Key Words: extended release, quetiapine, atypical antipsychotic, schizophrenia, clinical trial

A Failed 6-Week, Randomized, Double-Blind, Placebo-Controlled Study of Once-Daily Extended Release Quetiapine Fumarate in Patients with Acute Schizophrenia: Lessons Learned

By Andrew J. Cutler, Tram Tran-Johnson, Amir Kalali, Mikael Åström, Martin Brecher, Didier Meulien

ABSTRACT ~ **Objective:** *To demonstrate the efficacy of once-daily extended release quetiapine fumarate (quetiapine XR) versus placebo in adults with acute exacerbation of schizophrenia.* **Methods:** *A 6-week, double-blind, randomized, placebo-controlled study. In- or out-patients with a DSM-IV diagnosis of schizophrenia were randomized to fixed-dose quetiapine XR 400, 600, or 800 mg/day, quetiapine immediate release (IR) 800 mg/day, or placebo. Primary endpoint was change from baseline in Positive and Negative Syndrome Scale (PANSS) total score at Week 6. Other efficacy assessments included Clinical Global Impressions (CGI) of Severity (CGI-S) and of Improvement (CGI-I) ratings. Safety assessments included adverse event (AE) reporting and laboratory measures.* **Results:** *565 patients were randomized; 333 (58.9%) completed the study. Greater numeric improvements in PANSS total score were seen for quetiapine XR (all doses) and quetiapine IR versus placebo at Week 6; the differences were not statistically significant. Secondary efficacy endpoint results were similar. There was not a high placebo response in this study, but rather an attenuation of drug effect. In general, quetiapine XR was well tolerated over 6-weeks' treatment; there were no unexpected AEs.* **Conclusion:** *The efficacy of quetiapine XR (400, 600, and 800 mg/day) was not established at Week 6. Quetiapine IR, an agent with established efficacy in schizophrenia,*

Dr. Cutler, MD, Department of Psychiatry, University of Florida, Bradenton, FL. Dr. Tran-Johnson, PharmD, PsyD, CNRI-San Diego, San Diego, CA. Dr. Kalali, MD, Medical and Scientific Services (CNS), Quintiles Inc., and Department of Psychiatry, University of California, San Diego, CA. Drs. Åström, MSc, PhL, Meulien, MD, (on behalf of the Study 133 Investigators), AstraZeneca R&D, Södertälje, Sweden. Dr. Brecher, MD, formerly AstraZeneca Pharmaceuticals, Södertälje, Sweden.

To whom correspondence should be addressed: Dr. Andrew J. Cutler, MD, Department of Psychiatry, University of Florida, 3914 SR 64 E, Bradenton, FL 34208. Phone: +1 941-747-7900; Fax: +1 941-747-7992; E-mail: acutler@FLCRC.com

also did not separate from placebo at endpoint. Therefore, this is considered a failed study and possible reasons for this are discussed. Quetiapine XR was generally well tolerated and its safety profile was consistent with the known profile of quetiapine. Psychopharmacology Bulletin. *2010;43(4):37–69.*

INTRODUCTION

Quetiapine fumarate (quetiapine), a dibenzothiazepine derivative, is an atypical antipsychotic with proven efficacy in schizophrenia,[1–3] mania associated with bipolar disorder,[4] and bipolar depression.[5,6]

Treatment nonadherence is a well-known problem in patients with schizophrenia;[7,8] a cross-sectional review of the records of more than 34,000 patients with schizophrenia found that 36–37% were poorly adherent during a 1-year period.[9] In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, 74% (1061/1432) of patients with schizophrenia discontinued study treatment in less than 18 months.[10] Nonadherence to treatment has serious consequences, such as increasing the risk of relapse and suicide attempts.[11] The complexity of dosing regimens is one of the factors that contribute to patients' poor adherence to treatment.[12]

For the treatment of schizophrenia, quetiapine immediate release (IR) is administered orally twice or three times daily. Extended release quetiapine fumarate (quetiapine XR) was developed to simplify the dosing regimen and shorten the time to therapeutic dose range. Quetiapine XR is dosed once daily and is administered using a simpler dose titration schedule (300 mg on Day 1, 600 mg on Day 2, and up to 800 mg/day from Day 3) than that used with quetiapine IR. Both formulations of quetiapine are effective in, and approved for, the treatment of schizophrenia, bipolar mania, and bipolar depression. Indeed, recent studies of quetiapine XR have demonstrated its efficacy in the acute treatment of bipolar depression,[13] bipolar mania,[14] and schizophrenia.[15] The efficacy of quetiapine XR (400, 600 and 800 mg/day) was demonstrated in patients with acute schizophrenia in Study 132,[15] a 6-week, randomized, double-blind international study (conducted in 8 countries excluding the USA). This study found that quetiapine XR and IR statistically improved PANSS total score compared with placebo. The primary objective of the present study (Study 133; D1444C00133), which was of identical design but was performed only in sites in the USA, was to demonstrate the superior efficacy of quetiapine XR compared with placebo in patients with acute schizophrenia. Although Study 133 had an identical design to Study 132, there were some important differences in execution and study population. These are discussed herein.

This article presents the methods and results of Study 133, which did not demonstrate a statistical separation from placebo for either quetiapine XR or IR, an unexpected finding as quetiapine IR has clearly demonstrated efficacy in this indication. This study should not be considered as a negative study (where study drug does not separate from placebo but the active comparator does, suggesting that the study medicine is not efficacious for the indication studied), but rather as a failed study, since the active control also did not separate from placebo. Reasons for a failed study may include problems with the study design and/or its execution. This article discusses the most likely explanations for the failure of Study 133. Post hoc analyses conducted to elucidate the reasons for this unexpected finding in light of the results of Study 132 are presented and possible reasons for the non-significant outcome are discussed.

MATERIALS AND METHODS

Study Design

This was a 6-week, double-blind, randomized, placebo- and active-controlled study conducted at 40 sites in the USA.

The study was performed in accordance with the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice. The protocol was approved by the Institutional Review Board for each site. All patients (or their legally authorized representatives) provided written, informed consent.

Patient Population

Men or women, aged 18–65 years, who were in- or out-patients with a documented DSM-IV diagnosis of catatonic (DSM-IV diagnostic code 295.20), disorganized (295.10), paranoid (295.30), or undifferentiated (295.90) schizophrenia were enrolled.

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

The exclusion criteria included: any DSM-IV Axis I condition other than schizophrenia; DSM-IV diagnosis of substance abuse or dependence not in full remission; hospitalization for schizophrenia for longer

than 1 month immediately prior to randomization; risk of suicide; administration of a depot antipsychotic within one dosing interval before randomization; any other clinically relevant diseases (such as renal or hepatic impairment, significant coronary artery disease, cancer); use of fluoxetine 14 days before randomization; use of an antipsychotic agent, mood stabilizer, antidepressant, anxiolytic, hypnotic, or other psychoactive medication 48 hours prior to randomization and throughout the study (except for permitted medications listed below).

In addition, the following exclusion criteria were used to exclude treatment-resistant patients: lack of response to adequate doses of two or more antipsychotics given for at least 4 weeks; lack of response to previous quetiapine treatment; previously required clozapine for symptom control; received treatment with clozapine within 1 month of randomization.

Treatment

Patients were randomized to one of five treatment groups: quetiapine XR 400 mg/day; quetiapine XR 600 mg/day; quetiapine XR 800 mg/day; quetiapine IR 800 mg/day; or placebo. Since the dosing schedules for quetiapine XR and IR differ, a dual-matched placebo technique was used to maintain blinding. Treatment was administered orally twice daily (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.

