

Efficacy and Tolerability of Once-Daily Extended Release Quetiapine Fumarate in Acute Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Study

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Objective: To evaluate the efficacy and tolerability of extended release quetiapine fumarate (quetiapine XR) in a 6-week, double-blind, randomized study.

Method: Patients with a DSM-IV diagnosis of acute schizophrenia were randomly assigned to fixed-dose quetiapine XR 400, 600, or 800 mg/day (once daily in the evening), quetiapine immediate release (IR) 400 mg/day (200 mg twice daily), or placebo. Dual-matched placebo was used to maintain blinding. Quetiapine XR target doses were reached by day 2 (400 and 600 mg) and day 3 (800 mg). The primary endpoint was least squares mean change from baseline to week 6 in Positive and Negative Syndrome Scale (PANSS) total score. PANSS response rate (percentage of patients with $\geq 30\%$ reduction in total score), Clinical Global Impressions-Improvement scale (CGI-I) response rate (percentage of patients with score ≤ 3), change in CGI-Severity of Illness (CGI-S), and adverse events (AEs) were also assessed. The study was conducted from November 2004 to December 2005.

Results: 588 patients were enrolled and 446 (76%) completed the study. Improvement in PANSS total score at week 6 was significant versus placebo (-18.8) in all groups: -24.8 ($p = .03$), -30.9 ($p < .001$), and -31.3 ($p < .001$) for quetiapine XR 400, 600, and 800 mg, respectively, and -26.6 ($p = .004$) for quetiapine IR. There were also statistically significant differences in PANSS and CGI-I response rates for all active treatments versus placebo (all $p < .05$). The most common AEs in all quetiapine groups were somnolence and dizziness; there were no unexpected AEs with quetiapine XR. Incidence of AEs potentially related to extrapyramidal symptoms was similar to placebo.

Conclusion: Once-daily quetiapine XR (400–800 mg/day) was effective versus placebo in patients with acute schizophrenia. Treatment, including rapid dose escalation, was well tolerated, with a therapeutically effective dose reached by day 2.

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Quetiapine fumarate (quetiapine), a dibenzothiazepine derivative, is an atypical antipsychotic licensed for the treatment of schizophrenia and bipolar mania, and on the basis of the BOLDER studies,^{1,2} was recently approved for use in bipolar depression in the United States. It is currently available as immediate-release (IR) tablets and, for the treatment of schizophrenia, is generally administered twice daily. The maximum licensed dose is 750 mg/day in Europe and 800 mg/day in the United States, with a recommended 4-day treatment initiation period to reach a therapeutic dose.

Nonadherence to medication is a major issue in patients with schizophrenia. It is estimated that up to 50% of patients with schizophrenia do not adhere to their prescribed treatment regimen, and this can lead to treatment failure, relapse, and serious consequences, such as hospi-

talization or suicide.³⁻⁶ Several factors can affect adherence, including the perceived benefits and side effects of treatment, patients' insight into their illness, and the complexity of the dosing regimen.⁷⁻⁹

Extended release quetiapine fumarate (quetiapine XR) has been developed to reduce the frequency of quetiapine dosing by introducing once-daily administration and to simplify the treatment-initiation schedule. Once-daily administration may improve patient adherence, and simplified initiation will allow patients to reach an effective dose earlier without compromising the known safety profile of quetiapine.

Pharmacokinetic studies with quetiapine XR have shown that compared with the IR formulation, the time to maximum plasma concentration (t_{max}) is longer (approximately 6 hours vs. approximately 1 hour), but at the same total daily doses, the total daily exposure (as measured by the area under the plasma concentration-time curve, at steady state) for quetiapine XR dosed once daily is the same as that for quetiapine IR dosed twice daily (data on file, AstraZeneca, Wilmington, Del.). The elimination half-life of quetiapine XR (approximately 7 hours) is also similar to the IR formulation (data on file, AstraZeneca, Wilmington, Del.).

This study was designed to assess the efficacy and tolerability of quetiapine XR compared with placebo in patients with schizophrenia, as well as to identify a clinically relevant dose range for quetiapine XR. An additional arm, in which patients were treated with quetiapine IR, was included to assess the validity of the study, and to provide a reference group to evaluate the tolerability of quetiapine XR. The primary hypothesis was that quetiapine XR would provide superior efficacy against positive and negative symptoms compared with placebo. It was also hypothesized that quetiapine XR would be more effective than placebo for aggression and hostility, as previous studies with the IR formulation have shown it to be effective for these symptoms in patients with schizophrenia.¹⁰

METHOD

Study Design

This was a 6-week, international, multicenter, randomized, double-blind, placebo-controlled study. It was conducted at 39 centers in Bulgaria, Greece, India, Indonesia, the Philippines, Russia, Romania, and South Africa from November 2004 to December 2005.

The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference on Harmonization/Good Clinical Practice. Institutional review board approval was required for each study site. All patients (or their legal representatives) had to provide written, informed consent before initiation of any study procedures.

Patients

The study included male and female inpatients or outpatients, aged 18 to 65 years, with a DSM-IV diagnosis of acute schizophrenia: catatonic (DSM-IV diagnostic code 295.20); disorganized (295.10); paranoid (295.30); or undifferentiated (295.90). Diagnosis was made during a clinical interview with the patient.

Key inclusion criteria were a Positive and Negative Syndrome Scale (PANSS)¹¹ total score of 70 or above; a Clinical Global Impressions-Severity of Illness scale (CGI-S)¹² score of 4 or above (moderate to severe) and, in the opinion of the investigator, a worsening of the patient's condition in the previous 3 weeks; and a PANSS score of 4 or above for at least 1 of the following items: delusions, conceptual disorganization, hallucinatory behavior, or suspiciousness/persecution.

Exclusion criteria included DSM-IV diagnosis of any Axis I condition other than schizophrenia; DSM-IV diagnosis of substance abuse or dependence; hospitalization for the treatment of schizophrenia for more than a month immediately before the start of the study; administration of a depot antipsychotic within 1 dosing interval before the start of the study; clinically relevant other diseases (e.g., renal or hepatic impairment, significant coronary artery disease); diabetes mellitus; and known intolerance to quetiapine. In order to exclude treatment-resistant patients, the following groups were also excluded: patients with a known lack of response to adequate doses of 2 or more antipsychotics given for at least 4 weeks; patients with known lack of response to previous treatment with quetiapine; patients who required clozapine treatment for symptom control; and patients treated with clozapine within 1 month of randomization.

