AstraZeneca

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|---|---|---|---|
| Drug product: | SEROQUEL® | **SYNOPSIS** | |
| Drug substance(s): | Quetiapine fumarate | | |
| Study code: | 5077IL/0031 | | |
| Date: | 12 August 2005 | | |

# A Multicenter, Double-Blind, Randomized, Comparison of Quetiapine (SEROQUEL®) and Chlorpromazine in the Treatment of Subjects with Treatment-Resistant Schizophrenia

**Study center(s)**

This study was conducted in the US (28 centers) and in Canada (3 centers).

**Publications**

None at the time of writing this report.

**Study dates**

**First patient enrolled** 21 October 1994

**Last patient completed** 30 June 1997

**Phase of development**

Therapeutic confirmatory (III)

## Objectives

Primary objective:

The primary objective of this study was to compare the efficacy of SEROQUEL® (quetiapine fumarate; hereafter referred to as quetiapine) and chlorpromazine in the treatment of treatment-resistant schizophrenic patients as measured by:

- Response to treatment, which was defined as:
  - a ≥30% reduction from baseline in the Brief Psychiatric Rating Scale (BPRS) total score

    AND

  - either a Clinical Global Impression (CGI) Severity of Illness score of 3 (mildly ill) or less OR a BPRS total score of ≤17 after treatment.
- Change from baseline in the BPRS total score.
- Change from baseline in the CGI Severity of Illness score.

Secondary and tertiary objectives:

The secondary objective of this study was to compare the safety of quetiapine and chlorpromazine in the same patient population.

The tertiary objectives of this study were:

- To investigate the relative effects of quetiapine and chlorpromazine on negative symptoms, quality-of-life assessments, cognitive function, and nurses' evaluation of ward behavior in the above patient population; and
- To delineate a potential plasma concentration–therapeutic response relationship for quetiapine and ICI 214,227 [the active 7-hydroxy metabolite of quetiapine] in the treatment of the above patient population.

Open-label extension objectives:

The objective of the open-label extension phase was to obtain long-term safety data on patients treated with quetiapine.

## Study design

This was a randomized, double-blind, parallel-group, multicenter study comparing the efficacy and safety of quetiapine and chlorpromazine in adult patients with treatment-resistant schizophrenia.

**Target patient population and sample size**

The study population was composed of male and female patients between 18 and 65 years, with schizophrenia of catatonic (295.20), disorganized (295.10), paranoid (295.30), or undifferentiated (295.90) types according to Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria and who, by historical and prospective treatment criteria, were considered resistant to treatment with standard antipsychotic agents.

A study of treatment-resistant schizophrenic patients showed the rate of response to chlorpromazine to be approximately 4% (Kane et al 1988). A minimum increase in the rate of response that would be of clinical interest would be an increase of 15%, making the hypothetical response rate to quetiapine approximately 20% in the patient population for the current study. Using a 2-sided alpha equal to 0.05 and requiring a power of 0.90 to detect this difference, approximately 115 patients per treatment group would be required (Fleiss 1981). The withdrawal rate of patients from the above-referenced study was approximately 10%. The sample size of the current study was increased proportionately to accommodate this anticipated withdrawal rate, resulting in a sample size requirement of approximately 130 patients per treatment group. In order to obtain 264 randomized patients, approximately 330 patients had to enter the single-blind haloperidol treatment period (Segment B). This number was based on a dropout rate of 20% from Segments A and B, as defined in the original Clinical Study Protocol, which was approximately the rate observed in the study by Kane et al.

**Investigational product and comparator(s): dosage, mode of administration and batch numbers**

During the single-blind haloperidol treatment phase, patients received haloperidol tablets titrated to a dosage of 40 mg per day (2.0-mg tablets, formulation number F10108; 5.0-mg tablets, formulation number F10110), administered once a day for a period of 4 weeks. Patients who failed to have a clinical response to haloperidol, according to predefined criteria, continued in the study.