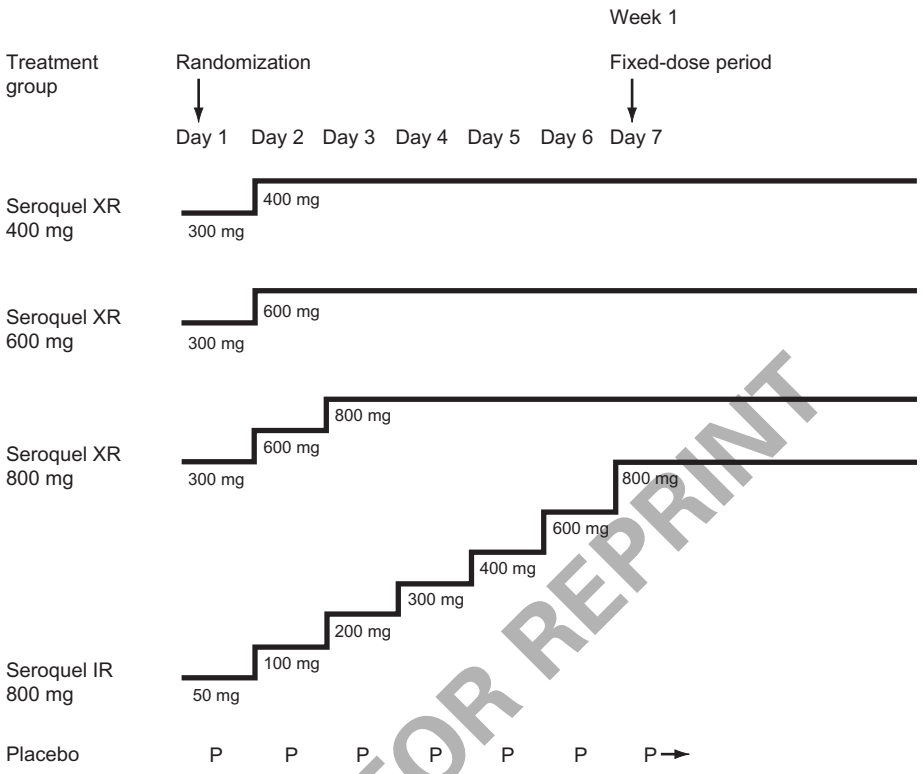
Quetiapine XR was initiated at 300 mg (Day 1); target doses were reached by Day 2 in the 400 mg/day and 600 mg/day groups and by Day 3 in the 800 mg/day group. Quetiapine IR was initiated at 50 mg (Day 1) and the target dose of 800 mg/day was reached by Day 7. For the remainder of the study (Days 7 to 42), patients continued to receive a fixed dose of quetiapine according to their treatment group (Figure 1).

Concomitant Medication

Anticholinergics were permitted only as treatment for emergent extrapyramidal symptoms (EPS), if required. Lorazepam (up to 6 mg/day) could be used to treat agitation during the first 6 days of the study only. Patients were permitted to continue taking hypnotics or sedatives for insomnia provided that they were taken at bedtime. Permitted sleep medications that could be initiated after enrollment were zolpidem, zaleplon, zopiclone, and chloral hydrate. No other psychoactive medication was permitted. Previous antipsychotics, mood stabilizers, hypnotics, antidepressants, anxiolytics, and anticholinergic medication were discontinued at least 48 hours before randomization.

FIGURE 1

STUDY DESIGN



Assessments

Post-randomization study visits were scheduled for Weeks 1, 2, 3, 4, and 6. An additional visit was scheduled on Day 5 for hospitalized patients; during this visit adverse events (AEs) and CGI assessments only were recorded.

Efficacy

PANSS total and subscale scores and CGI-S scores were assessed on all study visits. CGI (CGI-I) scores were assessed at all visits except randomization. PANSS and CGI ratings were performed only by personnel qualified to use the scales (training was provided) and, wherever possible, the same person conducted all assessments for a given patient to ensure consistency.

The primary endpoint was the change from baseline in PANSS total score at Week 6. The secondary efficacy endpoints included PANSS response rates (percentage of patients with a reduction from baseline in PANSS total score of ≥30% at Week 6) and CGI-I response rates

(percentage of patients with a CGI-I score ≤3 at Week 6). Other secondary efficacy endpoints were change from baseline in: PANSS total score at all other visits; PANSS positive, negative, and general psychopathology subscale scores at each visit; PANSS aggression/hostility and depression clusters at each visit; and CGI-S score at Week 6. The PANSS aggression and hostility cluster was comprised of Items P4 (excitement), P7 (hostility), G8 (uncooperativeness), and G14 (poor impulse control); the depression cluster was comprised of Items G1 (somatic concern), G2 (anxiety), G3 (guilt feelings), and G6 (depression).[16,17]

Safety and Tolerability

Safety and tolerability measures included: AE reporting; clinical chemistry, including prolactin; fasting lipid, glucose, insulin, and hemoglobin A_{1c} (HbA_{1c}) levels (patients were instructed not to eat or drink any fluids except water from midnight on the day before blood samples were taken); urinalysis; hematology; electrocardiogram (ECG); vital signs; body weight; and body mass index. The Barnes Akathisia Rating Scale (BARS) and Simpson-Angus Scale (SAS) scores were assessed at randomization and at all subsequent visits and the use of anticholinergic medication was recorded throughout the study to evaluate EPS. AEs potentially related to EPS were defined according to 37 relevant MedDRA preferred terms, including akathisia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesis, neck rigidity, and tremor. To better evaluate somnolence-related AEs, a number of MedDRA preferred terms were grouped (somnolence, sedation, lethargy, and sluggishness) and the results reported. To assess the tolerability of quetiapine XR during dose titration, AEs reported during the first week of treatment were evaluated.

Statistical Analysis

Data analyses were based on three patient populations: the modified intention-to-treat (MITT) population (all patients given the study medication to which they were randomized, with a baseline value and at least one post-baseline PANSS assessment); the per-protocol (PP) population (a subset of the MITT population who completed the study with no major protocol deviations or violations affecting efficacy); and the safety population (randomized patients given at least one dose of the study medication to which they were randomized). The PP population was only included to assess the robustness of the primary analysis; therefore, all efficacy results are based on data from the MITT population.

The sample size was calculated for the primary endpoint and the power calculations were based on data from previous studies.[18–20] It was

assumed that there would be a difference of 12 points for the primary efficacy endpoint between pair-wise comparisons of the three quetiapine XR groups and placebo, and a variability (i.e., standard deviation) of 22 points. For an overall power of 90% for all three tests, the power in each individual test was set to 96.5% and the significance level was set at 5%. Assuming that 90% of randomized patients would be included in the MITT analysis set (i.e., evaluable), the total number of randomized patients required was 535 to obtain 485 evaluable patients (97 per treatment group).

The primary efficacy endpoint was analyzed based on a comparison of each of the three quetiapine XR doses versus placebo. An analysis of covariance (ANCOVA) model stratified for treatment and center and with a baseline PANSS score as a covariate was used. Least squares means (LSMs) and confidence intervals (CIs) were generated for each treatment group. Between-treatment differences were estimated by calculating point differences between LSMs and associated two-sided 95% CIs. Multiplicity for the three comparisons of quetiapine XR versus placebo was assessed using the Hommel procedure[21] and adjusted p-values presented (unless otherwise stated).