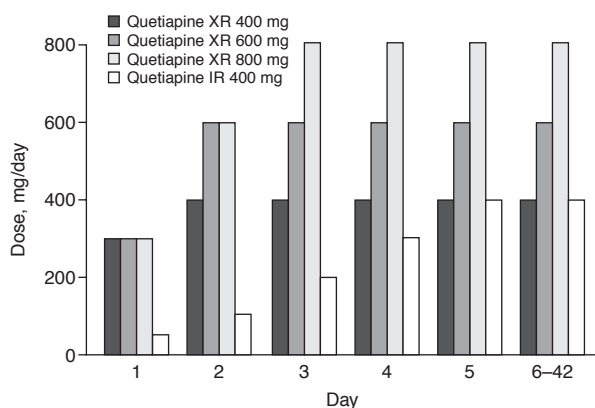
Treatment

Patients were randomly assigned to 1 of 5 treatment groups: quetiapine XR 400 mg/day, quetiapine XR 600 mg/day, quetiapine XR 800 mg/day, quetiapine IR 400 mg/day, or placebo. As the dosing frequencies for quetiapine XR and IR differ, dual-matched placebo was used to maintain blinding. Treatment was administered orally twice daily, in the morning and evening, with or without food. In the quetiapine XR groups, placebo was given in the morning and the active dose was given in the evening.

Quetiapine XR was initiated at 300 mg on day 1. Target doses were reached by day 2 in the quetiapine XR 400-mg and 600-mg groups, and by day 3 in the quetiapine XR 800-mg group. Quetiapine IR was initiated at 50 mg on day 1, and the target dose was reached by day 5; this dosing regimen was based on the prescribing information.¹³ For the remainder of the study (days 6-42), patients received the appropriate fixed dose of quetiapine (or placebo) (Figure 1).

Previous antipsychotic medication, as well as mood stabilizers, hypnotics, antidepressants, anxiolytics, and

Figure 1. Quetiapine Dose Escalation Schedule for Patients With Acute Schizophrenia



Abbreviations: IR = immediate release, XR = extended release.

anticholinergic medication, were discontinued at least 48 hours before randomization. During the study, anticholinergics could only be used to treat emergent extrapyramidal symptoms (EPS) if required.

Lorazepam (up to 6 mg/day) or oxazepam (up to 60 mg/day) could be used to treat agitation during the first 6 days of the study only. Patients were also permitted to continue taking hypnotics and sedatives for insomnia provided that they were only taken at bedtime. Zolpidem, chloral hydrate, zaleplon, and zopiclone could be used during the study to treat insomnia. No other psychoactive medication was permitted. Use of fluoxetine was prohibited from 14 days before randomization until the end of the study.

Assessments

Efficacy was assessed using PANSS¹¹ total and subscale scores and CGI-S¹² and Clinical Global Impressions-Improvement (CGI-I)¹² scores. Baseline PANSS and CGI-S scores were recorded at randomization on day 1. PANSS total and subscale scores and CGI-S scores were assessed at weeks 1, 2, 3, 4, and 6, and CGI-I was assessed at week 6. All center staff performing CGI and PANSS ratings were licensed psychiatrists with sufficient experience dealing with patients with schizophrenia and recent experience of using the PANSS rating scale; to ensure consistency, the same investigator was to conduct all assessments for a given patient. Training on the PANSS rating scale was also provided; this included use of a videotaped patient interview, which investigators were required to assess using the PANSS scale.

The primary efficacy endpoint was the change in PANSS total score from baseline to week 6. Secondary endpoints were the PANSS response rates (percentage of patients with a reduction in PANSS total score \geq 30% at week 6); the change in PANSS total score and PANSS

subscale scores for positive, negative, general psychopathology, aggression and hostility cluster, and depression cluster at each study visit; CGI-I response rates (percentage of patients with a CGI-I score \leq 3 at week 6); and the change in CGI-S at week 6. Post hoc analysis was performed to evaluate the effect of dose (quetiapine XR) on the change in PANSS total scores.

Tolerability measures included adverse events (AEs); laboratory measures (clinical chemistry, hematology, and urinalysis); glucose and insulin; hemoglobin A_{1c} (HbA_{1c}); electrocardiogram; vital signs; weight; Barnes Akathisia Scale (BAS)¹⁴ scores; Simpson-Angus Scale¹⁵ scores; and use of anticholinergic medication. Patients were instructed not to eat or drink fluids (except water) from midnight the day before blood samples were taken for the assessment of glucose, insulin, and lipid variables. For the BAS and Simpson-Angus Scale data, the percentage of patients in each treatment group whose score improved, remained the same, or worsened was also assessed. In order to evaluate somnolence in more detail, a number of MedDRA preferred terms were grouped (somnolence, sedation, lethargy, and sluggishness), and a post hoc analysis was conducted to assess the time to onset and duration of these AEs. If the end date was not available, the duration was assigned a value of 42 days. AEs potentially related to EPS were defined according to relevant MedDRA preferred terms (akathisia, akinesia, athetosis, bradykinesia, buccoglossal syndrome, cervical spasm, chorea, choreoathetosis, cogwheel rigidity, drooling, dyskinesia, dyskinesia oesophageal, dystonia, extrapyramidal disorder, freezing phenomenon, gait festinating, grimacing, hyperkinesia, hypertonia, hypokinesia, masked facies, micrographia, movement disorder, muscle contractions involuntary, muscle rigidity, nuchal rigidity, oculogyration, opisthotonus, parkinsonian gait, parkinsonism, pleurothotonus, posturing, psychomotor hyperactivity, restlessness, tardive dyskinesia, torticollis, and tremor).

Statistical Analysis

Data analyses were based on 3 patient populations: modified intention-to-treat (MITT); per-protocol; and safety. The MITT population consisted of all patients who were given study medication classified to the treatment to which they were randomly assigned, and who had a baseline value and at least 1 postbaseline PANSS assessment. The per-protocol population was a subset of the MITT population of patients with no major protocol deviations or violations affecting efficacy. The safety population consisted of all randomly assigned patients given at least 1 dose of study medication.

For the PANSS training data, κ values for each investigator relative to an expert rating of the PANSS scale were calculated to assess consistency.

