A Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Tolerability of High-Dose Quetiapine in Patients With Persistent Symptoms of Schizophrenia or Schizoaffective Disorder

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ABSTRACT

Objective: Quetiapine is often prescribed at higher than approved doses. We investigated the safety, tolerability, and efficacy of quetiapine > 800 mg/d.

Method: A trial was carried out from October 2003–September 2005 in 19 referral centers. Patients with *DSM-IV* schizophrenia or schizoaffective disorder were randomized on the basis of persistent symptoms of moderate severity (< 30% improvement in total Positive and Negative Syndrome Scale score after ≥ 4 weeks of quetiapine). The 8 week, double-blind study compared continuation of quetiapine 800 mg/d (n = 43) versus 1,200 mg/d (n = 88). The primary outcome measure was emergent or worsening parkinsonism (Simpson-Angus Scale). Secondary outcomes were adverse events, metabolic side effects, and symptom severity.

Results: Mean doses obtained were 799 mg/d and 1,144 mg/d in the 800-mg/d and > 800-mg/d groups, respectively. Emergent or deteriorating parkinsonism in the high-dose group was 3.1% greater (95% CI, −7.8% to 14.0%; *P* = .76) than in the 800-mg/d group, a value that was within the a priori limit of 16% defined as noninferiority. Both doses of quetiapine were safe and well tolerated. Weight gain was greater in the high-dose group (1.7 kg over 12 weeks; ≥ 7% body weight, n = 11 [12.5%]) versus the 800-mg/d group (1.1 kg over 12 weeks; ≥ 7% body weight, n = 4 [9.3%]). The mean adjusted difference in weight gain (1.3 kg) was greater in the high-dose group (95% CI, 0.0–2.5; *P* = .044). Symptom severity declined, with no significant difference between groups.

Conclusions: The results did not demonstrate any advantage for use of quetiapine outside the approved dose range.

Trial Registration: www.clinicaltrials.gov Identifier: NCT00328978

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Strategies for patients with a partial or incomplete response to antipsychotic drug treatment include increasing the dose of medication, changing the medication, or using antipsychotic polypharmacy. Although high doses of atypical antipsychotics are commonly prescribed, quetiapine has received less attention in controlled studies relative to risperidone and olanzapine.[1–5] Switching to quetiapine in poorly responsive patients may be associated with some improvement.[6] Combinations of quetiapine and other antipsychotic drugs are commonly used, but rarely studied.[5]

Concerning quetiapine dose-response relationships, a lower threshold of 250 mg/d may be required for response, but few studies have evaluated doses higher than 450 mg/d.[7–11] No conclusions can be drawn regarding plasma quetiapine levels and clinical response.[12] Overall adverse events do not appear to be more common at a dose of ≥ 250 mg/d compared with < 250 mg/d, nor are the commonly reported side effects of somnolence and dizziness.[13] Extrapyramidal symptoms do not appear to be different between placebo and quetiapine or to be dose related up to 750 mg/d.[13,14] Weight gain does not appear to be dose related.[15] Quetiapine is associated with a measurable increase in the QTc interval[16]; however, adding a metabolic inhibitor that increased the plasma concentration by 77% did not result in a significant additional change.

The goal of the present study was to investigate a high dose of quetiapine (1,200 mg/d) in patients with persistent symptoms of at least moderate severity following an incomplete response to the maximal approved dose of 800 mg/d. Our primary objective was to determine if the higher dose of quetiapine was associated with more extrapyramidal symptoms. The secondary objectives were to determine the safety, tolerability, and efficacy of high-dose quetiapine.