For secondary efficacy analyses, data were presented as point estimates and 95% CIs for treatment effects and treatment differences were provided; CIs and p-values were nominal, i.e., no adjustments for multiplicity were made. Changes from baseline in PANSS subscale and cluster scores and in CGI-S scores were analyzed using ANCOVA models. Both PANSS and CGI-I response rates were analyzed using a Cochran–Mantel–Haenszel technique, stratified by treatment group; number and percentage of responders, 95% CIs, and p-values were calculated. P-values for the change from baseline in PANSS total score at each study timepoint for active treatment versus placebo were provided post hoc.

All statistical tests were two-sided, with a significance level of 5%. The last observation carried forward (LOCF) approach was used for missing data.

Post hoc Analyses

To examine whether the outcome of the study was affected by the severity of illness at baseline, a post hoc analysis was conducted for the primary efficacy endpoint for the following sub-populations of the MITT: markedly ill patients (defined as patients with a baseline CGI-S score ≥ 5) and moderately ill patients (patients with a baseline CGI-S score <5).

To explore the reason for the lack of assay sensitivity, an additional post hoc analysis was conducted for the change from baseline in PANSS total

scores in a subset of the MITT population excluding patients exhibiting an unusually high reduction in PANSS total scores during the first week of treatment: 'initial outliers'. This subset of patients excluding the initial outliers is referred to as the modified analysis population. Initial outliers were retrospectively defined as patients with a decrease of ≥20 in PANSS total score by Week 1. The rationale for this definition of initial outliers was based on an examination of the literature, which suggested that typically a decrease of up to 20 points in PANSS total score would be expected at Week 1 in a schizophrenia clinical trial. Decreases substantially greater than that number may reflect potential issues with symptom assessment, such as rater inaccuracy,[22] or indirect effects due to participation in a clinical trial, such as higher response due to high patient expectation of improvement.[23] Another possible cause for such robust initial improvement could be the inclusion of patients with reversible situational stressors that might resolve acutely and lead to rapid improvement independent of medication.

A similar ANCOVA model to that used for the primary statistical analysis was used for the above post hoc analyses.

To investigate the high discontinuation rate in the study, discontinuations for any reason by time and the number of patients discontinuing due to an AE or lack of efficacy at each timepoint were analyzed post hoc.

RESULTS

Patients

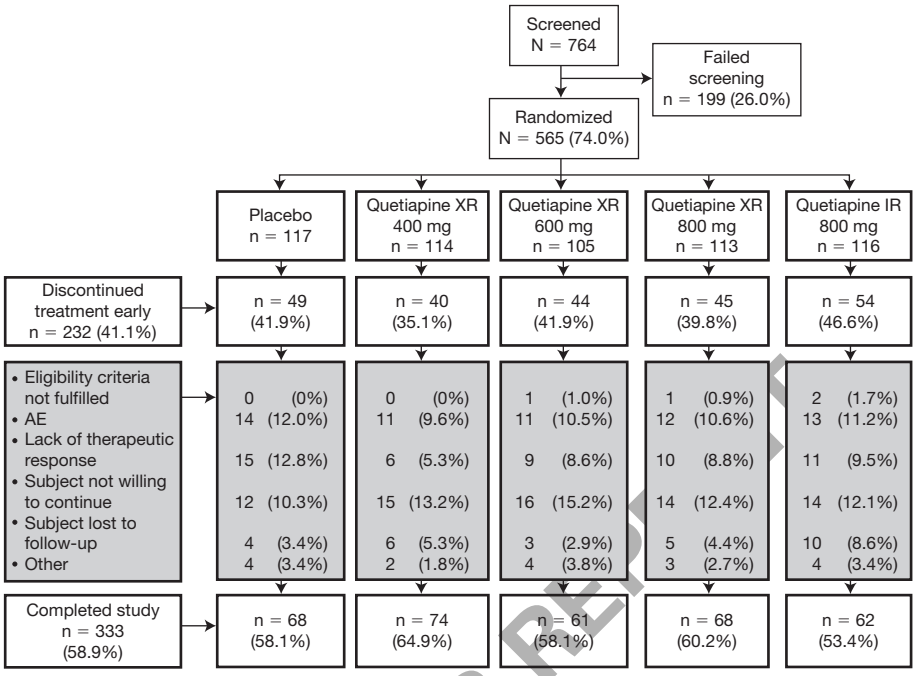
In total, 565 patients were randomized to treatment and 333 patients completed the study (Figure 2). Completion rates were: 58.1% for placebo; 64.9%, 58.1% and 60.2% for quetiapine XR 400 mg/day, 600 mg/day, and 800 mg/day, respectively; and 53.4% for quetiapine IR.

There were 544 patients in the MITT population: placebo, n = 111; quetiapine XR 400 mg/day, n = 113; quetiapine XR 600 mg/day, n = 101; quetiapine XR 800 mg/day, n = 110; and quetiapine IR, n = 109. There were 494 patients in the PP population (n = 104, 98, 94, 101, and 97, respectively). One patient randomized to quetiapine IR did not receive any treatment and thus was excluded from the safety population (n = 564).

In general, the treatment groups were well balanced with respect to demographic and clinical characteristics at baseline, including history of schizophrenia and previous use of antipsychotics (Table 1). There were slightly more men in the quetiapine XR 600 and 800 mg/day groups

FIGURE 2

PATIENT DISPOSITION



(81.2% and 74.5%, respectively) than in the other groups (63.3% to 69.9%), but this difference was not considered to have affected study outcome. The majority of patients had a DSM-IV subtype diagnosis of paranoid schizophrenia (82.6%) at enrollment.

There were only small differences between treatment groups in the proportion of patients who were using lorazepam during the study. At randomization, 19.3–27.4% of patients were using lorazepam; this proportion reduced to 13.0–16.2% by Day 6.

The proportion of patients using sleep medication was similar across treatment groups during the first seven days (34.9–44.5%). This proportion reduced over time and during the final week of the study the proportion ranged between 15.9% (quetiapine IR) and 27.0% (quetiapine XR 600 mg/day).

There was a similar proportion of hospitalized patients at randomization in all treatment groups (73.5–81.0%; Table 2). The percentage of in-patients had reduced considerably at Week 2 and continued to decrease over the 6-week study. Furthermore, at Week 6, the percentage of in-patients was lower in the quetiapine IR group (3.4%) than in the other groups (12.7%, placebo; 10.6%, 12.5%, and 11.3%, quetiapine XR 400, 600, and 800 mg/day, respectively).