The primary hypothesis was that each dose of quetiapine XR (400 mg, 600 mg, and 800 mg) would show supe-

rior efficacy to placebo. The study was not designed or powered to compare the efficacy of quetiapine XR with that of quetiapine IR.

The primary efficacy outcome variable was the change in PANSS total score from baseline to week 6 for quetiapine XR versus placebo, and was the basis for the sample size calculation. Assuming a treatment difference of 12 points between quetiapine XR and placebo, and within-patient variability of 22 points (based on data from previous studies),¹⁶⁻¹⁸ it was estimated that 485 evaluable patients (97 per treatment group) would be required to achieve an overall power of 90% for all 3 comparisons of quetiapine XR versus placebo. Each individual test was calculated with 96.5% power at the 5% α level. Assuming that 90% of randomly assigned patients would be evaluable, the total number of randomly assigned patients required was 535.

The change in PANSS total score was analyzed using 3 pairwise comparisons (each quetiapine XR dose versus placebo) using analysis of covariance. The model included independent variables for treatment and center and the baseline PANSS score as a covariate. Least squares means and confidence intervals (CIs) were calculated for change from baseline scores for each treatment group. Between-treatment differences were estimated using point estimates of differences between least squares means and associated 2-sided 95% CIs. Multiplicity for the 3 comparisons of quetiapine XR versus placebo was adjusted for using the Hommel procedure. For the comparison between the quetiapine IR and placebo arms, multiplicity was not adjusted for, as this comparison was included mainly to demonstrate the validity of the study.

The PANSS subscale scores and CGI-S scores were analyzed using analysis of covariance; PANSS and CGI-I response rates were analyzed using a Cochran-Mantel-Haenszel technique, stratified by treatment group. All secondary efficacy analyses were made to provide supportive evidence of the superiority of quetiapine XR versus placebo. Data were presented as point estimates and 95% CIs for treatment effects and treatment differences. Confidence intervals and p values were nominal, i.e., no adjustments for multiplicity were made.

For the primary efficacy endpoint, a post hoc repeated-measures analysis was performed as a sensitivity analysis; the model included baseline score as a covariate, treatment as a fixed effect, center as a random effect, and scheduled visit as a repeated-measures factor.

To test if there was evidence of increased effect with increased dose in the 3 quetiapine XR arms, the post hoc evaluation of the effect of increasing doses of quetiapine XR on PANSS total scores was analyzed using the non-parametric Jonckheere-Terpstra test¹⁹; the analysis was based on the change in scores from baseline to week 6.

All statistical tests were 2-sided, with a significance level of 5%. For the MITT population, missing values

were accounted for using last observation carried forward. Analysis using observed cases was also performed.

RESULTS

Patients

In total, 588 patients were randomly assigned to treatment; the mean (range) number of patients per center was 15 (2-66). There were 573 patients in the MITT population (placebo, N = 115; quetiapine XR 400 mg, N = 111; quetiapine XR 600 mg, N = 111; quetiapine XR 800 mg, N = 117; quetiapine IR, N = 119), and 556 in the per-protocol population (N = 112, 108, 108, 113, and 115, respectively). All randomly assigned patients were included in the safety population.

Overall, 446 patients (76%) completed the study. Completion rates were 73.5% for quetiapine XR 400 mg, 81.4% for quetiapine XR 600 mg, 74.4% for quetiapine XR 800 mg, 78.0% for quetiapine IR, and 72.0% for placebo (Figure 2).

Baseline demography and clinical characteristics were similar across the treatment groups, including ethnicity and the percentage of patients in hospital (Table 1). At study enrollment, approximately 50% of patients were taking an antipsychotic agent; of these, about 80% were taking conventional (first-generation) antipsychotics. The proportion of patients who were inpatients at randomization was similar across all treatment groups (Table 1). At week 6, the percentages of inpatients were 68.4% for placebo; 68.3%, 62.6%, and 55.6% for quetiapine XR 400, 600, and 800 mg/day; and 70.8% for quetiapine IR.

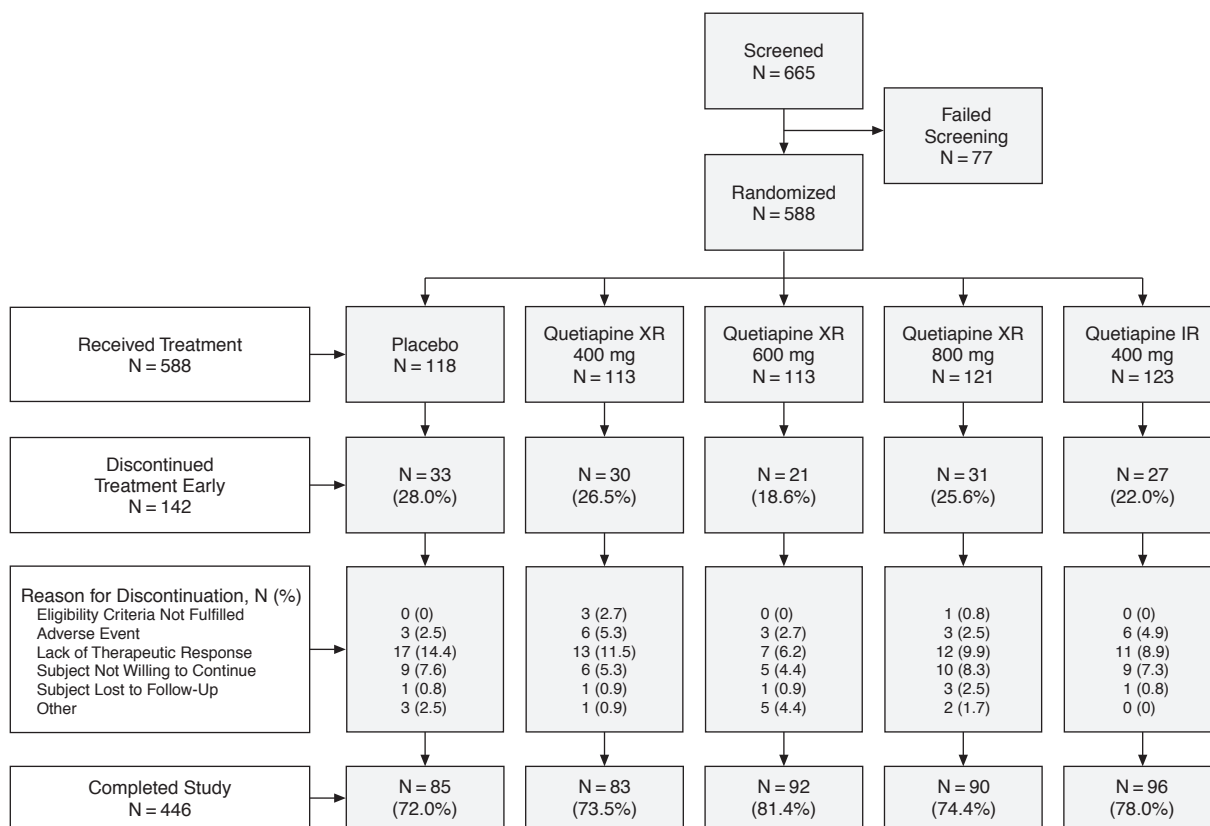
On day 6, the proportion of patients receiving lorazepam or oxazepam was 8.7% for placebo, 9.0% for quetiapine XR 400 mg, 4.6% for quetiapine XR 600 mg, 8.5% for quetiapine XR 800 mg, and 5.1% for quetiapine IR. After day 6, the percentages were 0.9%, 0%, 1.9%, 3.4%, and 1.7%, respectively. In accordance with the study protocol, unless these agents had been prescribed as sleep medication at bedtime from study start, patients receiving these agents after day 6 were excluded from the per-protocol analysis.

