600 mg/day, produced improvements in BPRS scores comparable to those of haloperidol, 20 mg/day (quetiapine, 600 mg/day, had greater symptom reduction than haloperidol, but the difference between the treatments did not reach statistical significance).¹⁷ In a recent post hoc re-analysis, quetiapine was significantly superior to haloperidol at the 30% response level in the BPRS total score ($p = .042$).²⁶

A secondary measure of efficacy used in the placebo-controlled clinical trials included response to treatment, defined as $\geq 40\%$ reduction in BPRS total score from baseline to endpoint. In the fixed-dose study, the proportion of patients showing a response to treatment in the quetiapine 150-, 300-, and 600-mg/day groups was significantly higher than in the placebo group ($p < .0083$).¹² In the lower (250 mg/day)/higher (750 mg/day)-dose trial, both dosages of quetiapine had a greater percentage of responders than the placebo group; however, the difference was statistically significant for only the high-dose group.¹³

In the placebo-controlled clinical trials, the higher doses of quetiapine produced significantly greater improvement in CGI-Severity of Illness (CGI-S) scores for quetiapine versus placebo.^{12,13} In a smaller study, quetiapine was marginally better than placebo.¹¹ In the clinical trials with active controls, both quetiapine and haloperidol produced reductions in CGI scores,¹⁶ and in 2 studies, the mean change in CGI-S scores was greater for quetiapine than for haloperidol.^{17,18}

In a comparative trial, both quetiapine, at a mean dose of 455 mg/day, and haloperidol, at a mean dose of 8 mg/day, produced marked reductions in PANSS total scores.¹⁶ The magnitude of these reductions was clinically significant (-18.7 ± 1.63 for quetiapine and -22.1 ± 1.63 for haloperidol), although the difference between the treatment groups was not ($p = .13$). In another comparative double-blind trial, patients treated with quetiapine (600 mg/day) tended to have numerically greater improvement in PANSS score than those receiving haloperidol (20 mg/day) after 4 weeks of treatment (-9.05 and -5.82 , respectively; $p = .061$) and at study end at 12 weeks (-11.50 and -8.87 , respectively; $p = .234$), but these differences were not statistically significant.¹⁷ Furthermore, significantly more patients treated with quetiapine than haloperidol were responders, with response defined as a $> 20\%$ reduction in PANSS total score between weeks 4 and 12; the rates were 52.2% for quetiapine and 38.0% for haloperidol ($p = .043$).

Positive Symptoms

In the placebo-controlled clinical trials, the efficacy of quetiapine in reducing the positive symptoms of schizophrenia as assessed by changes in the BPRS positive symptoms cluster score was significantly better for quetiapine versus placebo^{12,13} or was marginally better for quetiapine versus placebo.¹¹ Differences between quetiapine and haloperidol in reducing BPRS positive symptoms cluster scores were not statistically significant.¹² In the lower (250 mg/day)/higher (750 mg/day)-dose trial, both dosages of quetiapine resulted in greater improvements in positive symptoms than in the placebo groups; however, the improvements were statistically significant only in the higher-dose group.¹³

Negative Symptoms

In some clinical trials, improvement in negative symptoms was assessed by reductions in the SANS summary scores. Each of the doses in the fixed-dose trial showed improved scores, with the 300-mg/day group showing the greatest improvement ($p < .05$ versus placebo).¹² Patients receiving placebo experienced worsening scores, while patients receiving haloperidol showed improvements similar to those of quetiapine. In the lower (250 mg/day)/higher (750 mg/day)-dose clinical trial, patients receiving the higher dose experienced a superior improvement in negative symptoms score compared with placebo.¹³ In a titrated-dose trial, negative symptoms also improved as indicated by a significant reduction in SANS scores.¹¹

Overall, these studies suggest that quetiapine has efficacy similar to that of chlorpromazine, haloperidol, risperidone, and olanzapine in the treatment of positive and negative symptoms of schizophrenia. Furthermore, a long-term, open-label study suggests that the improvement is maintained over 52 weeks.²⁷

Cognition

Impairment in executive function, attention, working memory, secondary memory, and vigilance is characteristic of schizophrenia from the first episode of psychosis and persists even after positive symptoms resolve with appropriate antipsychotic drug treatment.²⁸ Deficits in secondary memory in patients with schizophrenia have been shown to be the most significant predictor of functional outcome measures such as work function, social function, and community survival.^{29,30} Although typical antipsychotic drugs such as chlorpromazine and haloperidol have minimal beneficial effects on cognition,^{31,32} atypical antipsychotics (e.g., clozapine, risperidone, olanzapine, and ziprasidone) have been shown to be effective in improving aspects of cognitive function.³³

Several studies have been conducted examining the effects of treatment with quetiapine on different cognitive functions. In a study by Sax et al.,³⁴ changes in attentional performance in patients with schizophrenia were exam-

ined during the 2 months after initiating treatment with quetiapine. Before treatment, attentional performance in 10 patients with schizophrenia was significantly worse than in 12 controls. During treatment with quetiapine, attentional performance in the patients improved and, by 2 months, did not differ significantly from that of the controls. These results suggest that quetiapine produces a significant improvement in attentional functioning in patients with schizophrenia.