METHOD

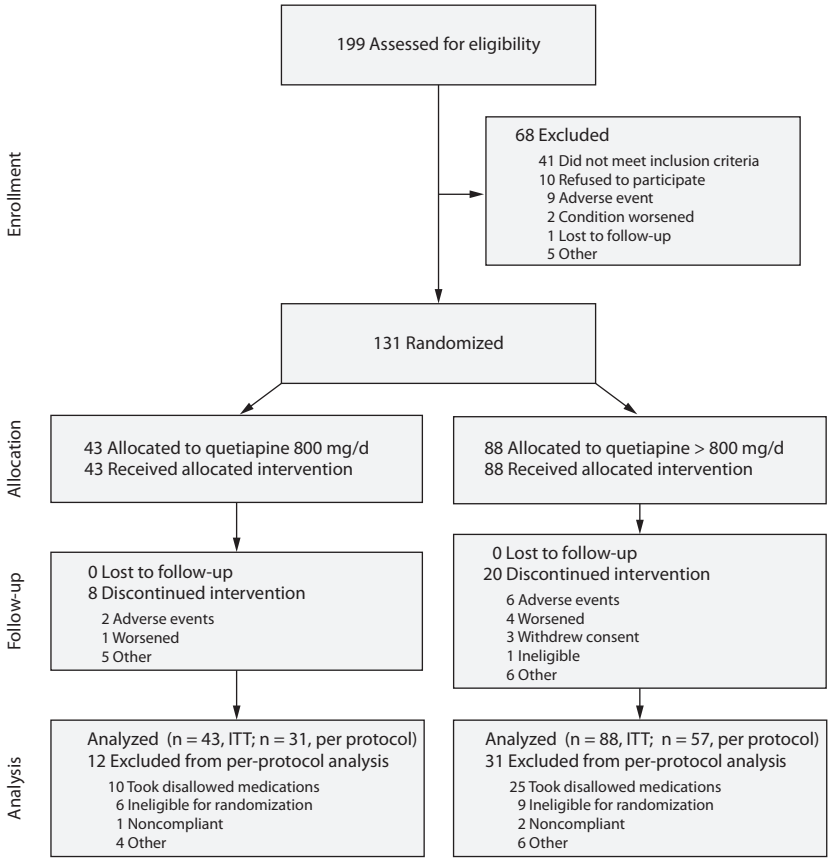
Participants

We assessed 199 patients for eligibility (inpatients and outpatients) from 19 medical centers in Canada (Figure 1). The inclusion criteria were a diagnosis of schizophrenia or schizoaffective disorder according to the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (*DSM-IV*),[17] age 18 to 65 years, and a total score of 70–110 on the Positive and Negative Syndrome Scale (PANSS).[18] Subjects had persistent positive and/or negative symptoms. *Persistent positive symptoms* were defined as a total score of 15 or more on the positive subscale of the PANSS, with a score of 4 (moderate) or more on at least 1 of the following symptoms: delusions, conceptual disorganization, hallucinations, or suspiciousness. *Persistent negative symptoms* were defined as a total score of 15 or more on the negative subscale of the PANSS, with a score of at least 4 (moderate) on blunted affect, emotional withdrawal, poor rapport, passive social withdrawal, or lack of spontaneity. The Clinical Global Impressions scale (CGI) score was required to be at least 4 (moderately ill).[19] Subjects were required to meet the inclusion criteria at screening and following the first 4 weeks of treatment. Exclusion criteria were level-6 treatment resistance according to the May scale,[20] significant alcohol or substance abuse in the previous 3 months, significant medical illness, previous treatment with quetiapine > 800 mg/d, or previous treatment with clozapine. Subjects with an

Clinical Points

- Like other atypical antipsychotics, quetiapine is often prescribed at higher than approved doses for patients with schizophrenia or schizoaffective disorder.
- While using quetiapine at doses greater than 800 mg/d does not increase extrapyramidal symptoms, weight gain is greater at higher than approved doses.
- Higher than approved doses offer no additional benefit in improving symptom severity.

Figure 1. CONSORT Diagram of the Trial



Abbreviation: ITT = intention to treat.

improvement in total PANSS score of 30% or greater during the initial open-label phase of treatment were excluded from the double-blind phase.

Study Design

The study was carried out from October 2003 to September 2005 and is registered at clinicaltrials.gov (identifier: NCT00328978). Subjects not taking quetiapine had their medication tapered over 1 week. By the end of 14 days, subjects were treated with quetiapine monotherapy at 800 mg/d. At the end of 28 days, eligible subjects continued quetiapine 800 mg/d, and were randomized (2:1, with a computerized schedule) to supplementation with quetiapine or with placebo. The person who generated the randomization schedule was not involved in determining subject eligibility, administering treatment, or determining outcome.

Supplementation was with quetiapine 400 mg/d (administered as 200 mg twice per day) or with an equal number of placebo tablets by day 35. After patients received treatment with the maximum dose at day 35, investigators could decrease the supplemental doses if side effects were present. Double-blind supplementation continued until day 84 (8 weeks total). Pill counting was used to assess adherence. If subjects were taking stable doses of antidepressant, mood stabilizing, or hypnotic medications for a 30-day period prior to trial entry, these were continued. New medications allowed were flurazepam 15–30 mg/d or zaleplon 10 mg/d for sleep and lorazepam to a maximum of 4 mg/d for agitation. Anticholinergic medication was allowed only for the treatment of emergent extrapyramidal symptoms.

Ethics approval was obtained from the appropriate hospital and/or university committees. All subjects provided written informed consent.