TABLE 1

PATIENTS' DEMOGRAPHIC AND CLINICAL CHARACTERISTICS AT BASELINE (MITT)

	PLACEBO (n = 111)	QUETIAPINE XR 400 mg (n = 113)	QUETIAPINE XR 600 mg (n = 101)	QUETIAPINE XR 800 mg (n = 110)	QUETIAPINE IR 800 mg (n = 109)
Gender, % male	69.4	69.9	81.2	74.5	63.3
Age, years, mean (SD)	42.5 (10.8)	42.1 (10.1)	41.2 (10.8)	40.2 (9.1)	40.8 (10.4)
Ethnicity %					
White	32.4	34.5	33.7	35.5	26.6
Black	53.2	58.4	62.4	56.4	62.4
Other	14.4	7.1	4.0	8.2	11.0
Body weight, kg, mean (SD)	87.8 (22.6)	93.0 (23.2)	91.0 (22.7)	93.1 (24.0)	90.2 (21.5)
History of schizophrenia,					
Age at first diagnosis, years (SD)	24.7 (8.4)	23.6 (9.7)	23.8 (8.8)	24.4 (9.0)	24.7 (8.6)
Time since first diagnosis, years (SD)	18.3 (10.8)	18.8 (11.2)	18.0 (11.6)	16.3 (10.3)	16.9 (11.2)
Number of episodes (SD)	11.8 (13.4)	11.3 (14.5)	10.8 (12.1)	12.4 (16.6)	11.7 (15.5)
Antipsychotic medication at enrollment, %					
Conventional	6.3	9.7	5.0	6.4	8.3
Atypical	55.0	47.8	52.5	45.5	41.3
Olanzapine	17.1	11.5	19.8	13.6	22.0
Risperidone	17.1	17.7	20.8	18.2	12.8
Anticholinergic medication use at enrollment, %	7.7	18.4	11.4	12.4	11.3
Mean (SD) scores					
PANSS total	90.8 (11.9)	91.1 (13.4)	93.1 (14.0)	92.6 (13.2)	93.0 (13.5)
CGI-S	4.5 (0.6)	4.4 (0.5)	4.5 (0.6)	4.5 (0.6)	4.5 (0.6)

TABLE 2

PROPORTION[a] OF HOSPITALIZED PATIENTS AT RANDOMIZATION AND THROUGHOUT THE STUDY (SAFETY POPULATION)

	PLACEBO (n = 117)	QUETIAPINE XR 400 mg (n = 114)	QUETIAPINE XR 600 mg (n = 105)	QUETIAPINE XR 800 mg (n = 113)	QUETIAPINE XR POOLED (n = 332)	QUETIAPINE IR 800 mg (n = 115)
Baseline	73.5% (86/117)	78.1% (89/114)	81.0% (85/105)	77.0% (87/113)	78.6% (261/332)	76.5% (88/115)
Day 5	68.1% (77/113)	73.2% (82/112)	73.8% (76/103)	71.4% (80/112)	72.8% (238/327)	71.8% (79/110)
Week 1	67.0% (69/103)	74.5% (79/106)	74.2% (72/97)	68.6% (70/102)	72.5% (221/305)	67.3% (70/104)
Week 2	37.6% (35/93)	36.5% (35/96)	45.6% (36/79)	42.7% (38/89)	41.3% (109/264)	36.4% (32/88)
Week 3	18.3% (15/82)	20.2% (18/89)	17.3% (13/75)	16.7% (14/84)	18.1% (45/248)	13.3% (10/75)
Week 4	14.7% (11/75)	15.3% (13/85)	16.4% (11/67)	13.7% (10/73)	15.1% (34/225)	7.4% (5/68)
Week 6	12.7% (8/63)	10.6% (7/66)	12.5% (7/56)	11.3% (7/62)	11.4% (21/184)	3.4% (2/59)

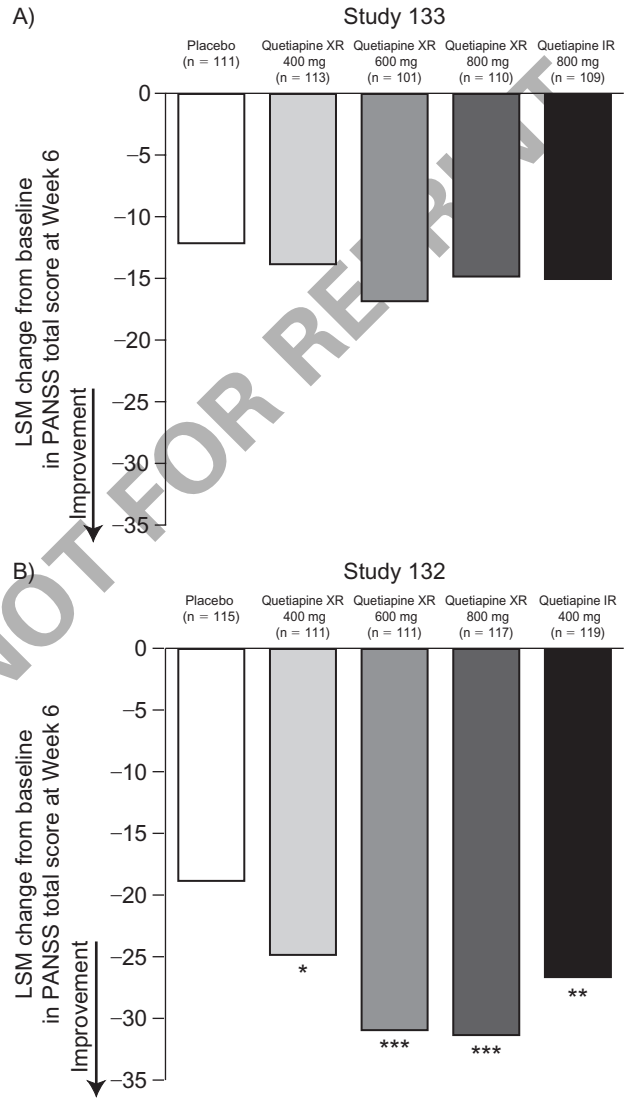
[a]Percentages were calculated from the number of hospitalized patients divided by the number of patients in the study at the start of the interval for each treatment group multiplied by 100.

Efficacy

The improvement from baseline to Week 6 for the primary efficacy endpoint was numerically larger in all quetiapine XR dose groups and the quetiapine IR group than with placebo (Figure 3A). However, these differences compared with placebo were not statistically significant. The greatest separation from placebo occurred in the quetiapine XR

FIGURE 3

CHANGE IN PANSS TOTAL SCORE FROM BASELINE AT WEEK 6, IN A) STUDY 133 AND B) STUDY 132 (LOCF; MITT POPULATION FOR EACH STUDY)



*p < 0.05; **p < 0.01; ***p < 0.001 versus placebo

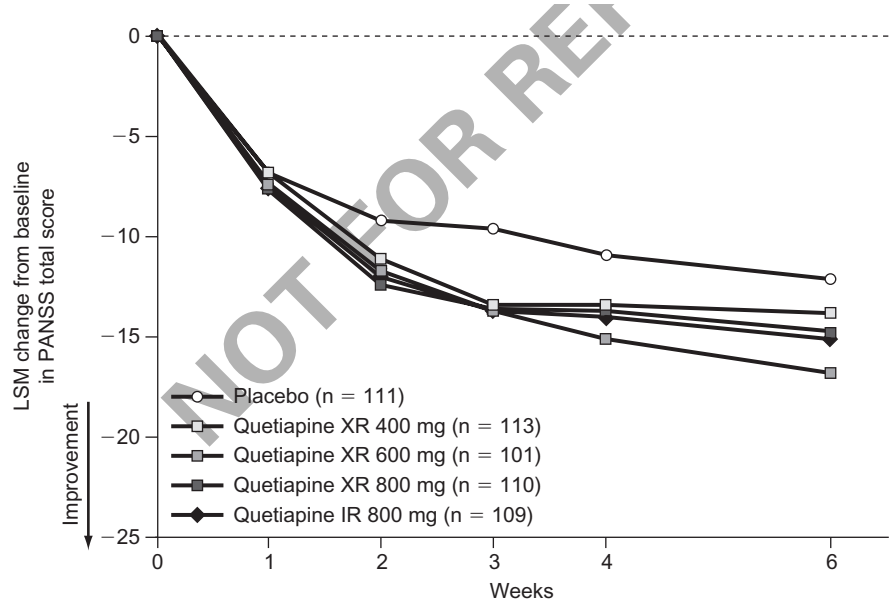
Figure 3B.[15] Adapted with kind permission. Copyright 2007, Physicians Postgraduate Press.