In a prospective, randomized, double-blind clinical trial conducted in 25 patients with schizophrenia, the patients were treated with quetiapine or haloperidol for 6 months.³⁵ The patients were evaluated with rating scales for psychotic symptoms, mood, EPS, and standardized neuropsychological tests measuring different cognitive domains. After 6 months of treatment, quetiapine improved psychosis and mood without inducing EPS. Treatment with quetiapine was also associated with beneficial effects on cognitive skills, particularly verbal reasoning, fluency skills, immediate recall, executive skills, and visuo-motor tracking. Patients taking haloperidol showed improvements in general clinical status but no specific improvements on the positive or negative symptoms of schizophrenia, mood, or cognitive skills. In contrast with haloperidol, treatment with quetiapine was associated with improvement in both psychotic symptoms and cognitive function.

Another study compared the effects of 24 weeks of treatment with quetiapine and haloperidol on measures of executive function, memory, and attention.³⁶ Fifty-eight patients with schizophrenia were randomly assigned to haloperidol (12 mg/day) or quetiapine (300 or 600 mg/day). Patients receiving the higher dose of quetiapine, 600 mg/day, improved on overall cognitive function to a greater extent than patients receiving haloperidol. Specific improvement was found for executive function, attention, and verbal memory. These treatment differences were not solely due to benztropine use, medication side effects, or changes in symptomatology. Treatment with quetiapine at higher doses (600 mg/day) had more beneficial effects on cognition than treatment with either haloperidol or a lower dose of quetiapine (300 mg/day).

In a study to examine the effectiveness of quetiapine versus conventional antipsychotics in improving cognitive and functional outcomes in standard treatment settings, 40 patients with schizophrenia in public outpatient clinics were randomly assigned to continue with conventional antipsychotics (N = 20) or to switch to quetiapine (N = 20).¹⁹ After 6 months of treatment, the average dosage of quetiapine was 319 ± 143 mg/day and the average dosage of conventional antipsychotics was 348 ± 348 mg/day of chlorpromazine equivalents. No significant differences were reported between the 2 treatments in their effects on positive or negative symptoms of psychosis. EPS were significantly different, however, with none of the

quetiapine-treated patients receiving benztropine at study endpoint in contrast to 60% of patients receiving conventional antipsychotics. Treatment with quetiapine improved overall neurocognitive performance, initiation, and verbal memory relative to treatment with conventional antipsychotics, and these treatment effects were not related to improvements in side effects, symptomatology, or benztropine use. In an extension of this study, patients taking quetiapine were better able to utilize semantic context to aid recall than those taking conventional antipsychotic medications after 6 months of treatment.³⁷ The quetiapine group was also less likely to produce intrusions during free recall, possibly a result of a minimization of interference. Thus, patients whose symptoms are well controlled with traditional antipsychotics may still receive significant neurocognitive benefit from being switched to quetiapine.

The effects of 6 weeks of treatment with quetiapine on measures of attention, verbal working memory, executive function, verbal fluency, and motor performance were evaluated in an open-label study in 19 patients with schizophrenia.³⁸ The mean dosage of quetiapine at the end of the study was 391 ± 214 mg/day. Quetiapine significantly improved overall psychopathology and positive symptoms as assessed by BPRS total and BPRS positive symptoms scores. Negative symptoms were reduced, but the difference was not statistically significant. Ratings for EPS or tardive dyskinesia did not change significantly during the study. At the same time, treatment with quetiapine significantly improved measures of attention, fine motor performance, and working memory. In these 4 different studies,³³⁻³⁸ treatment with quetiapine produced significant improvement in cognitive function in patients with schizophrenia.