On entry into the double-blind treatment phase, patients were randomized to receive either quetiapine or a combination of chlorpromazine and benztropine mesylate (hereafter, the latter group is referred to as the chlorpromazine group). All study medication was administered daily in 3 divided doses. Double-blind treatment consisted of various combinations of both placebo and active tablets.

Quetiapine tablets of 25 mg (formulation number F7134) and 100 mg (formulation number F7133) along with matching placebo tablets of 25 mg (formulation number F7142) and 100 mg (formulation number F7143) were given for total daily dosages of 75, 150, 225, 300, 375, 450, 600, 675, or 750 mg. Generic commercially-available chlorpromazine tablets were ground and placed in capsules in the following strengths: 50 mg (formulation number F7184), 100 mg (formulation number F7206), and 200 mg (formulation number F7204). Matching placebo capsules were available for each dose of chlorpromazine: 50 mg (formulation number F7185), 100 mg (formulation number F7203), and 200 mg (formulation number F7205).

Dosages during the final 4 weeks of the study could be flexibly increased, according to patient response and tolerability, to a maximum of 750 mg of quetiapine daily or a maximum of 1500 mg of chlorpromazine daily (plus 4 mg benztropine mesylate daily).

**Duration of treatment**

The total study duration was 15 weeks (for patients enrolled after Revision 2 of the Clinical Study Protocol) or 16 weeks (for patients enrolled prior to protocol Revision 2). The study was divided into the following 5 segments:

- Segment A (Visits 1 and 2; Week -6 to -5): a 1-week screening period;
- Segment B (Visits 3 through 5; Week -5 to -1): a 4-week, single-blind haloperidol (40 mg per day) period to prospectively establish a lack of clinical response to treatment with a standard antipsychotic agent. Patients discontinued all psychotropic medication at the start of this segment.
- Segment C (Visit 6; Week -1 to 0): a 1-week, single-blind placebo washout period prior to the start of the double-blind treatment (only patients enrolled prior to Revision 2 of the Clinical Study Protocol went through this segment; patients enrolled after Revision 2 proceeded to Segment D upon completing Segment B);
- Segment D (Visits 7 through 13; Week 0 to 6): a 6-week, double-blind fixed-dose treatment period. Patients were required to exhibit a lack of clinical response to haloperidol during Segment B to be enrolled in Segment D.

  Lack of clinical response to haloperidol treatment was defined as:

  – achievement of a total daily dose of haloperidol 40 mg per day for a minimum treatment duration of 2 weeks during Segment B

    AND

  – a <30% reduction from the end of Segment A (Week -5) in BPRS total score

    AND

  – either a CGI Severity of Illness score of ≥4 (moderately ill) OR a BPRS total score of ≥10.

  Randomization occurred at Week 0 to either quetiapine or chlorpromazine in a 1:1 ratio. Segment D began with a 2-week titration based on patient tolerability. Upon completion of the titration period, the dose of study medication was maintained at a fixed daily dose of 600 mg quetiapine or 1200 mg chlorpromazine for an additional 4 weeks.

- Segment E (Visits 14 through 17; Week 6 to 10): a 4-week, double-blind, flexible-dose treatment period. Doses of study medication could be flexibly increased (according to patient response and tolerability) to a maximum dose of 750 mg per day of quetiapine and 1500 mg per day of chlorpromazine. Incremental dosage increases of quetiapine (75 mg or 150 mg per day) or chlorpromazine (150 mg or 300 mg per day) could occur at weekly intervals.

Patients who completed Segment E were eligible, upon completion of all study assessments, for entry into an open-label extension phase with quetiapine for up to 156 weeks.

**Criteria for evaluation (main variables)**

**Efficacy**

- **Primary variable:** response to treatment, where response was defined at each timepoint as a ≥30% reduction from baseline in the BPRS total score **AND** either a CGI Severity of Illness score of 3 (mildly ill) or less **OR** a BPRS total score of ≤17.