600 mg/day group: the estimated treatment difference was −4.7; 95% CI −9.1, −0.4 ($p = 0.099$ adjusted for multiplicity; the unadjusted p-value was <0.05). These results were confirmed using the PP population analysis.

Figure 4 shows the change from baseline in PANSS total score at each assessment. Large clinical improvements were seen in all groups at Week 1. At Week 3, there were numerically greater improvements with quetiapine XR and quetiapine IR groups versus placebo. From this timepoint, all groups, with the exception of the quetiapine XR 400 mg/day group, continued to improve. The change from baseline in PANSS total score when analyzed post hoc was found to be statistically significant in all quetiapine groups versus placebo at Week 3 ($p < 0.05$ for all groups). There was no statistical separation from placebo for any of the quetiapine groups at Weeks 1, 2, and 4.

FIGURE 4

CHANGE IN PANSS TOTAL SCORE FROM BASELINE AT EACH ASSESSMENT (LOCF; MITT POPULATION)



p-value active treatment versus placebo (Week 1−4 data analyzed post hoc)

	Week 1[a]	Week 2[a]	Week 3[a]	Week 4[a]	Week 6[b]
Quetiapine XR 400 mg	ns	ns	<0.05	ns	ns
Quetiapine XR 600 mg	ns	ns	<0.05	ns	ns
Quetiapine XR 800 mg	ns	ns	<0.05	ns	ns
Quetiapine IR 800 mg	ns	ns	<0.05	ns	na[c]

[a]Unadjusted p-value
[b]p-value adjusted with Hommel procedure for multiplicity
[c]Adjusted p-value not assessed; unadjusted p-value = ns
na = not assessed; ns = no significant difference

Improvements from baseline occurred in all other secondary efficacy variables at Week 6 for the MITT population (Table 3). However, none of the quetiapine XR groups showed a statistically significant difference compared with placebo for any of the secondary efficacy variables at Week 6. This was also the case for patients in the quetiapine IR group.

Comparison with Study 132

The baseline mean PANSS total scores were lower in this study (90.8–93.1) than in Study 132 (95.8–97.3).[15] The primary efficacy endpoint results (change from baseline in PANSS total score at Week 6) for the MITT population for this study greatly differ from those of Study 132,[15] which found that all doses of quetiapine XR and quetiapine IR 400 mg/day were statistically superior to placebo (Figure 3B).

Post hoc Analyses

The inclusion criteria for this study specified that patients had to be at least moderately ill (rating of ≥4 on the CGI-S). Over half (54.8%) of the patients in this study population were moderately ill (CGI-S <5) at baseline; less than half were markedly or severely ill (CGI-S ≥5). In contrast, only 25.0% of patients in Study 132 were moderately ill at baseline. The post hoc analysis to examine the effect of baseline severity of illness on the primary efficacy variable (i.e., change from baseline at Week 6 in PANSS total scores for the subset of markedly ill patients [CGI-S ≥5]) demonstrated a statistically significant effect in the quetiapine XR 600 mg/day and 800 mg/day groups compared with placebo ($p < 0.05$) [Figure 5A]. A numerical separation from placebo was seen for the quetiapine XR 400 mg/day group and for quetiapine IR (Figure 5A). The reduction in PANSS total score in the placebo group in this subset of markedly ill patients was lower and had reached a plateau from Week 1, with a mean change at Week 6 of −6.9.

In the subset of the MITT population that were moderately ill at baseline, the change from baseline in PANSS total scores at Week 6 were similar in the four active treatment groups and the placebo group (Figure 5B); placebo response was robust and sustained.

The post hoc analysis of change from baseline in PANSS total scores for the modified analysis population (this population excludes initial outliers i.e., patients with a decrease of ≥20 in PANSS total score by the end of Week 1) showed a statistically significant difference for all three quetiapine XR groups versus placebo for the primary efficacy endpoint (Figure 6). The improvement from baseline was statistically significant compared with placebo from Week 1 onwards for

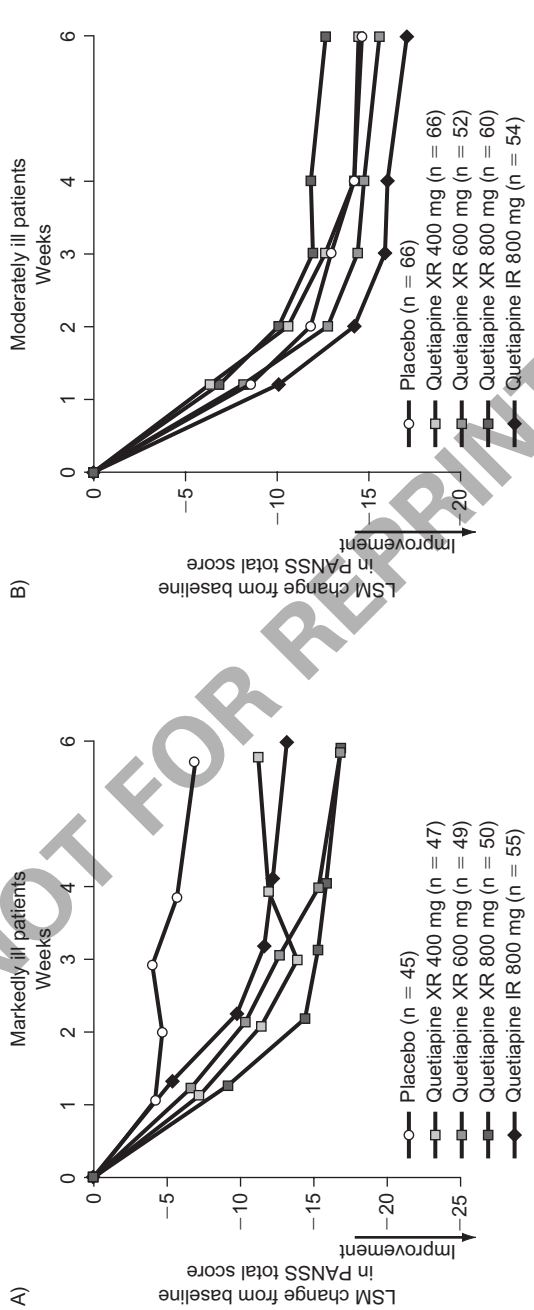
TABLE 3

RESULTS OF SECONDARY EFFICACY VARIABLES AT WEEK 6 (LOCF, MITT)