Mood

Depressive symptoms are present in up to 60% of patients with schizophrenia; these symptoms affect social and work function as well as quality of life and may contribute to the high lifetime rate of completed suicide (10%) and suicide attempts (30%–50%) in patients with schizophrenia.^{39,40} Because the most common correlates of suicidality in schizophrenia are depressive symptoms,⁴⁰ exhibiting therapeutic effects on mood is a highly desirable characteristic for an antipsychotic. A review of the literature regarding the efficacy of clozapine, risperidone, olanzapine, quetiapine, and ziprasidone in the treatment of depression, hostility, and suicidality in patients with schizophrenia concluded that atypical antipsychotics do improve depressive symptoms and hostility in addition to psychosis.⁴¹

Several studies have examined the effects of quetiapine on mood symptoms in patients with schizophrenia. In a study by Lee and Meltzer,⁴² 2 analyses were performed: (1) 4 randomized, double-blind, 6- to 12-week quetiapine (150–750 mg/day) versus haloperidol (12 mg/day) com-

parator trials (quetiapine, N = 676; haloperidol, N = 559) and (2) 3 randomized, double-blind, placebo-controlled, 6-week trials (quetiapine, N = 284; placebo, N = 116). Treatment with quetiapine resulted in significant improvements in BPRS Factor I (somatic concern, anxiety, guilt feelings, depressive mood) and Kay's Depressive Factor (sum of PANSS items: anxiety, guilt feelings, depression, somatic concern, preoccupation) compared with haloperidol. In the placebo-controlled studies, treatment with quetiapine was associated with significant improvements in BPRS mood cluster and BPRS Factor I compared with placebo. Quetiapine was significantly more effective than haloperidol and placebo in the treatment of mood symptoms associated with schizophrenia.

An analysis using results from fixed-dose, placebo- and haloperidol-controlled, and lower (250 mg/day)/higher (750 mg/day)-dose trials was conducted with affective symptoms assessed using BPRS Factor I and BPRS mood cluster scores.⁴³ The percentage of patients responding to treatment with quetiapine was significantly higher at the 150-mg/day dose than for placebo or haloperidol on both measures of affective symptoms. In lower (250 mg/day)/higher (750 mg/day)-dose trials, the percentage of responders treated with high-dose quetiapine was significantly greater than with placebo for BPRS Factor I and BPRS mood cluster scores.

In a multicenter, double-blind, randomized trial, the use of quetiapine (600 mg/day) and the use of haloperidol (20 mg/day) were compared in patients with schizophrenia with partial response to conventional antipsychotic treatment.⁴⁴ Depressive symptoms were measured by means of Kay's Depression Factor. Quetiapine was superior to haloperidol in treating depressive symptoms, and this effect was not secondary to effects on positive, negative, or extrapyramidal symptoms, but instead was the result of a direct effect of quetiapine on depressive symptoms.

Aggression

Schizophrenia is often associated with aggressive behavior during the acute psychotic phase.⁴¹ The presence of delusions has been specifically linked to an increased risk of violence.⁴⁵ Preliminary studies suggest that atypical antipsychotics may reduce hostility and aggressive behaviors associated with psychosis.⁴¹

The effectiveness of quetiapine in reducing aggression and hostility in patients with schizophrenia was examined using results from fixed-dose, placebo- and haloperidol-controlled trials.⁴³ Aggression and hostility were assessed using the BPRS hostility cluster score (mean of anxiety, tension, hostility, suspiciousness, uncooperativeness, excitement). Across a broad range of doses, treatment with quetiapine produced statistically significant improvements in hostility measures when compared with placebo, while haloperidol did not. This result suggests the possible

utility of quetiapine in improving symptoms of aggression and hostility in patients with schizophrenia.

SAFETY AND TOLERABILITY

In clinical studies, the most frequently reported adverse events (occurring with a frequency $\geq 10\%$ in controlled trials with quetiapine versus placebo) were headache (19% versus 18%), somnolence (18% versus 11%), and dizziness (10% versus 4%), with most occurrences being mild or moderate in intensity and of limited duration.⁴³ There was little difference in the overall incidence of discontinuation due to adverse events in quetiapine- versus placebo-treated patients (4% versus 3%).⁴³ The general tolerability of quetiapine in clinical trials was quite good and not much different from placebo.

EPS

After decades of use, conventional antipsychotics have been associated with high risk of acute EPS, including akathisia, dystonia, dyskinesia, and parkinsonism. Late-onset EPS such as tardive dyskinesia are known to develop in the same patients who develop EPS.^{46,47} In clinical trials, the occurrence of EPS is monitored in the following ways⁴³: (1) change in the Simpson-Angus Scale^{48,49} (a 10-item instrument used to measure drug-induced parkinsonism) score, (2) incidence of EPS events, (3) use of anticholinergic medications for the treatment of EPS, (4) number of withdrawals from treatment due to EPS, (5) change in Barnes Akathisia Scale^{50,51} (a 4-item scale used to assess drug-induced akathisia) score, and (6) change in Abnormal Involuntary Movement Scale⁵² (a 12-item instrument that assesses abnormal movements, such as tardive dystonia, chronic akathisia, and motor disturbance related to the illness itself) score.