Primary Outcome

The primary outcome measure was emergent or worsening extrapyramidal symptoms. Parkinsonism was measured by the Simpson-Angus Scale (SAS)[21] at screening and at the end of the open-label (day 29) and double-blind phases (day 85). Subjects were categorized as having no change, worsening, or improvement in SAS score. Akathisia was assessed using the Barnes Akathisia Rating Scale (BARS),[22] and dyskinesia using the Abnormal Involuntary Movement Scale (AIMS).[19]

Secondary Outcomes: Safety, Tolerability, and Efficacy

Adverse events were assessed with standardized questioning at each visit. Adverse events were defined as development of an undesirable medical condition or deterioration of a preexisting medical condition following or during exposure to medication, whether or not considered causally related to the medication. A serious adverse event was defined as an adverse event occurring during any study phase, and at any dose, fulfilling 1 or more of the following criteria: resulted in death, was immediately life threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity,

was a congenital abnormality or birth defect, and was an important medical event that might have jeopardized the subject or might have required medical intervention to prevent one of the outcomes listed above.

Laboratory measures included hemoglobin, a complete blood count and differential, liver and renal function tests, thyroid panel, and measurement of prolactin. Metabolic measures included measurement of weight; height; calculation of body mass index; measurement of fasting glucose; hemoglobin A_{1c}; total, low-density lipoprotein, and high-density lipoprotein cholesterol; and triglycerides. Serum levels of quetiapine were measured on days 29, 43, and 85. Cardiac safety was assessed with measurement of vital signs and the Fridericia-corrected QTc interval of the electrocardiogram. The PANSS was rated on days 29 and 85. Responders were defined as improvement ≥ 20%. Additional descriptive measures were the CGI-Severity of Illness and Improvement scales, and the Social and Occupational Functioning Assessment Scale (SOFAS).[17]

Statistical Analysis

Analysis of the primary outcome measure, severity of parkinsonism, was carried out using a noninferiority strategy. An intention-to-treat approach was used, including data from all randomized subjects. Worsening of parkinsonism was defined as an increase in the total SAS score (> 0) from randomization (day 29) to day 85 or last observation. We compared the proportion of subjects experiencing emergent or worsening of parkinsonism between groups. We assumed a rate of 8%, although this is quite arbitrary due to the low frequency of parkinsonism observed with quetiapine. We anticipated being able to randomize 120 subjects, using a 2:1 allocation ratio to allow collection of more safety data in the higher dose group. The noninferiority margin was set at 16%. By using a 1-sided, nonparametric analysis of covariance (ANCOVA) via the Cochran-Mantel-Haenszel test, a type-1 error of .05, and the estimated 8% worsening of parkinsonism for both groups, the statistical power was 0.8 for a noninferiority trial.

As measures of safety and tolerability, the proportions of patients with adverse events, serious adverse events, and extrapyramidal symptoms were compared separately between treatments using Fisher exact test. Changes in laboratory data from day 29 to day 85 were analyzed using ANCOVA, with treatment as the factor and the corresponding day 29 value as the covariate.

The secondary efficacy variable was the total PANSS score difference from randomization to end of trial. The statistical model (ANCOVA) included only the initial and final responses.

RESULTS

Study Population

Demographic and clinical characteristics appear in Table 1. In the 800-mg/d group, 35 subjects (81%) completed the study, compared with 68 subjects (77%) in the > 800-mg/d group (Figure 1). The mean daily doses were 799 mg (range, 773–800) in the 800-mg/d group and 1,144 mg (range, 760–1,193) in the > 800-mg/d group. In the 800-mg/d group, 14% of patients received doses less than maximal for at least some period of time; in the > 800-mg/d group, the proportion was 16%. Mean adherence was ≥ 95% in both groups; 1 subject in the 800-mg/d group and 2 in the > 800-mg/d group had adherence < 80%.

Primary Outcome: Extrapyramidal Symptoms

The measures of extrapyramidal symptoms appear in Table 2. The frequency of deterioration or emergence of parkinsonism in the > 800-mg/d group was 3.1% greater (95% CI, −7.8% to 14.0%; $P = .76$) than the 800-mg/d group, within the a priori limit defined as noninferiority. Results from the per protocol analysis revealed a 5.8% greater percentage of patients with parkinsonism in the > 800-mg/d group than in the 800-mg/d group (95% CI, −6.2% to 17.8%; $P = .54$). Overall, the mean scores for the SAS, Barnes Akathisia Rating Scale, and AIMS measures of extrapyramidal symptoms showed a decline over time during the double-blind phase of the study, with no statistically significant differences between groups.