	PLACEBO (n = 111)	QUETIAPINE XR 400 mg (n = 113)	QUETIAPINE XR 600 mg (n = 101)	QUETIAPINE XR 800 mg (n = 110)	QUETIAPINE IR 800 mg (n = 109)
PANSS response rate, %	20.7	19.6	26.7	23.6	22.9
PANSS subscale scores:					
LSM (SE) change from baseline					
Positive	−4.0 (0.6)	−4.3 (0.6)	−5.0 (0.6)	−4.4 (0.6)	−4.5 (0.6)
Negative	−2.9 (0.5)	−2.8 (0.5)	−3.3 (0.5)	−3.4 (0.5)	−3.1 (0.5)
General psychopathology	−5.1 (1.0)	−6.7 (1.0)	−8.3 (1.0)	−6.9 (1.0)	−7.3 (1.0)
PANSS cluster scores:					
LSM (SE) change from baseline					
Aggression/hostility	−0.7 (0.4)	−0.9 (0.4)	−1.6 (0.4)	−1.0 (0.4)	−1.1 (0.4)
Depression	−1.7 (0.3)	−2.1 (0.3)	−2.7 (0.3)	−2.3 (0.3)	−2.5 (0.3)
LSM (SE) change from baseline in CGI-S score	−0.5 (0.1)	−0.6 (0.1)	−0.6 (0.1)	−0.6 (0.1)	−0.6 (0.1)
CGI-I response rate, %	56.8	65.5	67.3	62.7	61.5

FIGURE 5

CHANGE FROM BASELINE OVER TIME IN PANSS TOTAL SCORE IN A) MARKEDLY ILL PATIENTS AND B) MODERATELY ILL PATIENTS (LOCF; MITT)

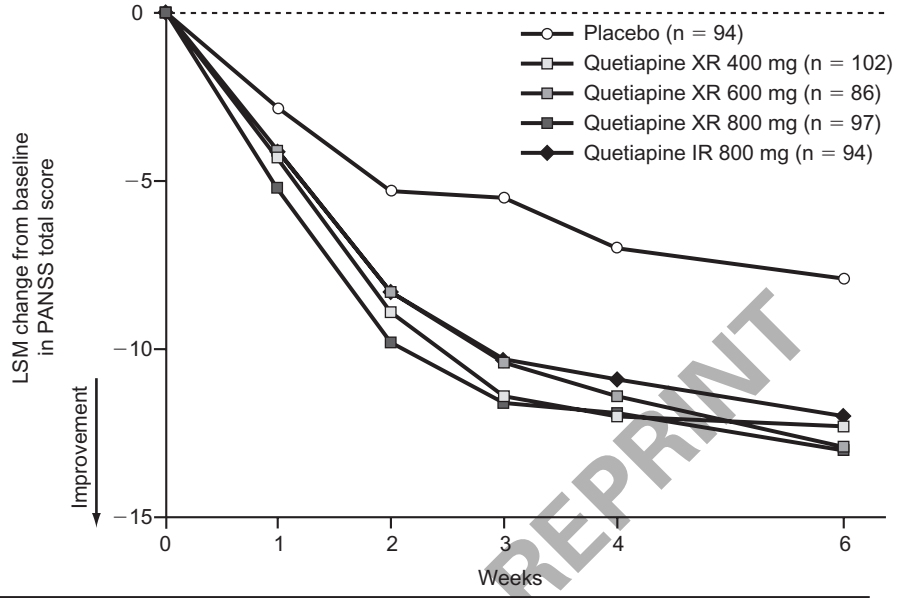


p-value active treatment versus placebo					
	Week 1	Week 2	Week 3	Week 4	Week 6
Quetiapine XR 400 mg	ns	<0.05	<0.01	ns	ns
Quetiapine XR 600 mg	ns	ns	<0.05	<0.01	<0.05
Quetiapine XR 800 mg	<0.05	<0.01	<0.01	<0.01	<0.05
Quetiapine IR 800 mg	ns	ns	<0.05	ns	ns

ns = no significant difference

FIGURE 6

CHANGE IN PANSS TOTAL SCORE FROM BASELINE OVER TIME AFTER EXCLUSION OF INITIAL OUTLIERS (PATIENTS WITH A DECREASE OF ≥20 IN PANSS SCORE BY WEEK 1) (LOCF; MITT)



p-value active treatment versus placebo					
	Week 1	Week 2	Week 3	Week 4	Week 6
Quetiapine XR 400 mg	ns	0.036	0.001	0.015	0.043
Quetiapine XR 600 mg	ns	ns	0.013	0.043	0.026
Quetiapine XR 800 mg	0.043	0.009	0.001	0.02	0.020
Quetiapine IR 800 mg	ns	ns	0.011	ns	ns

ns = no significant difference

At Week 1 n = 93 for quetiapine IR 800 mg
At Weeks 1 and 2 n = 101 for quetiapine XR 400 mg

quetiapine XR 800 mg/day, from Week 2 onwards for quetiapine XR 400 mg/day, and from Week 3 onwards for quetiapine XR 600 mg/day.

The post hoc analysis of discontinuations for any reason by time showed that in all groups, there was a higher rate of discontinuations at Week 1 than at any other time point (Table 4). Furthermore, the rate of discontinuations at Week 2 was slightly higher in patients receiving quetiapine IR 800 mg/day compared with that seen in the other groups. In addition, more discontinuations due to lack of efficacy occurred at Week 1 than at any other timepoint. However, no specific patterns were identified regarding the time at which discontinuations due to an AE occurred (data not shown).

TABLE 4

PROPORTION (%) OF PATIENTS WHO DISCONTINUED THE STUDY FOR ANY REASON BY TIMEPOINT (SAFETY POPULATION)

	PLACEBO (n = 117)	QUETIAPINE XR 400 mg (n = 114)	QUETIAPINE XR 600 mg (n = 105)	QUETIAPINE XR 800 mg (n = 113)	QUETIAPINE IR 800 mg (n = 115)
Baseline	3.4	1.8	1.9	0.9	4.3
Day 5	5.1	2.6	5.7	7.1	3.5
Week 1	12.0	11.4	16.2	13.3	14.8
Week 2	7.7	4.4	4.8	3.5	10.4
Week 3	6.0	5.3	7.6	9.7	7.8
Week 4	6.0	9.6	4.8	5.3	4.3
Week 6	0.9	0	1.0	0	0.9

Safety and Tolerability

Adverse Events

The incidences of AEs and treatment-related AEs in the quetiapine XR groups were slightly higher than in the placebo group and were similar to those seen with quetiapine IR (Table 5). The incidences across the quetiapine XR groups were similar, with no evidence of a dose effect. No deaths and few serious AEs (SAEs) occurred during the study. Four (0.7%) SAEs were judged by the investigator to be treatment related: grand mal convulsion in the placebo group; loss of consciousness in the quetiapine XR 400 mg/day group; psychotic disorder in the quetiapine XR 600 mg/day group; and syncope in the quetiapine IR group.

The proportions of patients withdrawing due to an AE in the quetiapine XR and quetiapine IR groups were low and similar to placebo (Table 5). The majority of AEs leading to discontinuation were psychotic disorders, schizophrenia, and agitation.