In placebo-controlled trials, the incidence of EPS with quetiapine was not different from placebo across the entire therapeutic range of quetiapine doses.⁴³ Fewer patients taking quetiapine (8.6%) were prescribed medications to offset EPS compared with the number of patients taking placebo (12.6%), which represents carryover EPS from the previous antipsychotic. In the quetiapine fixed-dose trial, the incidence of EPS was significantly lower in the quetiapine groups compared with the haloperidol group.¹² Consequently, in clinical trials, quetiapine was associated with an incidence of EPS that was no different from that of placebo, regardless of dosage. This placebo-level incidence of EPS across its entire dose range distinguishes quetiapine from risperidone, olanzapine, and ziprasidone, which are all characterized by a dose-dependent increase in EPS.⁵³

Prolactin and Sexual Function

Sustained hyperprolactinemia secondary to antipsychotic medications may result in side effects such as ga-

lactorrhea, gynecomastia, menstrual irregularities, and sexual dysfunction. These side effects may contribute to medication noncompliance.

An analysis of plasma prolactin concentrations was performed on data obtained during 3 clinical trials.⁵⁴ This analysis showed that, across the dose range studied, quetiapine did not differ from placebo in its effect on plasma prolactin levels after up to 6 weeks of treatment. Although no significant difference was found in the degree of decline of plasma prolactin levels when patients treated with quetiapine and placebo were compared, a significant difference was found between quetiapine-treated and chlorpromazine-treated patients; the prolactin levels in quetiapine-treated patients were lower than in chlorpromazine-treated patients. In all 3 trials, quetiapine did not cause a sustained elevation of serum prolactin levels.

Other Body Systems

Weight gain. Weight gain is an adverse effect that is associated with both medical complications and medication nonadherence.^{55,56} Although this is one of the significant side effects linked to the use of atypical antipsychotics, there are differences among the various antipsychotics in their propensity to produce weight gain.^{57,58} Results from 6-week trials show a modest increase in weight (2.08 kg [4.58 lb]) with quetiapine.⁵⁹ However, long-term results (>1 year) showed an increase of 0.41 kg (0.91 lb) with quetiapine.⁵⁸ Comparing these results to published information on studies of other atypical antipsychotic drugs suggests that quetiapine may have a more favorable side effect profile in terms of weight gain.⁴⁷

Patients with schizophrenia who had received quetiapine monotherapy were analyzed during open-label extensions of controlled and uncontrolled clinical trials.⁵⁸ For 178 patients with a mean duration of treatment of 563 days, the mean change in weight was 0.41 kg (0.91 lb). Only 1 patient (0.22%) withdrew as a result of weight gain, and weight changes with quetiapine monotherapy showed no association with dose or gender. Quetiapine appeared to have a favorable weight profile or normalizing effect, with a tendency toward favorable shifts in body weight in underweight patients (body mass index [BMI] < 18.5 kg/m²) and severely obese patients (BMI ≥ 35 kg/m²). As a result of this analysis, the conclusion was reached that long-term weight changes with quetiapine are minimal.

Diabetes. Hyperglycemia and type 2 diabetes mellitus are more common in patients with schizophrenia than in the general population.⁶⁰ Recently, numerous reports have linked the atypical antipsychotics to the emergence of hyperglycemia and diabetes mellitus.^{61,62} Current evidence suggests that some atypical antipsychotics may impair glucose metabolism and increase the risk of diabetes in patients with schizophrenia.⁶²

In an open-label, 10-month, retrospective comparative study,⁶³ the effects on weight and glycemic control of changing from monotherapy with clozapine to combination therapy with clozapine and quetiapine were assessed. A group of 65 patients who were residing in long-term care facilities had 25% of their clozapine dose replaced by quetiapine. All 65 patients showed total weight losses ranging from 0.45 to 18.6 kg (1.0 to 40.9 lb). Furthermore, 20% of the patients who had developed diabetes during the initial 6-month period of clozapine monotherapy exhibited significant improvement of disease status with the addition of quetiapine. During this study, compliance with medication was 100%. These results suggest the use of clozapine-quetiapine combination therapy in patients who develop weight gain, hyperglycemia, or diabetes while being treated with clozapine monotherapy.

Lenticular opacities. Potential risk factors associated with cataract formation are certain conventional antipsychotic medications (e.g., thioridazine and chlorpromazine),⁶⁴ increased age, high blood pressure, diabetes, cigarette smoking, alcohol use, dietary deficiencies, and trauma.⁶⁵

Preclinical findings from studies conducted in beagle dogs suggest a possible association between quetiapine and cataracts after 6 to 12 months of exposure.⁶⁶ Cataracts were observed in dogs administered 4 times the maximum recommended human dose (relative to body weight). Cataracts related to quetiapine use have not been seen in any other species.