Secondary Outcomes: Safety and Tolerability

Serious adverse events. Overall adverse event frequencies are reported in Table 3. A total of 7 subjects experienced serious adverse events, 3 prior to randomization and 4 during the randomized treatment phase. In the group of subjects not randomized, there was 1 suicide, a 26-year-old male outpatient. Treatment of this patient during the 30 days prior to entering the study included olanzapine, with poor response. Quetiapine was prescribed; however, compliance was uncertain. The investigator considered the event to be unrelated to the study therapy. A 37-year-old man experienced suicidal ideation that resolved after 4 days. This was not attributed to study treatment; he was withdrawn from the study. A 45-year-old woman developed increased anxiety during the open-label phase. This was not attributed to study treatment; she was withdrawn. Two serious adverse events during the randomized treatment phase were attributed to study treatment by the investigator: in the quetiapine 800-mg/d group, a 54-year-old woman experienced delirium; in the quetiapine > 800-mg/d group, a 24-year-old man experienced a seizure. Both subjects were withdrawn. Two serious adverse events during the randomized treatment phase were not attributed to study treatment; both were in the > 800-mg/d group. A 24-year-old woman experienced a worsening of schizophrenia, and a 47-year-old man developed depression with suicidal ideation. Both subjects continued in the study.

From randomization to treatment end, 13 adverse events associated with extrapyramidal symptoms were recorded: dyskinesia (n = 3 [7.0%]), tremor, torticollis, and sialorrhea (n = 1 [2.3%] each) in the 800-mg/d group; tremor (n = 4 [4.5%]), dyskinesia, restlessness, and hypokinesia (n = 1 [1.1%] each) in the > 800-mg/d group. The differences in proportions of

Table 1. Characteristics of Patients at Enrollment (day 1)

Characteristic	Quetiapine 800 mg/d (n = 43)	Quetiapine > 800 mg/d (n = 88)	Not Randomized (n = 34)
Age, mean ± SD, y	37.9 ± 10.9	40.6 ± 12.5	35.4 ± 11.7
Men, n (%)	32 (74)	58 (66)	26 (77)
Race, n (%)			
White	37 (86)	80 (91)	30 (88)
Black	3 (7)	5 (6)	3 (9)
Oriental	1 (2)	2 (2)	0 (0)
Other	2 (5)	1 (1)	1 (3)
Schizophrenia			
Yes	39	69	25
No	4	19	9
Outpatient, n (%)	36 (84)	68 (77)	23 (68)
SAS score, mean ± SD	2.7 ± 4.0	2.9 ± 4.4	3.1 ± 4.1
BARS global score, mean ± SD	0.4 ± 0.8	0.5 ± 0.8	0.4 ± 0.8
AIMS global score, mean ± SD	0.6 ± 1.1	0.6 ± 1.2	1.1 ± 2.1
Weight, mean ± SD, kg	81.7 ± 16.3	83.7 ± 18.7	86.5 ± 22.2
Body mass index, mean ± SD	28.4 ± 6.4	28.6 ± 6.1	29.0 ± 7.3
Body mass index, n (%)			
< 18.5,	1 (2)	1 (1)	1 (3)
18.5–< 25	12 (28)	28 (32)	11 (32)
≥ 25	30 (70)	59 (67)	22 (65)
Fasting blood glucose, mean ± SD, mmol/L (n)	5.32 ± 0.90 (43)	5.24 ± 0.81 (87)	5.14 ± 0.57 (34)
Insulin, mean ± SD, μU/mL (n)	7.5 ± 8.4 (42)	6.3 ± 5.3 (83)	9.4 ± 9.2 (33)
Hemoglobin A_{1c} ratio, mean ± SD (n)	0.054 ± 0.005 (43)	0.053 ± 0.006 (88)	0.053 ± 0.006 (33)
Total cholesterol, mean ± SD, mmol/L (n)	5.06 ± 1.18 (43)	5.25 ± 1.35 (88)	5.28 ± 1.19 (32)
Triglycerides, mean ± SD, mmol/L (n)	2.44 ± 1.87 (43)	2.16 ± 1.40 (88)	2.57 ± 1.91 (32)
HDL cholesterol, mean ± SD, mmol/L (n)	1.11 ± 0.25 (42)	1.18 ± 0.36 (87)	1.17 ± 0.33 (32)
LDL cholesterol, mean ± SD, calculated mmol/L (n)	2.82 ± 0.96 (42)	3.07 ± 1.13 (87)	2.95 ± 0.79 (32)
Prolactin, mean ± SD, ng/mL (n)	26.76 ± 29.38 (43)	26.96 ± 37.77 (88)	26.18 ± 31.89 (32)
PANSS total score, mean ± SD	88.9 ± 10.4	88.7 ± 10.7	85.4 ± 9.9
PANSS positive score, mean ± SD	21.6 ± 4.6	21.1 ± 4.2	20.9 ± 5.5
PANSS negative score, mean ± SD	24.2 ± 5.1	23.8 ± 4.9	22.9 ± 4.0
Clinical Global Impressions-Severity of Illness Scale, mean ± SD	4.4 ± 0.7	4.5 ± 0.6	4.6 ± 0.7
SOFAS score, mean ± SD	50.0 ± 10.2	49.0 ± 9.7	49.1 ± 10.2

Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BARS = Barnes Akathisia Rating Scale, HDL = high-density lipoprotein, LDL = low-density lipoprotein, PANSS = Positive and Negative Syndrome Scale, SAS = Simpson-Angus Scale, SOFAS = Social and Occupational Functioning Assessment Scale.

Table 2. Categorical Changes in Extrapyramidal Symptom Scores Related to Quetiapine Dosage From Randomization (day 29) to End of Treatment (day 84)

	Quetiapine 800 mg/d (n = 43)		Quetiapine > 800 mg/d (n = 88)	
Measure, n (%)	Intention-to-Treat Population (n = 43)	Per-Protocol Population (n = 30)	Intention-to-Treat Population (n = 88)	Per-Protocol Population (n = 57)
Simpson-Angus Scale				
Improved (change score < 0)	15 (35)		31 (35)	
No change	22 (51)		42 (48)	
Improved or no change	37 (86)	27 (90)	73 (83)	48 (84)
Worsened (change score > 0)	6 (14)	3 (10)	15 (17)	9 (16)
Barnes Akathisia Rating Scale				
Improved (change score < 0)	8 (19)		16 (18)	
No change	32 (74)		63 (72)	
Improved or no change	40 (93)	25 (86)	79 (90)	51 (89)
Worsened (change score > 0)	3 (7)	4 (14)	9 (10)	6 (11)
Abnormal Involuntary Movement Scale				
Improved (change score < 0)	6 (14)		19 (22)	
No change	30 (71)		51 (59)	
Improved or no change	36 (86)	27 (90)	70 (80)	45 (79)
Worsened (change score > 0)	6 (14)	3 (10)	17 (20)	12 (21)

patients in the 2 dosage groups with adverse events, serious adverse events, and extrapyramidal symptoms during the blinded phase of the study were not statistically significant ($P = .70$, $P > .99$, and $P = .21$ for adverse events, serious adverse events, and extrapyramidal symptoms, respectively).

Glucose regulation. Mean values for fasting blood glucose and hemoglobin A_{1c} ratio appear in Table 4. Comparison of the change in fasting glucose during the randomized phase did not reveal any statistically significant differences between the 2 groups. Numbers of patients shifting from normal to abnormal values appear in Table 5.

Body mass index and weight. There was a slight upward trend in the mean change in BMI during the full 12 weeks of treatment, with a 0.38 change in the 800-mg/d group (n = 35)

Table 3. Total Numbers of Adverse Events and Numbers of Subjects Who Had at Least 1 Adverse Event in Any Category[a]

Variable	Quetiapine 800 mg/d (n = 43)	Quetiapine > 800 mg/d (n = 88)	Not Randomized (n = 34)
Total number of adverse events, n			
Adverse events	140	374	95
Serious adverse events	1	3	3
Other significant adverse events	8	16	6
Subjects with an adverse event in each category, n (%)			
Any adverse events	34 (79)	76 (86)	28 (82)
Serious adverse events	1 (2)	3 (3)	3 (9)
Serious adverse event leading to death	0	0	1 (3)
Serious adverse event not leading to death	1 (2)	3 (3)	2 (6)
Discontinuation due to adverse event	2 (5)	6 (7)	10 (29)
Other significant adverse event	8 (19)	11 (13)	4 (12)
Subjects with an adverse event in each category during the randomized phase, n (%)			
Dizziness	7 (16)	13 (15)	
Headache	4 (9)	11 (13)	
Fatigue	3 (7)	7 (8)	
Somnolence	2 (5)	8 (9)	
Anxiety	1 (2)	5 (6)	
Dyskinesia	3 (7)	1 (1)	

[a]Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories. Other significant adverse events are adverse events associated with extrapyramidal symptoms, QT prolongation, diabetes, suicidality, neutropenia, and agranulocytosis. All serious adverse events and adverse events leading to discontinuation are excluded. The cutoff date for the open-label phase and blinded phase is the date of first dose of randomized medication. If adverse events started in the open-label phase and continued, they were categorized with treatments received in the open-label phase. The summary figures for the randomized phase represent the most commonly reported adverse events, with a frequency ≥ 5% across all treatment groups.