The percentages of patients taking medication for insomnia were higher in the placebo group compared with the quetiapine groups: 17.4% for placebo during week 1, compared with 9.0% to 10.8% for active treatment. During the last week of the study, the corresponding values were 15.3% and 2.3% to 5.1%, respectively.

PANSS Rating Scale Training

The overall κ value across all raters was 0.819, indicating a very high level of agreement between all raters, including investigators and the expert raters. The lowest individual rater κ value was 0.379, but all other values were above 0.49, and the majority of investigators had a κ value above 0.83.

Figure 2. Patient Disposition During the Study of Quetiapine in Acute Schizophrenia



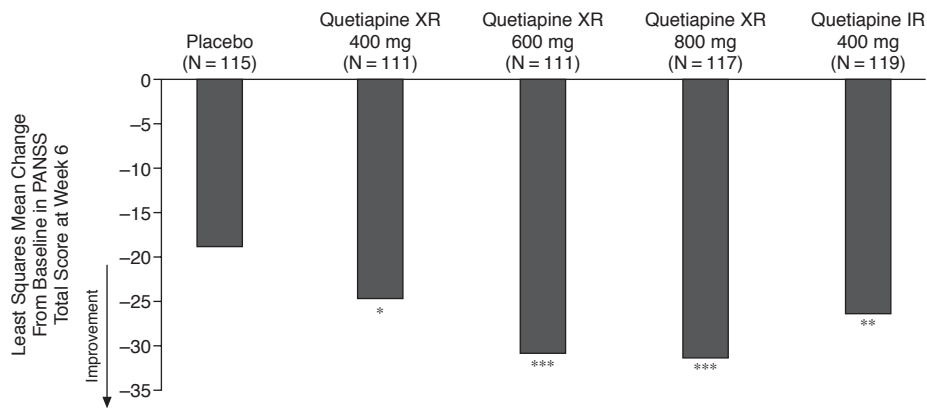
Abbreviations: IR = immediate release, XR = extended release.

Table 1. Baseline Demography and Clinical Characteristics of Patients With Acute Schizophrenia (MITT population)

Characteristic	Placebo (N = 115)	Quetiapine XR 400 mg (N = 111)	Quetiapine XR 600 mg (N = 111)	Quetiapine XR 800 mg (N = 117)	Quetiapine IR 400 mg (N = 119)
Sex, male, %	58.3	70.3	55.0	59.8	58.0
Age, mean (SD), y	34.1 (12.1)	34.1 (9.6)	34.2 (9.9)	34.4 (10.3)	34.4 (10.2)
Ethnicity, %					
White	59.1	56.8	59.5	60.7	59.7
Black	4.3	4.5	3.6	4.3	5.9
Asian	36.5	38.7	36.0	35.0	34.5
Other	0	0	0.9	0	0
DSM-IV schizophrenia subtype, %					
Disorganized (295.10)	4.3	7.2	4.5	4.3	1.7
Catatonic (295.20)	0.9	1.8	0	0	0.8
Paranoid (295.30)	68.7	64.0	64.9	64.1	73.9
Undifferentiated (295.90)	26.1	27.0	30.6	31.6	23.5
Psychiatric history (schizophrenia)					
Age at diagnosis, mean (SD), y	26.6 (9.2)	25.8 (7.9)	25.8 (7.7)	26.9 (8.4)	26.9 (8.7)
Time since diagnosis, mean (SD), y	8.0 (8.1)	8.8 (7.9)	8.9 (8.1)	8.0 (8.1)	8.0 (8.2)
No. of episodes, mean (SD)	4.8 (4.4)	5.1 (4.6)	4.8 (4.1)	5.0 (4.6)	4.6 (4.3)
Antipsychotic medication at enrollment, %	49.6	55.0	45.9	49.6	48.7
Typical	36.5	45.0	35.1	39.3	39.5
Atypical	15.7	13.5	12.6	12.8	13.4
Olanzapine	3.5	3.6	2.7	2.6	4.2
Risperidone	8.7	3.6	3.6	5.1	3.4
Inpatients, %	74.8	78.4	77.5	73.5	77.3
Baseline scores, mean (SD)					
PANSS total	96.2 (13.3)	95.8 (13.9)	96.8 (14.1)	97.3 (14.7)	96.5 (16.0)
CGI-S	4.9 (0.7)	4.9 (0.7)	4.9 (0.7)	5.0 (0.7)	4.9 (0.6)

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, IR = immediate release, MITT = modified intention-to-treat, PANSS = Positive and Negative Syndrome Scale, XR = extended release.

Figure 3. Change in PANSS Total Score From Baseline to Week 6 (MITT, LOCF)



* $p < .05$ vs. placebo.

** $p < .01$ vs. placebo.

*** $p < .001$ vs. placebo.

Abbreviations: IR = immediate release, LOCF = last observation carried forward, MITT = modified intention-to-treat, PANSS = Positive and Negative Syndrome Scale, XR = extended release.