- **Secondary variables:** changes from baseline in BPRS total score, BPRS cluster and factor scores, CGI Severity of Illness score, Modified Scale for the Assessment of Negative Symptoms (SANS) summary score, Quality of Life Scale (QLS) score, cognitive function test battery scores, and the Nurses' Observation Scale for Inpatient Evaluation (NOSIE-30) total score; as well as the CGI Global Improvement score.

**Safety**

The primary safety variables were the change from baseline in the neurological assessments: the Simpson Scale and the Abnormal Involuntary Movement Scale (AIMS).

Safety and tolerability were also assessed in terms of adverse events (AEs), hematology, clinical chemistry, physical examination, electrocardiograms (ECGs), and vital signs. The use of chloral hydrate or lorazepam for insomnia or severe agitation was also examined.

**Statistical methods**

Two analysis sets were used:

- An intention-to-treat (ITT) analysis set, which included all randomized patients who received at least 1 dose of study medication, had a baseline BPRS or CGI assessment, and had at least 1 set of BPRS or CGI assessments after baseline. This was the primary data set for efficacy analysis.

- A safety analysis set, which included all randomized patients who received at least 1 dose of double-blind study treatment.

Values for missing assessments were imputed using the principle of last observation carried forward (LOCF). Analysis was performed on the LOCF data and also using observed data

only. All efficacy analyses were conducted with data from the ITT analysis set. A per-protocol analysis was not performed. All safety analyses were conducted with the safety analysis set.

Response rates to treatment were compared between treatment groups with Fisher's Exact test.

Changes from baseline in BPRS total score, BPRS cluster and factor scores, CGI Severity of Illness score, SANS summary score, and NOSIE-30 total score were analyzed using an analysis of covariance (ANCOVA). The model included treatment and baseline score for the particular scale as covariates. Type III sums of squares were used to estimate treatment effects. A 95% confidence interval around the difference between least squares means for the 2 treatment groups was constructed. The CGI Global Improvement score was analyzed using an analysis of variance (ANOVA) model that included treatment as a factor.

Extrapyramidal symptoms and involuntary movements were evaluated using total scores from the Simpson Scale and the AIMS, respectively. Based on data from previous studies, most patients, if any, report few of these symptoms. Distributions are severely skewed, rendering parametric analysis techniques (such as the ANCOVA) inappropriate. As a result of these findings, the analysis strategy for these data was based on grouping data and using categorical analysis techniques. As a result of these findings, the analysis strategy for these data was based on grouping data and use of Fisher's Exact test.

All laboratory, weight, ECG, and vital signs data were summarized by week using descriptive statistics for actual data and for the change from baseline. Shift tables were constructed to further analyze selected hematology and clinical chemistry data, as well as ECG and vital signs data. The shift tables showed the number of patients within each treatment group showing categorical shifts from baseline (Week 0) to clinically significant (low or high) values at the end of double-blind treatment (Week 10). Only patients with both baseline and final (end of treatment) values were included in the shift tables. In addition, clinically significant postural changes in vital signs were summarized by week using descriptive statistics for actual data. The proportion of patients with a clinically significant change in weight (≥7%) from baseline to the end of the double-blind treatment phase was also tabulated. Only patients with both baseline and final (end of treatment) values were included in the tabulation of weight change.

**Patient population**

Of 260 patients randomized to the double-blind treatment phase, 253 patients were included in the ITT analysis set (a per-protocol analysis was not performed). Seven patients were excluded from the ITT analysis set (5 in the quetiapine group and 2 in the chlorpromazine group) because of protocol deviations (lack of valid CGI and/or BPRS assessments at baseline or during double-blind treatment). The number of randomized patients that completed the study was 89 in each treatment group. The reasons for discontinuation from the study were lack of efficacy, AE or concurrent illness, refused to continue, and protocol noncompliance. Randomized patients were predominantly Caucasian, men, had a mean age of 41 years, were diagnosed with paranoid or undifferentiated schizophrenia, and had a Global Assessment

Scale score of 32. The treatment groups were well balanced regarding demographic and baseline disease characteristics.