The most common AEs in the quetiapine groups were dry mouth, sedation, and somnolence (Table 5). Headache, insomnia, and sedation were the most common AEs in the placebo group. In the quetiapine groups the most common AEs that were considered by the investigator to be related to treatment were sedation (12.4–20.9%), dry mouth (13.9–19.3%), and somnolence (10.5–15.8%). Most of these AEs were mild or moderate in intensity, with <1% of each of these AEs reported as severe. In the placebo group, the most common treatment-related AEs were sedation (6.8%), constipation (6.8%), nausea (6.8%), and dizziness (6.0%). All of these AEs were mild or moderate in intensity. The proportions of patients who experienced an AE associated with somnolence were higher in the quetiapine XR 400, 600, and

TABLE 5

OVERALL SAFETY PROFILE (NUMBER AND PERCENTAGE OF PATIENTS REPORTING AES) (SAFETY POPULATION)

n (%)	PLACEBO (n = 117)	QUETIAPINE XR 400 mg (n = 114)	QUETIAPINE XR 600 mg (n = 105)	QUETIAPINE XR 800 mg (n = 113)	QUETIAPINE IR 800 mg (n = 115)
Any AE	82 (70.1)	90 (78.9)	83 (79.0)	83 (73.5)	86 (74.8)
Serious AEs	9 (7.7)	10 (8.8)	10 (9.5)	10 (8.8)	7 (6.1)
AEs leading to discontinuation	13 (11.1)	11 (9.6)	11 (10.5)	12 (10.6)	13 (11.3)
Overall drug-related AEs[a]	43 (36.8)	64 (56.1)	51 (48.6)	52 (46.0)	62 (53.9)
Most common AEs[b]					
Dry mouth	3 (2.6)	24 (21.1)	18 (17.1)	20 (17.7)	19 (16.5)
Sedation	11 (9.4)	24 (21.1)	18 (17.1)	15 (13.3)	25 (21.7)
Somnolence	3 (2.6)	19 (16.7)	11 (10.5)	15 (13.3)	17 (14.8)
Dizziness	8 (6.8)	14 (12.3)	10 (9.5)	8 (7.1)	11 (9.6)
Headache	18 (15.4)	12 (10.5)	7 (6.7)	12 (10.6)	10 (8.7)
Constipation	9 (7.7)	9 (7.9)	5 (4.8)	9 (8.0)	9 (7.8)
Dyspepsia	2 (1.7)	9 (7.9)	6 (5.7)	7 (6.2)	10 (8.7)
Insomnia	12 (10.3)	9 (7.9)	4 (3.8)	2 (1.8)	1 (0.9)
Arthralgia	2 (1.7)	7 (6.1)	0	2 (1.8)	2 (1.7)
Psychotic disorder	5 (4.3)	7 (6.1)	4 (3.8)	2 (1.8)	2 (1.7)
Agitation	7 (6.0)	6 (5.3)	6 (5.7)	3 (2.7)	4 (3.5)
Fatigue	0	4 (3.5)	5 (4.8)	3 (2.7)	6 (5.2)
Nausea	10 (8.5)	4 (3.5)	7 (6.7)	7 (6.2)	5 (4.3)
Schizophrenia	2 (1.7)	4 (3.5)	6 (5.7)	6 (5.3)	5 (4.3)
Diarrhea	2 (1.7)	2 (1.8)	2 (1.9)	6 (5.3)	7 (6.1)
Stomach discomfort	3 (2.6)	2 (1.8)	1 (1.0)	3 (2.7)	6 (5.2)
Vomiting	6 (5.1)	2 (1.8)	4 (3.8)	8 (7.1)	3 (2.6)

[a]As judged by the investigator.
[b]Occurring at an incidence of ≥5% in any treatment group.

800 mg/day groups (37.7%, 27.6%, and 28.3%, respectively) and in the quetiapine IR group (34.8%) than in the placebo group (12.0%).

During dose titration, the overall AE profile in the quetiapine XR group was similar to that observed in the quetiapine IR group. The most common AEs occurring in Week 1 in the quetiapine XR and IR groups were sedation, dry mouth, and somnolence. The number of discontinuations due to AEs during Week 1 were low and similar across treatment groups: 4 (3.4%) patients in the placebo group discontinued due to an AE in Week 1, compared with 4 (3.5%), 4 (3.8%), and 6 (5.3%) in the

quetiapine XR 400, 600, and 800 mg/day groups, respectively, and 3 (2.6%) in the quetiapine IR group. AEs leading to discontinuation and judged to be drug-related by the investigator occurred in 1 (0.9%) patient in the placebo group compared with 1 (0.9%), 2 (1.9%), and 2 (1.8%) in the quetiapine XR 400, 600, and 800 mg/day groups, respectively, and 3 (2.6%) in the quetiapine IR group.

Extrapyramidal Symptoms

The incidence of AEs associated with EPS was slightly higher in the quetiapine XR 800 mg/day and quetiapine IR 800 mg/day groups (9.7% and 7.8%, respectively) than in the other treatment groups (4.3%, placebo; 6.1%, quetiapine XR 400 mg/day; and 5.7%, quetiapine XR 600 mg/day). All AEs associated with EPS were mild or moderate in intensity. Two patients in the quetiapine XR 800 mg/day group withdrew because of an AE associated with EPS of moderate intensity; one patient had a history of EPS requiring anticholinergic treatment prior to entering the study and the other had a concurrent AE of sedation and the primary AE leading to withdrawal was not specified.

Mean SAS total scores at baseline ranged from 1.17 in the quetiapine IR group to 1.81 in the quetiapine XR 800 mg/day group. Decreases in mean scores were seen across treatment groups and at Week 6 mean (SD) scores were similar in all groups: 0.96 (2.26), placebo; 1.03 (2.19), quetiapine XR 400 mg/day; 0.99 (1.97), quetiapine XR 600 mg/day; 1.11 (1.92), quetiapine XR 800 mg/day; and 0.83 (2.44), quetiapine IR. For the majority of patients, the SAS total score at the end of treatment had either improved or not changed from baseline: 87.4%, 88.1%, 86.3%, 79.1%, and 90.7% of patients in the placebo, quetiapine XR 400, 600, and 800 mg/day, and quetiapine IR groups, respectively.

Mean BARS scores at baseline ranged from 0.30 in the quetiapine XR 400 mg/day group to 0.42 in the quetiapine XR 800 mg/day group. Decreases in mean scores were seen across groups and at Week 6 mean (SD) scores were similar in all groups: 0.21 (0.51), placebo; 0.19 (0.55), quetiapine XR 400 mg/day; 0.17 (0.42), quetiapine XR 600 mg/day; 0.30 (0.64), quetiapine XR 800 mg/day; and 0.25 (0.69), quetiapine IR. The proportions of patients who had improved, worsened or not changed from baseline in BARS total score at treatment end were similar in the five treatment groups. The BARS total score at the end of treatment had either improved or not changed from baseline for 91.9%, 92.7%, 93.1%, 92.7%, and 92.6% of patients in the placebo, quetiapine XR 400, 600, and 800 mg/day, and quetiapine IR groups, respectively.

The use of anticholinergic medication throughout the study was low. The numbers of patients receiving any anticholinergic medication for the treatment of EPS symptoms were: 5 (4.3%), placebo group; 11 (9.6%), quetiapine XR 400 mg/day; 7 (6.7%), quetiapine XR 600 mg/day; 7 (6.2%), quetiapine XR 800 mg/day; and 8 (7.0%), quetiapine IR.

Laboratory Data, Vital Signs, and Body Weight

Changes in clinical laboratory parameters and the number of patients with a potentially clinically relevant shift in fasting glucose and lipid levels are given in Table 6. Mean prolactin levels decreased in all groups (Table 6). The changes in clinical laboratory parameters in the quetiapine XR groups were generally similar to those seen in the IR group and there was no evidence of a dose effect.

An increase in mean supine pulse rate from baseline at treatment end was observed with quetiapine XR (0.35 bpm for quetiapine XR 400 mg; 2.18 bpm for quetiapine XR 600 mg/day; 5.78 bpm for quetiapine XR 800 mg/day) and quetiapine IR (3.50 bpm) but not with placebo (−1.17 bpm). ECG data also showed small increases in mean heart rate with quetiapine XR and quetiapine IR but not with placebo. Small increases in mean QTcF were seen at treatment end with quetiapine XR (0.46 ms for quetiapine XR 400 mg; 0.65 ms for quetiapine XR 600 mg/day; 1.62 ms for quetiapine XR 800 mg/day) and quetiapine IR (2.30 ms) but not with placebo (−1.79 ms). These changes in heart rate and QTcF were not considered to be clinically meaningful.