Efficacy

Compared with placebo, the least squares mean change in PANSS total score from baseline to week 6 (the primary endpoint) was statistically significant for all active treatments (Figure 3). The magnitude of the change from baseline was -24.8 ($p = .03$), -30.9 ($p < .001$), and -31.3 ($p < .001$) for quetiapine XR 400, 600, and 800 mg, respectively, and -26.6 ($p = .004$) for quetiapine IR, versus -18.8 for placebo. Post hoc analysis of the PANSS total score data for increasing doses of quetiapine XR was statistically significant ($p = .013$), indicating a dose response for quetiapine XR.

There were also statistically significant changes compared with placebo for all active treatment groups using observed-cases analysis, as well as in the per-protocol population (last-observation-carried-forward and observed-cases analyses), and the repeated-measures post hoc analysis. Mean changes in PANSS total scores for quetiapine XR 400, 600, and 800 mg; quetiapine IR; and placebo were as follows: MITT, observed-cases analysis: -31.1 ($p = .006$), -35.1 ($p < .001$), -37.7 ($p < .001$), -33.1 ($p < .001$), -23.1 ; per-protocol, last-observation-carried-forward: -24.6 ($p = .03$), -30.2 ($p < .001$), -30.7 ($p < .001$), -26.9 ($p = .003$), -18.0 ; and per-protocol, observed-cases: -30.9 ($p = .014$), -34.5 ($p = .001$), -37.1 ($p < .001$), -33.0 ($p = .001$), -23.3 . For the repeated-measures analysis, the estimated treatment difference versus placebo at day 42 was -6.0 for quetiapine XR 400 mg ($p = .039$), -11.9 for quetiapine XR 600 mg ($p < .001$), -12.9 for quetiapine XR 800 mg ($p < .001$), and -8.1 for quetiapine IR ($p = .005$).

At week 6, changes from baseline in PANSS positive and general psychopathology subscale scores and the PANSS aggression/hostility cluster were statistically sig-

nificantly different from placebo for all active treatments. Reductions in the PANSS negative subscale and depression cluster scores were statistically significant versus placebo for the 2 higher doses of quetiapine XR (600 and 800 mg/day) (Table 2, Figure 4).

The results for the other secondary efficacy variables are shown in Table 2. The PANSS and CGI-I response rates were significantly greater with all active treatments compared with placebo. The change in CGI-S score was statistically significant versus placebo for quetiapine XR 600 and 800 mg/day and for quetiapine IR.

Tolerability

Adverse events. The incidences of AEs and drug-related AEs were higher in the quetiapine XR groups than in the placebo group, but were comparable with quetiapine IR (Table 3). Most AEs were mild to moderate in intensity, and there was no evidence of a dose effect with quetiapine XR. The incidences of serious AEs and AEs leading to discontinuation were low in all treatment groups (Table 3). Overall, there were 5 serious AEs attributed to drug treatment by the investigator: psychotic disorder (placebo), suicidal ideation (quetiapine XR 400 mg/day), suicide attempt (quetiapine XR 600 mg/day), urinary retention (quetiapine XR 600 mg/day), and hypotension (quetiapine IR). There was 1 death of unknown cause of a 42-year-old man in the quetiapine IR group at day 41; this was not considered to be related to treatment.

The most common AEs in the quetiapine groups were somnolence and dizziness; incidences of somnolence were 7.1%, 8.8%, and 11.6% for quetiapine XR 400, 600, and 800 mg/day, respectively, and 7.3% for quetiapine IR, versus 1.7% for placebo. Corresponding values for dizziness were 5.3%, 8.8%, 6.6%, 5.7%, and 0.8%, respec-

Table 2. Results for Secondary Efficacy Variables^a

Variable	Placebo (N = 115)	Quetiapine XR 400 mg (N = 111)	Quetiapine XR 600 mg (N = 111)	Quetiapine XR 800 mg (N = 117)	Quetiapine IR 400 mg (N = 119)
PANSS positive subscale score					
Least squares mean change at week 6	-5.9	-7.7 ^b	-10.1 ^b	-9.5 ^b	-8.9 ^b
Estimated difference (95% CI) from placebo	NA	-1.8 (-3.5 to -0.0)	-4.2 (-5.9 to -2.4)	-3.6 (-5.3 to -1.9)	-3.0 (-4.7 to -1.3)
PANSS negative subscale score					
Least squares mean change at week 6	-4.2	-5.5	-6.3 ^b	-7.3 ^b	-5.6
Estimated difference (95% CI) from placebo	NA	-1.3 (-2.8 to 0.2)	-2.1 (-3.6 to -0.6)	-3.1 (-4.6 to -1.6)	-1.4 (-2.8 to 0.1)
PANSS general psychopathology subscale score					
Least squares mean change at week 6	-8.8	-11.7 ^b	-14.6 ^b	-14.4 ^b	-12.2 ^b
Estimated difference (95% CI) from placebo	NA	-2.9 (-5.6 to -0.3)	-5.8 (-8.4 to -3.2)	-5.7 (-8.3 to -3.1)	-3.5 (-6.0 to -0.9)
PANSS aggression and hostility cluster score					
Least squares mean change at week 6	-1.8	-3.0 ^b	-4.1 ^b	-3.8 ^b	-3.2 ^b
Estimated difference (95% CI) from placebo	NA	-1.1 (-2.1 to -0.2)	-2.3 (-3.3 to -1.3)	-2.0 (-3.0 to -1.0)	-1.3 (-2.3 to -0.4)
PANSS depression cluster score					
Least squares mean change at week 6	-2.6	-2.8	-3.5 ^b	-3.3 ^b	-3.2
Estimated difference (95% CI) from placebo	NA	-0.2 (-0.8 to 0.5)	-0.9 (-1.5 to -0.3)	-0.6 (-1.3 to -0.0)	-0.6 (-1.2 to 0.1)
PANSS response rate, % ^c	30.4	44.1*	60.4***	56.4***	52.9***
CGI-I response rate, % ^d	60.0	73.9*	79.3**	76.9**	75.6*
Change in CGI-S score	-1.0	-1.3	-1.5***	-1.6***	-1.3*

*p < .05 vs. placebo.

**p < .01 vs. placebo.

***p < .001 vs. placebo.

^aModified intention-to-treat, last observation carried forward.