Patient population and disposition are presented in Table S1.

**Table S1 Patient population and disposition (all randomized patients)**

| | | Quetiapine | | Chlorpromazine | | Total | |
|---|---|---|---|---|---|---|---|
| **Population** | | | | | | | |
| N randomized (N planned) | | 130 | (130) | 130 | (130) | 260 | (130) |
| **Demographic characteristics** | | | | | | | |
| Sex, n (%) | Male | 103 | (79.2) | 103 | (79.2) | 206 | (79.2) |
| | Female | 27 | (20.8) | 27 | (20.8) | 54 | (20.8) |
| Age, years | Mean (SD) | 41.0 | (9.7) | 40.8 | (9.2) | 40.9 | (9.5) |
| | Range | 18 to 65 | | 18 to 62 | | 18 to 65 | |
| Race, n (%) | Caucasian | 70 | (53.8) | 83 | (63.8) | 153 | (58.8) |
| | Black | 45 | (34.6) | 29 | (22.3) | 74 | (28.5) |
| | Asian | 1 | (0.8) | 1 | (0.8) | 2 | (0.8) |
| | Hispanic | 12 | (9.2) | 15 | (11.5) | 27 | (10.4) |
| | Other | 2 | (1.5) | 2 | (1.5) | 4 | (1.5) |
| **Baseline characteristics** | | | | | | | |
| DSM-IV diagnosis, n (%) | Catatonic | 1 | (0.8) | 0 | (0) | 1 | (0.4) |
| | Disorganized | 11 | (8.5) | 9 | (6.9) | 20 | (7.7) |
| | Paranoid | 57 | (43.8) | 64 | (49.2) | 121 | (46.5) |
| | Undifferentiated | 61 | (46.9) | 57 | (43.8) | 118 | (45.4) |
| Weight, lb | | n=106 | | n=106 | | n=212 | |
| | Mean (SD) | 174.1 | (35.1) | 174.3 | (34.4) | 174.2 | (34.7) |
| | Range | 106 to 256 | | 106 to 325 | | 106 to 325 | |
| **Disposition, n (%)[a]** | | | | | | | |
| Patients who were: | Randomized | 130 | (100) | 130 | (100) | 260 | (100) |
| | Evaluable | 128 | (98.5) | 128 | (98.5) | 256 | (98.5) |
| | Discontinued | 41 | (31.5) | 41 | (31.5) | 82 | (31.5) |
| | Completed | 89 | (68.5) | 89 | (68.5) | 178 | (68.5) |

| | Quetiapine | Chlorpromazine | Total |
|---|---|---|---|
| **Analysis sets**[b] | | | |
| N analyzed for safety[c] | 130 | 130 | 260 |
| N analyzed for efficacy (ITT) | 125 | 128 | 253 |

[a] Haloperidol non-responders who entered the double-blind study treatment phase (Segments D and E).
[b] Although a per-protocol analysis set was defined, no data were subjected to a per-protocol analysis.
[c] Number of patients who received at least 1 dose of double-blind study treatment
DSM-IV=Diagnostic and Statistical Manual 4th edition; SD=standard deviation; lb=pounds; ITT=Intention-to-treat; N=Number

### Drug exposure

The mean median daily doses and mean duration of treatment are shown in Table S2. The duration of treatment was similar in the quetiapine and chlorpromazine groups.

**Table S2 Overview of exposure (all randomized patients)**

| | | Quetiapine (N=130) | Chlorpromazine (N=130) |
|---|---|---|---|
| Exposure by duration of treatment, days | Mean (SD) | 57.1 (21.8) | 55.6 (23.9) |
| | Range | 3 to 79 | 2 to 78 |
| Exposure by dose, mg | Mean of median daily doses (SD) | 571.2 (101.7) | 1040.4 (271.7) |
| | Range of median daily doses | 113 to 750 | 225 to 1200 |

SD=Standard deviation.