Since its approval in September 1997 and through January 2002, quetiapine has been prescribed for an estimated 3 million patients worldwide (data on file, AstraZeneca Pharmaceuticals, L.P., Wilmington, Del.). During this period, the reports of lens abnormalities in patients exposed to quetiapine have been very rare (defined as occurring in fewer than 1/10,000 patients). Although no causal relationship between lens changes and quetiapine use has been established, the possibility of lenticular changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to detect cataract formation, such as slit lamp or other appropriately sensitive methods, is recommended at the initiation of treatment with quetiapine, or shortly thereafter, and every 6 months during chronic treatment.

Thyroid. A 20% decrease in total and free thyroxine (T₄) was observed at the higher end of quetiapine's therapeutic dose range; however, this effect occurred early during treatment, and further changes did not occur during chronic therapy.⁴³ Generally, changes in T₄ levels were of no clinical significance and thyroid-stimulating hormone (TSH) was unchanged in most patients; however, a small percentage of patients (0.4%) did experience TSH increases.

Liver enzymes. Asymptomatic, transient, and reversible elevations in serum transaminases (primarily aspartate transaminase [AST]) have been observed in patients

treated with quetiapine during clinical trials.⁴³ In placebo-controlled trials, the proportion of patients showing elevations of greater than 3 times the upper limit of the normal reference range was approximately 6% with quetiapine compared with 1% with placebo.⁴³ These hepatic enzyme elevations usually occurred within the first 3 weeks of drug treatment and returned to pretreatment levels with continued treatment.⁴³

Cardiovascular system. Antipsychotic drugs, including quetiapine, may induce orthostatic hypotension, especially during the initial titration period. These symptoms are a reflection of α_1 -adrenergic antagonist properties.⁴³ The risk of orthostatic hypotension and syncope may be minimized by ensuring adequate hydration and following the recommended upward titration of the dose of quetiapine.

Antipsychotic drugs, including some atypical antipsychotics, may cause electrocardiogram (ECG) changes involving a prolongation of QT interval. The risks are substantially higher for drugs such as thioridazine and droperidol than for the atypical antipsychotics.⁶⁷ This lengthening of the QT interval may lead to drug-induced arrhythmia or sudden unexplained death. Because the QT interval is affected by heart rate, it is usually corrected and called QTc. Although Bazett's correction,⁶⁸ dividing the measured QT interval by the square root of the measured RR interval, is the simplest, this formula overcorrects the QT interval at high heart rates and undercorrects it at low heart rates. Another common correction is the cubic root Fridericia's formula.⁶⁹ In a study in 881 men, an evaluation of 10 different formulas for correcting QT intervals concluded that Fridericia's correction fit the data better than Bazett's square root formula.⁷⁰

A review of ECG recordings for patients exposed to quetiapine in clinical trials revealed little mean change in QTc interval and no relationship between plasma levels of quetiapine and any changes in QTc interval.⁴³ A review of antipsychotic drugs and QTc prolongation concluded that there was no association with treatment with quetiapine.⁷¹

Because of FDA concerns about the possibility of QTc prolongation by the atypical antipsychotic ziprasidone, Pfizer Inc conducted a clinical trial, Study 54.⁷² In this open-label study of 164 patients with schizophrenia, the effects of various antipsychotics (haloperidol, 15 mg; olanzapine, 20 mg; quetiapine, 750 mg; risperidone, 16 mg; thioridazine, 300 mg; and ziprasidone, 160 mg) on QTc were determined. Mean QTc intervals were calculated using Bazett's correction, both in the absence and presence of a cytochrome P450 inhibitor. The only serious increases in QTc with a metabolic inhibitor was with thioridazine (which was given a black box warning by the FDA after the completion of the study). None of the atypical antipsychotics showed a clinically significant increase in QTc, although ziprasidone had the highest. These increases still resulted in QTc intervals that were < 425 milliseconds for most patients and were within the normal range.

SUMMARY

Compliance with medication and adherence to treatment have a significant impact on relapse prevention and long-term treatment outcome for patients with schizophrenia; consequently, antipsychotics with minimal side effects are desirable. The efficacy, safety, and tolerability of quetiapine for the treatment of psychosis in patients with schizophrenia have been determined in a number of randomized, double-blind, clinical trials.

The efficacy of quetiapine in reducing psychotic symptoms in patients with schizophrenia has been measured with improvements in BPRS total scores, BPRS positive symptoms scores, SANS scores, PANSS scores, and CGI scores. In randomized, double-blind clinical trials, quetiapine produced greater improvement than placebo and psychotic symptom improvement either greater than or comparable to haloperidol or chlorpromazine. In an open-label study, the improvement with quetiapine treatment was maintained over a period of a year.