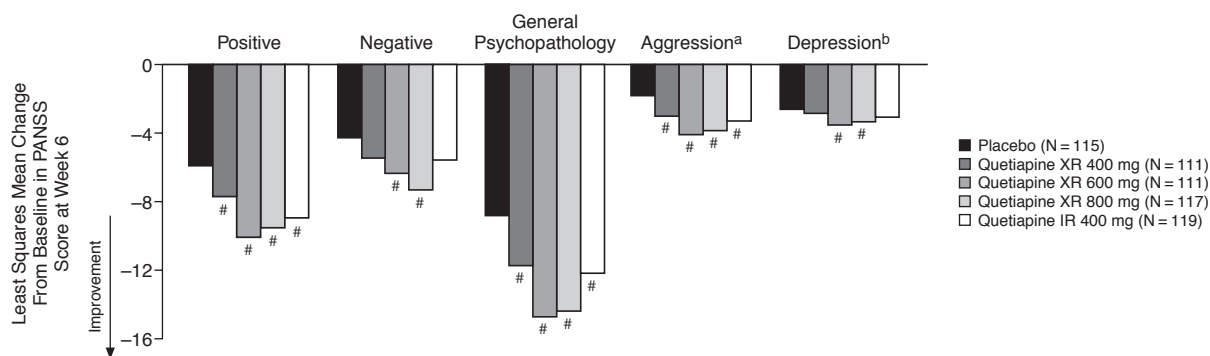
^bSeparation from placebo based on 95% confidence intervals for treatment difference (active treatment vs. placebo).

^cPANSS response rate = percentage of patients with a reduction in PANSS total score ≥ 30%.

^dCGI-I response rate = percentage of patients with a CGI-I score ≤ 3.

Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, IR = immediate release, NA = not applicable, PANSS = Positive and Negative Syndrome Scale, XR = extended release.

Figure 4. Change in PANSS Subscale and Cluster Scores From Baseline to Week 6 (MITT, LOCF)



^aThe PANSS aggression and hostility cluster comprises items P4 (excitement), P7 (hostility), G8 (uncooperativeness), and G14 (poor impulse control).²⁰

^bThe PANSS depression cluster comprises items G1 (somatic concern), G2 (anxiety), G3 (guilt feelings), and G6 (depression).²¹

^cSeparation from placebo based on 95% confidence intervals for treatment difference (active treatment vs. placebo).

Abbreviations: IR = immediate release, LOCF = last observation carried forward, MITT = modified intention-to-treat, PANSS = Positive and Negative Syndrome Scale, XR = extended release.

tively (Table 4). These AEs were generally mild and did not lead to discontinuation: 1 patient (in the quetiapine XR 600-mg group) withdrew because of sedation (and dysarthria) and 1 patient (in the quetiapine IR group) withdrew because of dizziness.

Somnolence-related AEs (somnolence, sedation, lethargy, and sluggishness) were reported by 8 (7.1%), 12 (10.6%), and 16 (13.2%) patients for quetiapine XR 400,

600, and 800 mg/day; corresponding values were 10 (8.1%) for quetiapine IR and 2 (1.7%) for placebo. Median time to onset was less than 3 days in all quetiapine groups, and median duration was 14, 18, 13.5, 10, and 17.5 days, respectively. Intensity of somnolence-related AEs was mild in most patients: 87.5%, 58.3%, and 68.8% for quetiapine XR 400, 600, and 800 mg, 70.0% for quetiapine IR, and 100% for placebo.

Table 3. Overall Adverse Event (AE) Profile (safety population)

Category	Patients Reporting Adverse Events, N (%)				
	Placebo (N = 118)	Quetiapine XR 400 mg (N = 113)	Quetiapine XR 600 mg (N = 113)	Quetiapine XR 800 mg (N = 121)	Quetiapine IR 400 mg (N = 123)
Adverse events	50 (42.4)	51 (45.1)	62 (54.9)	56 (46.3)	66 (53.7)
Drug-related AEs	15 (12.7)	23 (20.4)	34 (30.1)	27 (22.3)	27 (22.0)
Serious AEs	2 (1.7)	2 (1.8)	3 (2.7)	1 (0.8)	6 (4.9)
AEs leading to discontinuation	3 (2.5)	6 (5.3)	3 (2.7)	3 (2.5)	6 (4.9)

Abbreviations: IR = immediate release, XR = extended release.

Table 4. Common Adverse Events (incidence ≥ 5% in any treatment group) During the Study of Quetiapine in Acute Schizophrenia (safety population)

Adverse Event	Patients Reporting Adverse Events, N (%)				
	Placebo (N = 118)	Quetiapine XR 400 mg (N = 113)	Quetiapine XR 600 mg (N = 113)	Quetiapine XR 800 mg (N = 121)	Quetiapine IR 400 mg (N = 123)
Insomnia	23 (19.5)	13 (11.5)	7 (6.2)	9 (7.4)	13 (10.6)
Somnolence	2 (1.7)	8 (7.1)	10 (8.8)	14 (11.6)	9 (7.3)
Dizziness	1 (0.8)	6 (5.3)	10 (8.8)	8 (6.6)	7 (5.7)
Headache	8 (6.8)	6 (5.3)	4 (3.5)	4 (3.3)	2 (1.6)
Sleep disorder	11 (9.3)	4 (3.5)	6 (5.3)	4 (3.3)	6 (4.9)
Constipation	5 (4.2)	2 (1.8)	6 (5.3)	5 (4.1)	1 (0.8)

Abbreviations: IR = immediate release, XR = extended release.

Tolerability during first week of treatment. Quetiapine was generally well tolerated during the first week of treatment. The incidences of somnolence were 5.3%, 6.2%, and 9.9% for quetiapine XR 400, 600, and 800 mg/day; 7.3% for quetiapine IR; and 0.8% for placebo. The corresponding values for dizziness were 1.8%, 6.2%, 5.8%, 4.1%, and 0.8%, respectively. There were 2 reports of postural hypotension (both in the IR group) and no reports of syncope during the first week. There were 4 discontinuations due to AEs: 1 in the quetiapine XR 400-mg group (increased blood pressure, tachycardia, and fever), 1 in the quetiapine XR 600-mg group (nausea and feeling of heaviness), and 2 in the IR group (dizziness; wound infection and anorexia); wound infection and anorexia were not related to treatment. There were no discontinuations due to AEs during the 3-day dose escalation period.