Table 4. Plasma Levels and Metabolic Measures During the Randomized Treatment Phase of the Study

	Quetiapine 800 mg/d				Quetiapine > 800 mg/d				Treatment Comparison (> 800 mg – 800 mg), Least Squares Mean Difference (95% CI)[a]
Variable	n	Day 29, mean ± SD	Day 85, mean ± SD	Mean Change	n	Day 29, mean ± SD	Day 85, mean ± SD	Mean Change	
Quetiapine level, ng/mL	30	220 ± 237	233 ± 305	14	65	199 ± 189	266 ± 257	67	49 (−47 to 145)
Weight, kg	35	83.0 ± 17.3	83.0 ± 17.9	0.0	70	83.6 ± 15.7	84.8 ± 15.3	1.2	1.3 (0.0 to 2.5)
Body mass index	35	28.3 ± 5.8	28.3 ± 6.0	0	70	28.4 ± 5.3	28.8 ± 5.2	0.4	0.4 (−0.01 to 0.9)
Fasting blood glucose, mmol/L	33	5.20 ± 0.88	5.33 ± 0.89	0.12	64	5.42 ± 0.82	5.53 ± 1.46	0.11	−0.05 (−0.43 to 0.34)
Insulin, μU/mL	32	8.97 ± 8.89	9.72 ± 22.20	0.75	62	6.31 ± 5.48	5.65 ± 4.54	−0.66	−2.53 (−8.19 to 3.13)
Hemoglobin A_{1c} ratio	36	0.054 ± 0.006	0.054 ± 0.005	−0.001	70	0.054 ± 0.006	0.054 ± 0.007	0.0003	0.001 (−0.001 to 0.003)
Total cholesterol, mmol/L	31	5.15 ± 1.29	5.23 ± 1.43	0.08	69	5.53 ± 1.23	5.66 ± 1.27	0.14	0.08 (−0.19 to 0.36)
Triglycerides, mmol/L	31	2.63 ± 1.61	2.53 ± 1.94	−0.10	69	2.37 ± 1.58	2.64 ± 1.64	0.27	0.31 (−0.22 to 0.84)
HDL cholesterol, mmol/L	31	1.15 ± 0.24	1.15 ± 0.25	0.00	69	1.21 ± 0.36	1.23 ± 0.36	0.01	0.02 (−0.05 to 0.09)
LDL cholesterol, mmol/L[b]	31	2.80 ± 0.93	2.93 ± 1.06	0.13	69	3.24 ± 1.02	3.24 ± 1.03	−0.0001	−0.05 (−0.33 to 0.24)
Prolactin, ng/mL	31	14.87 ± 14.98	11.68 ± 11.58	−3.18	68	9.95 ± 11.37	8.97 ± 8.52	−0.98	−0.38 (−3.67 to 2.90)

[a]Analysis of covariance in subjects with both time points, with treatment as factor and the day 29 value as covariate. None of the treatment differences were statistically significant except for body weight ($P = .044$).
[b]Low-density lipoprotein cholesterol was a calculated value.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

and 0.60 change in the > 800-mg/d treatment group (n = 70). For subjects with data available from the beginning and end of the randomized period (Table 4), the change in BMI over time was greater in the > 800-mg/d group, but this change was not statistically significant ($P > .05$).

Both groups increased weight during the full 12 weeks of treatment, with increases of 1.1 kg in the 800-mg/d group (n = 35) and 1.7 kg in the > 800-mg/d group (n = 70). Fifteen subjects increased weight ≥ 7% (n = 4 [9.3%] in the 800-mg/d group and n = 11 [12.5%] in the > 800-mg/d group). During the randomized period, greater increase in weight occurred in the > 800-mg/d group ($P = .044$). A total of 10 subjects had a weight increase of ≥ 7% (n = 1 [2.3%] in the 800-mg/d group and n = 9 [10.2%] in the > 800-mg/d group).

Lipids. Lipid results appear in Table 4; no statistically significant changes were noted. Numbers of patients shifting from normal to abnormal values appear in Table 5.

Prolactin. As seen in Table 4, the mean prolactin values were slightly higher for the 800-mg/d treatment group. The mean change (decrease) was greater for this group as well.