### Efficacy results

Patients in both groups were unresponsive to study treatment. The response rate was <10% for both quetiapine and chlorpromazine. The differences in the rate of response between quetiapine and chlorpromazine did not reach statistical significance at any timepoint during the 10-week double-blind treatment phase. The results of the primary variable, response to treatment, are summarized in Table S3.

The components of treatment response were the BPRS total score and the CGI Severity of Illness score (see Table S4). At Week 10 compared to baseline, the improvement in the BPRS total score was significantly better in the chlorpromazine group compared to the quetiapine patients. The change from baseline in the CGI Severity of Illness score was similar in the 2 treatment groups at Week 10.

**Table S3 Response to treatment (LOCF, ITT analysis set)**

| Timepoint | Quetiapine (N=125) | | | Chlorpromazine (N=128) | | | p-Value[a] |
|---|---|---|---|---|---|---|---|
| | n | Responders, n (%) | | n | Responders, n (%) | | |
| Week 1 | 121 | 3 | (2.5) | 125 | 2 | (1.6) | 0.680 |
| Week 2 | 125 | 4 | (3.2) | 127 | 2 | (1.6) | 0.445 |
| Week 3 | 125 | 6 | (4.8) | 127 | 2 | (1.6) | 0.170 |
| Week 4 | 125 | 7 | (5.6) | 127 | 2 | (1.6) | 0.101 |
| Week 5 | 125 | 9 | (7.2) | 127 | 5 | (3.9) | 0.285 |
| Week 6 | 125 | 10 | (8.0) | 127 | 5 | (3.9) | 0.194 |
| Week 7 | 125 | 10 | (8.0) | 127 | 5 | (3.9) | 0.194 |
| Week 8 | 125 | 9 | (7.2) | 127 | 10 | (7.9) | 1.000 |
| Week 9 | 125 | 12 | (9.6) | 127 | 9 | (7.1) | 0.502 |
| Week 10 | 125 | 10 | (8.0) | 127 | 9 | (7.1) | 0.816 |

[a] Quetiapine vs. Chlorpromazine (Fisher's Exact Test)
LOCF=Last observation carried forward; ITT=intention-to-treat

The results from the other secondary efficacy analyses are summarized in Table S4. In addition to the CGI Severity of Illness score, no statistically significant differences between quetiapine and chlorpromazine were evident at Week 10 for the BPRS Factor I and Factor II scores, and the SANS summary score. The differences between the 2 treatment groups at Week 10 were statistically significant for the remaining assessments, with some scores favoring quetiapine and others favoring chlorpromazine; however, the differences were small and, especially when considering the results for the primary efficacy variable, no clinically meaningful efficacy advantage was evident in either treatment group.

**Table S4 Summary of psychiatric assessments of efficacy (ITT analysis set)**

| Efficacy variable | Change from baseline at Week 10 (end of double-blind treatment) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Quetiapine (N=125) | | Chlorpromazine (N=128) | | Quetiapine versus Chlorpromazine | | |
| | n | LS Mean[a] (SE) | n | LS Mean[a] (SE) | Difference[b] (SE) | Confidence limits[c] | P-value[d] |
| BPRS total score | 125 | -3.11 (1.14) | 127 | -7.22 (1.13) | 4.11 (1.60) | 0.95, 7.26 | 0.011* |
| BPRS positive cluster score | 125 | -1.11 (0.39) | 128 | -2.45 (0.38) | 1.34 (0.54) | 0.28, 2.41 | 0.014* |
| BPRS negative cluster score | 125 | -0.79 (0.24) | 128 | -0.04 (0.24) | -0.75 (0.34) | -1.43, -0.08 | 0.029* |