Beneficial effects of quetiapine have also been reported in a spectrum of mood symptom domains, such as cognition, mood, anxiety, and aggression, in patients with schizophrenia. For example, patients whose symptoms are well controlled with conventional antipsychotics may still receive significant cognitive benefit from being switched to quetiapine.

All studies support the minimal propensity of quetiapine to produce EPS or hyperprolactinemia. In clinical trials, the incidence of EPS with treatment with quetiapine across the dosage range of 250 to 750 mg/day was no different from that associated with placebo. With respect to other safety concerns, long-term weight gain with quetiapine is less than that observed with other atypical antipsychotic agents. The risk of developing diabetes appears to be less for quetiapine than for some of the other antipsychotics. A causal relationship between cataracts and quetiapine treatment has not been established, and treatment with quetiapine is not associated with clinically significant QTc prolongation. Overall, quetiapine has many desirable tolerability and safety features for the treatment of patients with schizophrenia.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), droperidol (Inapsine and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), thioridazine (Mellaril and others), thyroxine (Levoxyl, Synthroid), ziprasidone (Geodon).

REFERENCES

1. Buchanan RW, Carpenter WT. Schizophrenia: introduction and overview. In: Sadock BJ, Sadock VA, eds. *Kaplan & Sadock's Comprehensive Textbook of Psychiatry*. 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins;2000:1096-1110
2. Fenton WS, Blyler CR, Heinssen RK. Determinants of medication compliance in schizophrenia: empirical and clinical findings. *Schizophr Bull* 1997;23:637-651