Extrapyramidal symptoms. Incidences of AEs potentially related to EPS were 2.7%, 8.0%, and 4.1% for quetiapine XR 400, 600, and 800 mg/day; 4.9% for quetiapine IR; and 5.1% for placebo. No individual AE potentially related to EPS occurred in more than 3 patients (< 3%) in any treatment group.

At week 6, there was a reduction in mean Simpson-Angus Scale scores from baseline in all treatment groups. Mean (SD) changes were -1.14 (2.56), -0.47 (2.03), and -0.83 (2.23) for quetiapine XR 400, 600, and 800 mg; -1.19 (3.25) for quetiapine IR; and -0.87 (2.19) for placebo. For the majority of patients, Simpson-Angus Scale scores were either unchanged or improved (88%–94% for quetiapine XR, 89% for quetiapine IR, and 92% for placebo). There was also a reduction in mean BAS

scores from baseline to week 6 in all treatment groups: mean (SD) changes were -0.15 (0.59), -0.05 (0.57), and -0.12 (0.59) for quetiapine XR; -0.10 (0.62) for quetiapine IR; and -0.12 (0.44) for placebo. Overall, there was no change or an improvement in BAS scores in most patients (94%–95%, 93%, and 97%, respectively). Use of anticholinergic medication during the study was low (0.9%, 0.9%, and 1.7% for quetiapine XR 400, 600, and 800 mg; 4.1% for quetiapine IR; 2.5% for placebo), and there was no indication of an increase in use over time in the active treatment groups.

Laboratory data and vital signs. There were small changes in some laboratory measures with quetiapine XR and quetiapine IR, including hemoglobin and alkaline phosphatase levels, but these were not deemed clinically significant. The results for prolactin, lipids, HbA_{1c}, glucose, insulin, and body weight are shown in Table 5. There was a high degree of interindividual variation in these parameters, particularly for insulin levels, but overall, there was a small increase in cholesterol and triglyceride levels in the quetiapine groups relative to placebo. The HbA_{1c} and glucose levels were relatively unchanged across groups, and mean prolactin levels decreased in all groups.

Three patients reported orthostatic hypotension during the study, 1 patient in the quetiapine XR 800-mg group and 2 patients in the quetiapine IR group. There was a small increase in mean supine pulse rate from randomization to treatment end in the quetiapine XR and IR groups; mean (SD) changes were 2.57 (12.06) bpm for quetiapine XR 400 mg/day; 2.16 (11.18) bpm for quetiapine XR 600

Table 5. Changes in Prolactin, Lipids, Hemoglobin A_{1c} (HbA_{1c}), Glucose, Insulin, and Body Weight During the Study of Quetiapine in Acute Schizophrenia (safety population)

Measure, mean (SD)	Placebo (N = 118)	Quetiapine XR 400 mg (N = 113)	Quetiapine XR 600 mg (N = 113)	Quetiapine XR 800 mg (N = 121)	Quetiapine IR 400 mg (N = 123)
Prolactin, ng/mL					
Baseline	40.03 (46.21)	36.74 (38.90)	38.18 (43.61)	31.48 (39.06)	38.55 (53.38)
Change at week 6	-24.11 (50.02)	-24.37 (38.38)	-19.83 (50.22)	-14.18 (41.87)	-24.09 (55.97)
Total cholesterol, mmol/L^a					
Baseline	4.77 (1.13)	4.78 (1.04)	4.78 (1.09)	4.87 (1.09)	4.80 (1.13)
Change at week 6	-0.15 (0.80)	0.17 (0.85)	0.25 (0.93)	0.17 (0.85)	0.36 (0.82)
LDL cholesterol, mmol/L^a					
Baseline	2.87 (0.93)	2.92 (0.89)	2.81 (0.87)	2.94 (0.94)	2.86 (0.93)
Change at week 6	-0.10 (0.66)	0.07 (0.67)	0.22 (0.74)	0.04 (0.76)	0.25 (0.66)
HDL cholesterol, mmol/L^a					
Baseline	1.27 (0.36)	1.21 (0.28)	1.30 (0.38)	1.23 (0.29)	1.26 (0.31)
Change at week 6	-0.01 (0.24)	0.01 (0.23)	-0.02 (0.26)	-0.01 (0.25)	0.00 (0.28)
Triglycerides, mmol/L^a					
Baseline	1.36 (0.75)	1.42 (0.86)	1.52 (1.37)	1.50 (1.02)	1.42 (0.79)
Change at week 6	-0.11 (0.78)	0.17 (0.92)	0.15 (1.12)	0.31 (1.11)	0.32 (0.85)
HbA_{1c}, %^a					
Baseline	5.23 (0.40)	5.28 (0.47)	5.26 (0.42)	5.22 (0.43)	5.31 (0.45)
Change at week 6	-0.02 (0.26)	0.03 (0.26)	-0.01 (0.29)	0.07 (0.30)	-0.01 (0.25)
Glucose, mmol/L^a					
Baseline	5.19 (0.82)	5.19 (1.17)	5.15 (0.64)	5.37 (0.87)	5.22 (0.65)
Change at week 6	0.02 (0.94)	-0.04 (0.95)	0.09 (0.81)	-0.08 (0.76)	-0.08 (0.79)
Insulin, pmol/L^a					
Baseline	78.76 (70.21)	63.69 (55.28)	83.99 (101.85)	73.71 (66.42)	75.05 (81.81)
Change at week 6	0.48 (93.92)	21.99 (127.41)	2.14 (106.29)	7.39 (97.70)	31.69 (139.53)
Body weight, kg					
Baseline	64.75 (17.45)	64.05 (16.09)	62.88 (14.52)	64.58 (15.94)	65.63 (18.17)
Change at week 6	0.48 (3.23)	1.09 (2.44)	1.80 (3.10)	1.54 (2.47)	1.40 (2.49)

^aUnder presumed fasting conditions.Abbreviations: HbA_{1c} = hemoglobin A_{1c}, HDL = high-density lipoprotein, IR = immediate release, LDL = low-density lipoprotein, XR = extended release.

mg/day; 3.64 (10.89) bpm for quetiapine XR 800 mg/day; 2.02 (10.81) bpm for quetiapine IR; and -0.49 (12.49) bpm for placebo. The change in pulse rate was confirmed by the electrocardiogram results; the small increase in mean heart rate from baseline at treatment end was well tolerated, with only 9 related AEs reported.