| Efficacy variable | Quetiapine (N=125) | | Chlorpromazine (N=128) | | Quetiapine versus Chlorpromazine | | |
|---|---|---|---|---|---|---|---|
| | n | LS Mean[a] (SE) | n | LS Mean[a] (SE) | Difference[b] (SE) | Confidence limits[c] | P-value[d] |
| **Change from baseline at Week 10 (end of double-blind treatment)** | | | | | | | |
| BPRS Factor I score[e] | 125 | -1.45 (0.30) | 127 | -1.87 (0.29) | 0.42 (0.42) | -0.40, 1.24 | 0.317 |
| BPRS Factor II score[e] | 125 | -0.73 (0.29) | 128 | -0.10 (0.29) | -0.62 (0.41) | -1.43, 0.18 | 0.129 |
| BPRS Factor III score[e] | 125 | -0.87 (0.37) | 127 | -2.38 (0.37) | 1.51 (0.52) | 0.49, 2.54 | 0.004* |
| BPRS Factor IV score[e] | 125 | 0.08 (0.29) | 128 | -1.49 (0.28) | 1.57 (0.41) | 0.77, 2.37 | 0.000* |
| BPRS Factor V score[e] | 125 | -0.14 (0.34) | 128 | -1.27 (0.34) | 1.13 (0.48) | 0.18, 2.08 | 0.020* |
| CGI Severity of Illness score | 124 | -0.14 (0.08) | 127 | -0.29 (0.08) | 0.15 (0.12) | -0.08, 0.38 | 0.195 |
| SANS summary score | 110 | -0.57 (0.30) | 118 | -0.31 (0.29) | -0.26 (0.42) | -1.09, 0.57 | 0.535 |
| NOSIE-30 total score | 116 | -1.52 (0.78) | 122 | 1.79 (0.76) | -3.32 (1.09) | -5.46, -1.18 | 0.003* |
| **Score at Week 10 (end of double-blind treatment)** | | | | | | | |
| CGI Global Improvement score | 125 | 4.09 (0.12) | 128 | 3.58 (0.12) | 0.51 (0.17) | 0.17, 0.85 | 0.004* |

* Statistically significant difference between quetiapine and chlorpromazine treatment groups.

[a] For all variables except the NOSIE-30: a negative LS mean change indicates a decrease (improvement) from the baseline mean. For the NOSIE-30, a positive LS mean change indicates an increase (improvement) from the baseline mean.

[b] Quetiapine LS mean minus chlorpromazine LS mean

[c] 95% Confidence interval

[d] Analysis of covariance (ANCOVA) of the difference between the 2 treatment groups for all variables except the CGI Global Improvement score (for which an analysis of variance [ANOVA] model was used)

[e] BPRS Factor scores: I=Anxiety/Depression; II=Anergia; III=Thought Disturbances; IV=Activation; and V=Hostile/Suspiciousness

LOCF=Last observation carried forward; ITT=intention-to-treat; LS=Least squares; SE=Standard error; BPRS=Brief Psychiatric Rating Scale; CGI=Clinical Global Impression; SANS=Scale for the Assessment of Negative Symptoms; NOSIE-30=Nurses' Observation Scale for Inpatient Evaluation; QLS=Quality of Life Scale

There were no significant changes from baseline for chlorpromazine in any of the 11 cognitive function tests. Significant positive changes from baseline occurred for quetiapine patients in 6 cognitive tests. Among these 6 tests, a statistically significant treatment difference favoring quetiapine over chlorpromazine occurred in 4 of the tests (paragraph memory, Stroop color-word, Hopkins verbal learning free recall, and Hopkins verbal learning, recognition true positives). Although the direction of cognitive changes generally favored quetiapine, the clinical relevance of the magnitude of change is uncertain, especially in view of the low rate of clinical response.