Changes in vital signs and electrocardiogram. Nonclinically significant changes were observed in both treatment groups. For heart rate, each group had 1 subject who went from normal heart rate at randomization to a high heart rate (120 beats per minute) at the end of treatment (data not shown). Two subjects in the quetiapine > 800-mg/d group shifted from normal to high QTcF (≥ 450 milliseconds) from day of randomization to the end of the study. For 1 subject,

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Table 5. Categorical Assignments of Patients' Metabolic Laboratory Values at Randomization and at the End of Study Treatment[a]

		At End of Treatment					
		Quetiapine 800 mg/d			Quetiapine > 800 mg/d		
Variable	At Randomization	Low, n (%)	Normal, n (%)	High, n (%)	Low, n (%)	Normal, n (%)	High, n (%)
Fasting blood glucose	High			1 (100)			1 (100)
	Normal		31 (97)	1 (3)		60 (95)	3 (5)
Hemoglobin A_{1c} ratio	High						1 (100)
	Normal		36 (100)			67 (97)	2 (3)
Total cholesterol	High		2 (25)	6 (75)		5 (28)	13 (72)
	Normal		26 (93)	2 (7)		46 (88)	6 (12)
Triglycerides	High		5 (33)	10 (67)		4 (14)	25 (86)
	Normal		20 (95)	1 (5)		32 (78)	9 (22)
HDL cholesterol	Normal	5 (22)	18 (78)		2 (5)	41 (95)	
	Low	9 (69)	4 (31)		22 (81)	5 (19)	
LDL cholesterol	High		2 (67)	1 (33)		5 (38)	8 (62)
	Normal		31 (94)	2 (6)		53 (93)	4 (7)

[a]Percentages were calculated in relation to total number in the respective category at randomization.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

the shift was transient. For the second subject, the shift occurred at the end of study treatment.

Secondary Outcome: Efficacy

During the open-label phase of the study, as expected, there was little change in PANSS score. The total PANSS scores in both treatment groups dropped after the first week of randomized treatment, suggesting nonspecific effects. The total PANSS score difference between randomization and end of treatment did not show a statistically significant difference between the 800-mg/d and > 800-mg/d groups (Table 6). Similar results were observed in the per protocol subset. In the intention-to-treat analysis set, 23 subjects (54%) in the quetiapine 800-mg/d group were classified as responders compared with 49 (56%) in the > 800-mg/d group. Similar results were observed in the per protocol subset, with 12 subjects (40%) in the quetiapine 800-mg/d group classified as responders compared with 23 (40%) in the > 800-mg/d group.

Doses and Plasma Levels

Dose and plasma level information appears in Table 4. Although a close to 50% increase in daily dose of quetiapine was achieved in the > 800-mg/d group, the change in trough quetiapine plasma level was highly variable, with a median increase of 37 ng/mL (range, –415 to 817). The correlation between changes in quetiapine plasma level and in total PANSS score in the > 800-mg/d group was low ($r = 0.03$).

Table 6. Secondary Measures of Efficacy (expressed as last observation carried forward)

Measure, mean ± SD	Quetiapine 800 mg/d (n = 43)		Quetiapine > 800 mg/d (n = 88)		
	Day 29	Day 85	Day 29	Day 85	*P*[a]
PANSS total score	82.2 ± 8.8	65.4 ± 17.8	82.7 ± 10.7	64.6 ± 20.9	.89
PANSS positive score	20.4 ± 4.3	15.4 ± 5.7	19.8 ± 3.9	14.9 ± 5.8	.97
PANSS negative score	22.3 ± 5.3	18.4 ± 5.9	23.3 ± 5.1	18.4 ± 6.5	.57
CGI-S score	4.4 ± 0.6	3.7 ± 1.1	4.4 ± 0.5	3.6 ± 1.2	.70
SOFAS score[b]	51.1 ± 10.9	54.3 ± 11.2	49.2 ± 11.7	54.8 ± 12.9	.75

[a]*P* values were calculated by analysis of covariance.
[b]SOFAS data were missing for 1 subject in the 800-mg/d group at day 85.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, PANSS = Positive and Negative Syndrome Scale, SOFAS = Social and Occupational Functioning Assessment Scale.

DISCUSSION

This study enrolled a group of patients with chronic illness and a moderately high level of symptomatology that persisted after 28 days of treatment with quetiapine to 800 mg/d. During the subsequent 8 weeks of continued treatment with quetiapine 800 mg/d or > 800 mg/d, there was little evidence for extrapyramidal side effects and no differences in extrapyramidal symptoms between groups. Concerning other side effects, in the high-dose group, glucose and lipid dysregulation were more prevalent, but differences in the 800-mg/d group were not statistically significant. Prolactin was not elevated in the high-dose group. However, more weight gain and a greater increase in BMI were observed in the > 800-mg/d group, with statistical significance for the greater weight gain. The severity of symptoms decreased over time, but there was no detectable difference between high-dose quetiapine compared with the maximum approved dose.