3. Kampman O, Lehtinen K. Compliance in psychoses. *Acta Psychiatr Scand* 1999;100:167–175
4. Oehl M, Hummer M, Fleischhacker WW. Compliance with antipsychotic treatment. *Acta Psychiatr Scand Suppl* 2000;102:83–86
5. DeQuardo JR. Pharmacologic treatment of first-episode schizophrenia: early intervention is key to outcome. *J Clin Psychiatry* 1998;59(suppl 19): 9–17
6. DeQuardo JR, Tandon R. Do atypical antipsychotic medications favorably alter the long-term course of schizophrenia? *J Psychiatr Res* 1998;32: 229–242
7. Cornblatt BA, Lencz T, Kane JM. Treatment of the schizophrenia prodrome: is it presently ethical? *Schizophr Res* 2001;51:31–38
8. McGlashan TH. Psychosis treatment prior to psychosis onset: ethical issues. *Schizophr Res* 2001;51:47–54
9. Tandon R, Miller K, Jibson MD. Antipsychotics from theory to practice: integrating clinical and basic data. *J Clin Psychiatry* 1999;60(suppl 8): 21–28
10. Jibson MD, Tandon R. Treatment of schizophrenia. *Psychiatr Clin North Am Annu Drug Ther* 2000;7:83–113
11. Borison RL, Arvanitis LA, Miller BG, and the U.S. SEROQUEL Study Group. ICI 204,636, an atypical antipsychotic: efficacy and safety in a multicenter, placebo-controlled trial in patients with schizophrenia. *J Clin Psychopharmacol* 1996;16:158–169
12. Arvanitis LA, Miller BG, and the Seroquel Trial 13 Study Group. Multiple fixed doses of “Seroquel” (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. *Biol Psychiatry* 1997;42:233–246
13. Small JG, Hirsch SR, Arvanitis LA, et al, and the Seroquel Study Group. Quetiapine in patients with schizophrenia: a high- and low-dose double-blind comparison with placebo. *Arch Gen Psychiatry* 1997;54:549–557
14. Peuskens J, Link CG. A comparison of quetiapine and chlorpromazine in the treatment of schizophrenia. *Acta Psychiatr Scand* 1997;96:265–273
15. King DJ, Link CG, Kowalczyk B. A comparison of bid and tid dose regimens of quetiapine (Seroquel) in the treatment of schizophrenia. *Psychopharmacology (Berl)* 1998;137:139–146
16. Copolov DL, Link CG, Kowalczyk B. A multicentre, double-blind, randomized comparison of quetiapine (ICI 204,636, ‘Seroquel’) and haloperidol in schizophrenia. *Psychol Med* 2000;30:95–105
17. Emsley RA, Raniwalla J, Bailey PJ, et al, on behalf of the PRIZE Study Group. A comparison of the effects of quetiapine (‘Seroquel’) and haloperidol in schizophrenic patients with a history of and a demonstrated, partial response to conventional antipsychotic treatment. *Int Clin Psychopharmacol* 2000;15:121–131
18. Goldstein JM, Buckley P, Emsley R. Comparison of the effects of quetiapine and haloperidol in a cohort of patients with treatment-resistant schizophrenia. Presented at the 4th annual meeting of the College of Psychiatric and Neurologic Pharmacists; March 25–28, 2001; San Antonio, Texas
19. Velligan DI, Prihoda T, Sui S, et al. Effectiveness of quetiapine versus conventional antipsychotics in improving cognitive and functional outcomes. Presented at the 40th annual meeting of the American College of Neuropsychopharmacology; Dec 9–13, 2001; Waikoloa, Hawaii
20. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol Rep* 1962;10:799–812
21. Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. *Arch Gen Psychiatry* 1988;45:789–796
22. Tandon R, Ribeiro SC, DeQuardo JR, et al. Covariance of positive and negative symptoms during neuroleptic treatment in schizophrenia: a replication. *Biol Psychiatry* 1993;34:495–497
23. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13:261–276
24. Andreasen NC. The Scale for the Assessment of Negative Symptoms (SANS): conceptual and theoretical foundations. *Br J Psychiatry* 1989; 155(suppl 7):49–58
25. 12-CGI: clinical global impressions. In: Guy W, Bonate RR, eds. *Manual for the ECDEU Assessment Battery*. Chevy Chase, Md: National Institute of Mental Health; 1970:12-1–12-6
26. Nasrallah HA, Barker N, Emsley R. Patterns of clinical response in patients with schizophrenia treated with quetiapine or haloperidol after a suboptimal response to a fluphenazine trial. Presented at the 40th annual meeting of the American College of Neuropsychopharmacology; Dec 9–13, 2001; Waikoloa, Hawaii
27. Arvanitis LA, Rak IW. The long-term efficacy and safety of ‘Seroquel’ (quetiapine) [abstract]. *Schizophr Res* 1997;24:196
28. Saykin AJ, Shtasel DL, Gur RE, et al. Neuropsychological deficits in neuroleptic naive patients with first-episode schizophrenia. *Arch Gen Psychiatry* 1994;51:124–131
29. Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry* 1996;153:321–330
30. Velligan DI, Mahurin RK, Diamond PL, et al. The functional significance of symptomatology and cognitive function in schizophrenia. *Schizophr Res* 1997;25:21–31
31. Heaton R, Crowley T. Effects of psychiatric disorders and their somatic treatments on neuropsychological results. In: Filskov S, Bell TJ, eds. *Handbook of Clinical Neuropsychology*. New York, NY: John Wiley & Sons; 1981:481–525
32. Spohn HE, Strauss ME. Relation of neuroleptic and anticholinergic medication to cognitive functions in schizophrenia. *J Abnorm Psychol* 1989;98: 367–380
33. Meltzer HY, McGurk SR. The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. *Schizophr Bull* 1999; 25:233–255
34. Sax KW, Strakowski SM, Keck PE Jr. Attentional improvement following quetiapine fumarate treatment in schizophrenia. *Schizophr Res* 1998;33: 151–155
35. Purdon SE, Hellewell JSE. The effect of quetiapine in improving cognitive impairment in schizophrenia. Presented at the 8th International Congress on Schizophrenia Research; April 28–May 2, 2001; Whistler, British Columbia, Canada
36. Velligan DI, Newcomer J, Pultz J, et al. Does cognitive function improve with quetiapine in comparison to haloperidol? *Schizophr Res* 2002;53: 239–248
37. Mueller J, Velligan D, DiCocco M, et al. Quetiapine improves verbal memory in patients with schizophrenia. Presented at the 42nd annual meeting of the New Clinical Drug Evaluation Unit; June 10–13, 2002; Boca Raton, Fla
38. Meltzer HY, Lee MA. Quetiapine improves cognitive function in schizophrenia. Presented at the 8th International Congress on Schizophrenia Research; April 28–May 2, 2001; Whistler, British Columbia, Canada
39. Siris SG. Depression in schizophrenia: perspective in the era of “Atypical” antipsychotic agents. *Am J Psychiatry* 2000;157:1379–1389
40. Siris SG. Suicide and schizophrenia. *J Psychopharmacol* 2001;15:127–135
41. Keck PE Jr, Strakowski SM, McElroy SL. The efficacy of atypical antipsychotics in the treatment of depressive symptoms, hostility, and suicidality in patients with schizophrenia. *J Clin Psychiatry* 2000;61(suppl 3):4–9
42. Lee M, Meltzer H. Quetiapine is significantly superior to haloperidol and placebo in improving mood in patients with schizophrenia. Presented at the 7th World Congress of Biological Psychiatry; July 1–6, 2001; Berlin, Germany
43. Goldstein J. Quetiapine fumarate (Seroquel): a new atypical antipsychotic. *Drugs Today* 1999;35:193–210
44. Emsley R, Buckley P, Jones AM, et al. Treatment of depressive symptoms in partially refractory schizophrenia: efficacy of quetiapine versus haloperidol. Presented at the 40th annual meeting of the American College of Neuropsychopharmacology; Dec 9–13, 2001; Waikoloa, Hawaii
45. Taylor PJ. Motives for offending among violent and psychotic men. *Br J Psychiatry* 1985;147:491–498
46. Tarsy D, Baldessarini RJ, Tarazi FI. Effects of newer antipsychotics on extrapyramidal function. *CNS Drugs* 2002;16:23–45
47. Nasrallah HA, Muvihill T. Iatrogenic disorders associated with conventional vs atypical antipsychotics. *Ann Clin Psychiatry* 2001;13:215–227
48. Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand* 1970;45(suppl 212):11–19
49. Simpson GM, Lee JH, Zoubok B, et al. A rating scale for tardive dyskinesia. *Psychopharmacology (Berl)* 1979;64:171–179
50. Barnes TRE. A rating scale for drug-induced akathisia. *Br J Psychiatry* 1989;154:672–676
51. Barnes TR. Clinical assessment of the extrapyramidal side effects of antipsychotic drugs. *J Psychopharmacol* 1992;6:214–221
52. Lane RD, Glazer WM, Hansen TE, et al. Assessment of tardive dyskinesia using the Abnormal Involuntary Movement Scale. *J Nerv Ment Dis* 1985; 173:353–357
53. Tandon R, Jibson MD. Extrapyramidal side effects of antipsychotic treatment: scope of problem and impact on outcome. *Ann Clin Psychiatry*. In press
54. Hamner MB, Arvanitis LA, Miller BG, et al. Plasma prolactin in schizo-