The QLS total score (mean ± standard deviation) decreased from 29.3 ± 19.0 to 27.5 ± 19.3 in the quetiapine group and increased from 29.3 ± 17.9 to 31.5 ± 18.6 for chlorpromazine

patients following 10 weeks of study treatment. As with the other efficacy variables, the changes were small in both treatment groups and not clinically meaningful.

**Safety results**

The primary safety variables were the neurological measures of extrapyramidal symptoms (EPS) (the Simpson Scale) and involuntary movements (the AIMS). Quetiapine had a more beneficial effect on EPS than on involuntary movements. For both the Simpson Scale and AIMS score at the final assessment, however, the percentage of patients whose score had not worsened from baseline was not statistically different between quetiapine and chlorpromazine. For the Simpson Scale total score, the percentage of patients whose final score had not worsened from baseline was 81.4% in the quetiapine group and 75.7% in the chlorpromazine group. For the AIMS total score, the percentage of patients whose final score had not worsened from baseline was 67.5% in the quetiapine group and 78.8% for the chlorpromazine patients.

A summary of AEs in each category is presented in Table S5. The overall incidence of AEs was approximately 75% in the quetiapine group and 88% in chlorpromazine patients. SAEs were reported for 3% and 7% of the quetiapine and chlorpromazine patients, respectively. The incidence of study medication–related AEs also favored the quetiapine patients (48.5%) over the chlorpromazine group (68.5%). Withdrawals from the study owing to an AE occurred for 5% of quetiapine patients and 16% of the chlorpromazine group.

**Table S5 Number (%) of patients who had at least 1 adverse event in any category, and total numbers of adverse events (safety analysis set)**

| Category of adverse event | N (%) of patients who had an adverse event in each category[a] | | | | | |
|---|---|---|---|---|---|---|
| | Quetiapine (N=130) | | Chlorpromazine (N=130) | | Total (N=260) | |
| Any adverse events | 98 | (75.4) | 115 | (88.5) | 213 | (81.9) |
| Serious adverse events | 4 | (3.1) | 9 | (6.9) | 13 | (5.0) |
| Serious adverse events leading to death | 1 | (0.8) | 0 | | 1 | (0.4) |
| Serious adverse events not leading to death | 3 | (2.3) | 9 | (6.9) | 12 | (4.6) |
| Study medication–related adverse events | 63 | (48.5) | 89 | (68.5) | 152 | (58.5) |
| Study withdrawals due to adverse events | 7 | (5.4) | 21 | (16.2) | 28 | (10.8) |

| Category of adverse event | N (%) of patients who had an adverse event in each category[a] | | |
|---|---|---|---|
| | Quetiapine (N=130) | Chlorpromazine (N=130) | Total (N=260) |
| | Total number of adverse events[b] | | |
| Any adverse events | 488 | 671 | 1159 |
| Serious adverse events | 6 | 10 | 16 |
| Study medication–related adverse events | 135 | 275 | 410 |
| Study withdrawals due to adverse events | 12 | 33 | 45 |

The onset of an adverse event was during double-blind treatment, including non-serious events that started within 7 days after the last day of double-blind treatment, and serious adverse events that started within 30 days after the last day of double-blind treatment; adverse events that started during the open-label extension phase are not included in this report.

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

[b] Events are counted by preferred term, ie, for patients with multiple events falling under the same preferred term, only 1 occurrence of the event is counted.

The most frequently reported AEs are presented in Table S6. The most common AEs were agitation (23.8%) and constipation (17.7%) in the quetiapine group, and dizziness (32.3%) and postural hypotension (22.3%) in chlorpromazine patients. One death occurred—a case of accidental drowning in a quetiapine patient. No instances of clinical hypothyroidism were observed in either treatment group.