Several studies have investigated quetiapine in patients poorly responsive to other antipsychotic medications. One randomized clinical trial[6] compared the response to quetiapine (600 mg/d) versus haloperidol (20 mg/d). The treatments did not differ statistically in the primary outcome measure of symptom severity. Post hoc analyses indicated an advantage for quetiapine in those patients with no response to fluphenazine[23] and an advantage for quetiapine in depressive symptoms.[24] Weight increased more in the quetiapine group. Subsequently, 2 open studies[3,4] investigated

the strategy of high-dose quetiapine (1,000–2,400 mg/d) for treatment-refractory patients, with encouraging results. Weight gain appeared to be the most problematic side effect, occurring in both reports, with 1 patient developing diabetes mellitus. Extrapyramidal symptoms were measured in 1 of the 2 studies, with some increase in akathisia noted.[3]

The present study of high-dose quetiapine confirms the side effect profile observed in the open studies, with no increase in extrapyramidal symptoms and greater weight gain relative to the 800-mg/d dose. Although the safety profile was favorable, there was no obvious difference in extent of improvement of severity of symptoms between the dosage groups.

This study has several limitations. Analysis of safety and tolerability was the primary goal. Parkinsonism was chosen as the primary outcome, since this side effect of antipsychotics appears to have the clearest dose-response relationship. The study was not powered for a thorough evaluation of efficacy, particularly for small or medium effect sizes. Although patients were required to have persistent symptoms of moderate severity following open-label quetiapine, the similarity and magnitude of response in both dosage groups following randomization and blinding could be consistent with rater bias toward improvement. The high-dose quetiapine group was prescribed nearly a 50% greater dose than the comparator group; this was not reflected in a similar percentage increase in plasma level. However, quetiapine dosage is inconsistently predictive of plasma levels.[12,25] Finally, the doses investigated may not differ enough to demonstrate differences in efficacy.

These results indicate that, in acute schizophrenia or schizoaffective disorder, quetiapine at doses greater than 800 mg/d is not associated with any greater extrapyramidal side effects than 800 mg/d. Greater weight gain occurred with the higher dose. Both dosages were associated with improvement of symptom severity over time; however, there was no difference in amount of improvement between the dosage groups. In summary, the results of this study did not demonstrate any advantage for use of quetiapine at doses outside of the approved dose range.

Drug names: clozapine (Clozaril, FazaClo, and others), flurazepam (Dalmane and others), haloperidol (Haldol and others), lorazepam (Ativan and others), quetiapine (Seroquel), olanzapine (Zyprexa), risperidone (Risperdal and others), zaleplon (Sonata and others).

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Author contributions: The initial proposal and design of the study was by Drs Honer and MacEwan, and the study was submitted to AstraZeneca Canada as an investigator-initiated trial. The manuscript was written by Drs Honer, MacEwan, and Gendron. All authors critically reviewed the manuscript.

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Potential conflicts of interest: **Dr Honer** has received consulting fees or has served on paid advisory boards for In-Silico, Wyeth, Janssen, Novartis, and AstraZeneca; has received lecture fees from Janssen and AstraZeneca; and has received educational grant support from Janssen, Eli Lilly, and AstraZeneca. **Dr MacEwan** has received consulting or advisory board fees from AstraZeneca, Janssen, Eli Lilly, Pfizer, and Novartis; has received lecture fees from GlaxoSmithKline and Apotex; and has received grant support from AstraZeneca. **Drs Gendron** and **Eriksson** are employees of AstraZeneca. **Dr Stip** has received funding for clinical trials from AstraZeneca, Pfizer, Eli Lilly, and Janssen; and holds the Eli Lilly Schizophrenia Research Chair at the University of Montreal. **Dr Labelle** has received funding for research projects and honoraria for advisory boards from Eli Lilly, Janssen, Pfizer, Solvay, and Bristol-Myers Squibb; and has received lecture fees from Eli Lilly, Janssen, Pfizer, and Solvay. **Dr Williams** has received research grants from Janssen, Pfizer, AstraZeneca, Sanofi-Aventis, Organon, Solvay, and OBEcure Ltd; and has received honoraria for talks from Janssen, Pfizer, AstraZeneca, and Eli Lilly.

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Role of sponsor: With the agreement of the investigators, AstraZeneca subsequently took over the study, made amendments to the design (with consultation from Drs Honer, MacEwan, Stip, Labelle, and Williams), and retained Drs Honer and MacEwan as paid consultants for the study. The original data from the study were provided to Drs Honer and MacEwan as part of the Clinical Study Report. AstraZeneca carried out the majority of statistical analyses, and selected analyses were confirmed by Dr Honer.

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