DISCUSSION

Results from this randomized, double-blind, placebo-controlled study indicate that once-daily quetiapine XR (400, 600, and 800 mg/day) is effective for the management of acute schizophrenia. The improvement was significantly larger than that observed for placebo, expressed as the change from baseline in PANSS total score at week 6 (the primary endpoint). This effect applied to all doses tested. Similar results were obtained in both the modified intention-to-treat and the per-protocol populations, using both last-observation-carried-forward and observed-cases analyses. Efficacy was further supported by the results from secondary efficacy variables, i.e., PANSS and CGI-I response rates. Moreover, the higher doses of quetiapine XR (600 and 800 mg/day) demonstrated significant improvement compared with placebo for the CGI-S score.

Quetiapine XR was effective against a broad range of psychotic symptoms, as shown by improvements in PANSS subscale and cluster scores. At week 6, all 3 doses of quetiapine XR showed significant superiority compared with placebo for the PANSS positive and general psychopathology subscale scores and the aggression and hostility cluster score. In addition, quetiapine XR 600 and 800 mg/day demonstrated significant improvement compared with placebo for the PANSS negative subscale score and PANSS depression cluster score at week 6.

The validity of the study was confirmed by the results for quetiapine IR, which has established efficacy in the treatment of schizophrenia.²²⁻²⁵ Compared with placebo, quetiapine IR 400 mg was associated with statistically significant improvements in PANSS total score, the primary efficacy endpoint, and all key secondary variables.

Although the study was not powered to compare doses of quetiapine XR, treatment effects, including the change in the primary endpoint, were generally numerically greater for fixed doses of quetiapine XR 600 and 800 mg/day than for 400 mg/day. Also, a statistically significant difference from placebo was achieved for more of the secondary efficacy parameters with the 2 higher doses of quetiapine XR compared with 400 mg/day. In addition, the post hoc analysis indicated that there was a statisti-

cally significant dose response for the change in PANSS total scores with quetiapine XR. These results suggest that patients may benefit more from doses of 600 mg/day or higher compared with a lower dose (400 mg/day).

Quetiapine XR was generally well tolerated at all doses used in the study. As expected, the incidence of adverse events was higher with quetiapine XR than with placebo. However, serious AEs and AEs leading to discontinuation were relatively infrequent in all treatment groups, and the incidence in quetiapine-treated patients was similar to that in the placebo group. Furthermore, the side-effect profile was similar to that of quetiapine IR, and there were no unexpected AEs specific to the XR formulation. With the exception of somnolence, there was no evidence of a dose relationship for AEs, AEs related to treatment, or other common AEs. During the first week of treatment, there were no unexpected AEs and only 2 discontinuations due to AEs in the quetiapine XR groups. These results indicate that rapid initiation of quetiapine XR, reaching 600 mg by day 2 and 800 mg by day 3, is well tolerated.

Somnolence was the most common AE during treatment with quetiapine XR, which is consistent with the established safety profile of quetiapine IR. Studies with quetiapine IR show that somnolence is usually mild and transient and occurs early in treatment.²⁶ The results of the current study confirm this and demonstrate a similar profile for quetiapine XR. Only 1 patient in the current study discontinued treatment with quetiapine XR because of somnolence.

Other AEs that are of interest in the context of this study are EPS, prolactin elevation, and body weight and metabolic parameters. The results for quetiapine XR show that the incidence of all AEs potentially related to EPS was generally comparable to that of placebo, with an overall mean improvement in BAS and Simpson-Angus Scale scores. Similarly, there was an overall mean decrease in prolactin levels between baseline and the end of the study in all treatment groups. These results probably reflect the proportion of patients taking conventional antipsychotics at study enrollment (approximately 40%). The results are also consistent with previous studies with quetiapine IR in patients with schizophrenia, in which the incidence of EPS and prolactin levels were comparable to those observed with placebo, with improvements noted in patients switched from antipsychotics associated with higher EPS and hyperprolactinemia risk.²⁷⁻³¹

The change in body weight (1.09 to 1.80 kg) with quetiapine XR was similar to that observed with quetiapine IR, and the magnitude of the change is also comparable with the results obtained in previous studies with quetiapine IR.^{32,33} There were also small changes in presumed fasting cholesterol and triglyceride levels with quetiapine XR in the current study, although conclusions are limited by the large interindividual variation in these parameters.

Nevertheless, the changes with quetiapine XR were similar to those observed with quetiapine IR, and consistent with the known safety profile of quetiapine IR in general. There was no evidence of a dose relationship for the change in metabolic parameters for quetiapine XR. The design of the current study (use of a dual-matched placebo) precluded assessment of patient adherence to quetiapine XR. However, its tolerability profile, together with the simplified treatment regimen, is expected to encourage patient adherence, a significant factor in preventing psychotic relapse.

On the basis of the dose escalation used in the current study, together with the efficacy and tolerability results, it is suggested that quetiapine XR can be initiated at 300 mg on day 1, then increased to 600 mg on day 2 and to 800 mg on day 3, if needed, administered as a single daily dose in the evening. The dose can then be adjusted according to the efficacy and tolerability in individual patients. Although a clear incremental benefit of 800 mg/day versus 600 mg/day was not observed for the mean changes from baseline in the current study, it is expected that in clinical practice, individual patients may require doses of up to 800 mg/day to achieve an adequate response.

Strengths of this study were the high completion rates in all treatment arms, inclusion of a quetiapine IR group to assess the validity of the study, and the fact that the patient population included both inpatients and outpatients. Obviously, it must be taken into account that patients were followed for only 6 weeks; the longer-term efficacy of quetiapine XR in a placebo-controlled relapse prevention study is currently being evaluated.

In conclusion, quetiapine XR (400 to 800 mg/day) was effective across a broad range of symptom domains in acute schizophrenia and was as well tolerated as the IR formulation. Rapid dose escalation of quetiapine XR (300 mg on day 1, 600 mg on day 2, and 800 mg on day 3) was also well tolerated, with a therapeutically effective dose reached by day 2. As such, this new, once-daily formulation of quetiapine offers clinicians and patients a valuable new treatment option for managing schizophrenia.

Drug names: clozapine (FazaClo, Clozaril, and others), fluoxetine (Prozac and others), lorazepam (Ativan and others), quetiapine (Seroquel), zaleplon (Sonata), zolpidem (Ambien), zopiclone (Lunesta).

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