- phrenia subjects treated with Seroquel (ICI 204,636). *Psychopharmacol Bull* 1996;32:107–110
55. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 1999;156:1686–1696
 56. Allison DB, Casey DE. Antipsychotic-induced weight gain: a review of the literature. *J Clin Psychiatry* 2001;62(suppl 7):22–31
 57. Sussman N. Review of atypical antipsychotics and weight gain. *J Clin Psychiatry* 2001;62(suppl 23):5–12
 58. Brecher M, Rak IW, Melvin K, et al. The long-term effect of quetiapine (Seroquel) monotherapy on weight in patients with schizophrenia. *Int J Psychiatry Clin Pract* 2000;4:287–291
 59. Jones A, Rak I, Raniwalla J, et al. Weight changes in patients treated with quetiapine. Presented at the 153rd annual meeting of the American Psychiatric Association; May 13–18, 2000; Chicago, Ill
 60. Mukherjee S, Decina P, Bocola V, et al. Diabetes mellitus in schizophrenic patients. *Compr Psychiatry* 1996;37:68–73
 61. Henderson DC. Atypical antipsychotic-induced diabetes mellitus: how strong is the evidence? *CNS Drugs* 2002;16:77–89
 62. Newcomer JW, Haupt DW, Fucetola R, et al. Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. *Arch Gen Psychiatry* 2002;59:337–345
 63. Reinstein M, Sirotovskaia L, Jones L, et al. Effect of clozapine-quetiapine combination therapy on weight and glycaemic control. *Clin Drug Invest* 1999;18:99–104
 64. Isaac NE, Walker AM, Jick H, et al. Exposure to phenothiazine drugs and risk of cataract. *Arch Ophthalmol* 1991;109:256–260
 65. Johnson GJ. Limitations of epidemiology in understanding pathogenesis of cataracts. *Lancet* 1998;351:925–926
 66. Seroquel [prescribing information]. Wilmington, Del: AstraZeneca Pharmaceuticals, LP; Revised Jan 2001
 67. Reilly JG, Ayis SA, Ferrier IN, et al. QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. *Lancet* 2000;355:1048–1052
 68. Bazett HC. An analysis of the time-relations of electrocardiograms. *Heart* 1920;7:353–370
 69. Fridericia LS. Die Systolendauer im Elektrokardiogramm bei normalen Menschen und bei Herzkranken. *Acta Med Scand* 1920;53:469–486
 70. Puudu PE, Jouve R, Mariotti S, et al. Evaluation of 10 QT prediction formulas in 881 middle-aged men from the seven countries study: emphasis on the cubic root Fridericia's equation. *J Electrocardiol* 1988;21:219–229
 71. Glassman AH, Bigger JT Jr. Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. *Am J Psychiatry* 2001;158:1774–1782
 72. Pfizer, Inc. Food and Drug Administration Psychopharmacological Drugs Advisory Committee. Briefing document for Zeldox capsules (ziprasidone HCl). July 19, 2000. Available at: <http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3619b1a.pdf>. Accessed Sept 30, 2002

Copyright © 2002 Physicians Postgraduate Press, Inc.
One personal copy may be printed