**Table S6 Number (%) of patients with the most commonly reported adverse events, sorted by decreasing order of frequency as summarized over all treatment groups (safety analysis set)**

| COSTART preferred term[a] | Number (%) of patients who had an adverse event | | | |
|---|---|---|---|---|
| | Quetiapine | | Chlorpromazine | |
| Dizziness | 16 | (12.3) | 42 | (32.3) |
| Agitation | 31 | (23.8) | 15 | (11.5) |
| Postural hypotension | 5 | (3.8) | 29 | (22.3) |
| Dry mouth | 14 | (10.8) | 27 | (20.8) |
| Constipation | 23 | (17.7) | 26 | (20.0) |
| Somnolence | 19 | (14.6) | 25 | (19.2) |
| Vomiting | 9 | (6.9) | 23 | (17.7) |
| Headache | 21 | (16.2) | 18 | (13.8) |
| Insomnia | 20 | (15.4) | 8 | (6.2) |
| Dyspepsia | 7 | (5.4) | 20 | (15.4) |

| COSTART preferred term[a] | Number (%) of patients who had an adverse event | | | |
|---|---|---|---|---|
| | Quetiapine | | Chlorpromazine | |
| Pharyngitis | 10 | (7.7) | 17 | (13.1) |
| Tachycardia | 3 | (2.3) | 16 | (12.3) |
| Rash | 4 | (3.1) | 15 | (11.5) |
| Pain | 8 | (6.2) | 13 | (10.0) |
| Rhinitis | 5 | (3.8) | 13 | (10.0) |
| Abdominal pain | 9 | (6.9) | 12 | (9.2) |
| Accidental injury | 11 | (8.5) | 3 | (2.3) |
| Nausea | 5 | (3.8) | 10 | (7.7) |
| Hypotension | 1 | (0.8) | 10 | (7.7) |
| Chest pain | 3 | (2.3) | 9 | (6.9) |
| Asthenia | 4 | (3.1) | 8 | (6.2) |
| Diarrhea | 2 | (1.5) | 8 | (6.2) |
| Back pain | 7 | (5.4) | 6 | (4.6) |
| Amblyopia | 3 | (2.3) | 7 | (5.4) |

The onset of an adverse event was during the double-blind treatment phase.
[a] Events with a total frequency of ≥5% across all treatment groups are included in this table.
COSTART=Coding Symbols for Thesaurus of Adverse Reaction Terms

There were no clinically meaningful differences between the quetiapine and chlorpromazine groups with respect to changes from baseline in hematology parameters. Chlorpromazine treatment appeared to be associated with a prolongation of the QTc interval and with hemodynamic effects consistent with postural hypotension. The QTc interval decreased by a mean ± standard deviation (SD) of 4.8 ± 23.2 msec in the quetiapine group and increased by a mean of 15.0 ± 38.3 msec in the chlorpromazine group. The AE incidence of postural hypotension was 4% for quetiapine and 22% for chlorpromazine. The mean increase in weight was approximately 3 lb in the quetiapine group and 1 lb in chlorpromazine patients. The proportion of patients with a ≥7% weight gain was similar (13% to 14%) in each treatment group.

The most notable difference in clinical chemistry parameters was the large decline from baseline in prolactin levels in quetiapine patients (mean change, -23.5 μg/L) compared to the small decline in the chlorpromazine group (mean change, -3.8 μg/L). Prolactin levels were elevated at baseline in the 2 treatment groups (possibly owing to haloperidol treatment). Since quetiapine does not elevate prolactin levels, the prolactin levels declined during quetiapine treatment. In contrast, prolactin levels remained approximately constant during chlorpromazine treatment.

Overall, quetiapine showed an advantage over chlorpromazine in terms of its safety profile (as indicated by a lower incidence of AEs, SAEs, study medication–related AEs, and withdrawals owing to AEs compared to chlorpromazine) and its tolerability (as indicated by a lower incidence of EPS, less pronounced hemodynamic postural changes, and no elevation of prolactin levels). The strong advantage of quetiapine over chlorpromazine in terms of safety and tolerability, combined with only small differences in efficacy, results in a clear risk/benefit advantage for quetiapine.