Mean changes in body weight from baseline to treatment end were −0.14, 0.89, 1.50, 0.32, and 0.94 kg in the placebo, quetiapine XR 400, 600, and 800 mg/day, and quetiapine IR groups, respectively (Table 6). The percentages of patients with body weight increases of ≥7% were 5.6%, 6.5%, 14.1%, 6.5%, and 12.1% in the placebo, quetiapine XR 400, 600, and 800 mg/day, and quetiapine IR groups, respectively (Table 6).

DISCUSSION

The primary objective of this 6-week study was to demonstrate the superior efficacy of quetiapine XR compared with placebo in patients with schizophrenia. Unexpectedly, both quetiapine XR and quetiapine IR were not statistically superior to placebo as assessed by the primary efficacy endpoint, change from randomization in PANSS total score at Week 6, although there were numerical improvements in both the XR and IR treatment groups. The improvement in this endpoint for quetiapine IR (800 mg/day) was −15.0 and is of a similar magnitude to that reported previously in a double-blind study of the same duration in patients with

TABLE 6

Changes in Clinical Laboratory Parameters and Body Weight from Randomization to End of Treatment and The Number of Patients with Potentially Clinically Relevant Shifts in Levels (Safety Population)

	Placebo (n = 117)	Quetiapine XR 400 mg (n = 114)	Quetiapine XR 600 mg (n = 105)	Quetiapine XR 800 mg (n = 113)	Quetiapine IR 800 mg (n = 115)
Glucose, mg/dL[a]	n = 78	n = 86	n = 75	n = 81	n= 76
Baseline, mean (SD)	90.21 (11.21)	89.26 (13.56)	91.75 (17.20)	95.06 (23.91)	91.47 (18.61)
Change, mean (SD)	0.82 (15.69)	5.60 (15.47)	6.57 (23.78)	4.91 (16.15)	9.82 (33.65)
Patients with potentially clinically relevant shift to elevated values (≥126 mg/dL), n (%)	2 (2.6)	8 (9.4)	4 (5.6)	4 (5.5)	3 (4.2)
HbA_{1C}, %[a]	n = 73	n = 74	n = 64	n = 75	n = 72
Baseline, mean (SD)	5.68 (0.62)	5.53 (0.57)	5.73 (0.69)	5.67 (0.63)	5.63 (0.70)
Change, mean (SD)	0 (0.30)	0.06 (0.32)	0.09 (0.34)	0.10 (0.30)	0.08 (0.45)
Insulin, μIU/mL[a]	n = 75	n = 83	n = 73	n = 77	n = 74
Baseline, mean (SD)	18.03 (16.58)	14.04 (11.60)	24.56 (36.52)	19.34 (18.41)	13.20 (8.83)
Change, mean (SD)	0.19 (14.31)	9.33 (26.24)	3.64 (38.69)	8.97 (44.13)	4.15 (15.45)
Total cholesterol, mg/dL[a]	n = 72	n = 77	n = 66	n = 74	n = 71
Baseline, mean (SD)	194.72 (41.15)	188.05 (40.96)	195.17 (51.33)	188.76 (34.16)	204.68 (61.62)
Change, mean (SD)	−8.03 (28.27)	−0.74 (24.94)	−2.45 (32.03)	5.31 (34.62)	3.96 (33.09)

Patients with potentially clinically relevant shift to elevated values (≥240 mg/dL), n (%)	6 (18.8)	5 (10.9)	7 (19.4)	11 (22.4)	8 (22.2)
LDL, mg/dL[a]	n = 71	n = 73	n = 63	n = 69	n = 67
Baseline, mean (SD)	113.96 (36.16)	108.67 (35.27)	111.44 (39.17)	110.51 (30.22)	122.28 (58.01)
Change, mean (SD)	−4.55 (24.59)	−1.48 (23.49)	−3.08 (28.90)	2.48 (30.21)	−0.46 (28.95)
Patients with potentially clinically relevant shift to elevated values (≥160 mg/dL), n (%)	2 (4.2)	6 (11.1)	8 (17.0)	10 (18.5)	6 (13.0)
HDL, mg/dL[a]	n = 72	n = 77	n = 66	n = 74	n = 71
Baseline, mean (SD)	52.68 (16.92)	51.45 (14.04)	49.42 (14.76)	49.47 (11.05)	53.77 (14.14)
Change, mean (SD)	−0.19 (7.56)	−2.09 (8.23)	?1.45 (8.98)	0.51 (8.34)	0.73 (9.73)
Patients with potentially clinically relevant shift to lowered values (≤40 mg/dL), n (%)	3 (5.3)	8 (13.3)	7 (14.6)	3 (4.8)	1 (1.8)
Triglycerides, mg/dL[a]	n = 72	n = 77	n = 66	n = 74	n = 71
Baseline, mean (SD)	140.82 (82.74)	140.56 (87.38)	152.17 (84.34)	153.43 (85.75)	148.08 (115.23)
Change, mean (SD)	−17.58 (68.29)	18.99 (78.65)	20.59 (79.74)	10.07 (83.78)	14.58 (95.14)

(*continued*)

TABLE 6 (*CONTINUED*)

	PLACEBO (n = 117)	QUETIAPINE XR 400 mg (n = 114)	QUETIAPINE XR 600 mg (n = 105)	QUETIAPINE XR 800 mg (n = 113)	QUETIAPINE IR 800 mg (n = 115)
Patients with potentially clinically relevant shift to elevated values (≥200 mg/dL), n (%)	2 (3.2)	7 (10.3)	7 (11.9)	5 (7.6)	5 (7.6)
Prolactin, μg/L	n = 92	n = 94	n = 88	n = 97	n = 90
Baseline, mean (SD)	15.81 (16.83)	23.31 (30.66)	17.71 (22.14)	16.55 (22.89)	17.28 (26.76)
Change, mean (SD)	−6.55 (16.14)	−8.42 (26.81)	−7.89 (19.56)	−5.15 (17.05)	−6.00 (23.21)
Body weight, kg	n = 108	n = 109	n = 101	n = 109	n = 107
Baseline, mean (SD)	87.51 (22.40)	92.06 (22.09)	90.99 (22.68)	93.12 (23.97)	90.33 (21.57)
Change, mean (SD)	−0.14 (3.54)	0.89 (3.13)	1.50 (3.91)	0.32 (5.92)	0.94 (6.69)
Patients with a ≥7% increase in body weight at treatment end, n (%)[b]	6 (5.6)	7 (6.5)	14 (14.1)	7 (6.5)	13 (12.1)

Système International (SI) conversion factors (multiply by) for the above laboratory parameters: glucose mg/dL to mmol/L 0.0555; cholesterol, HDL and LDL cholesterol mg/dL to mmol/L 0.0259; triglycerides mg/dL to mmol/L 0.0113; prolactin μg/L to pmol/L 43.478.

[a]Fasting documented by patient report of ≥8 hours since last meal before blood sample taken for baseline and post-baseline laboratory measurements.

[b]Numbers of patients were 107, 108, 99, 108, and 107 in the placebo, quetiapine XR 400, 600, 800 mg/day, and quetiapine IR 800 mg/day groups, respectively.

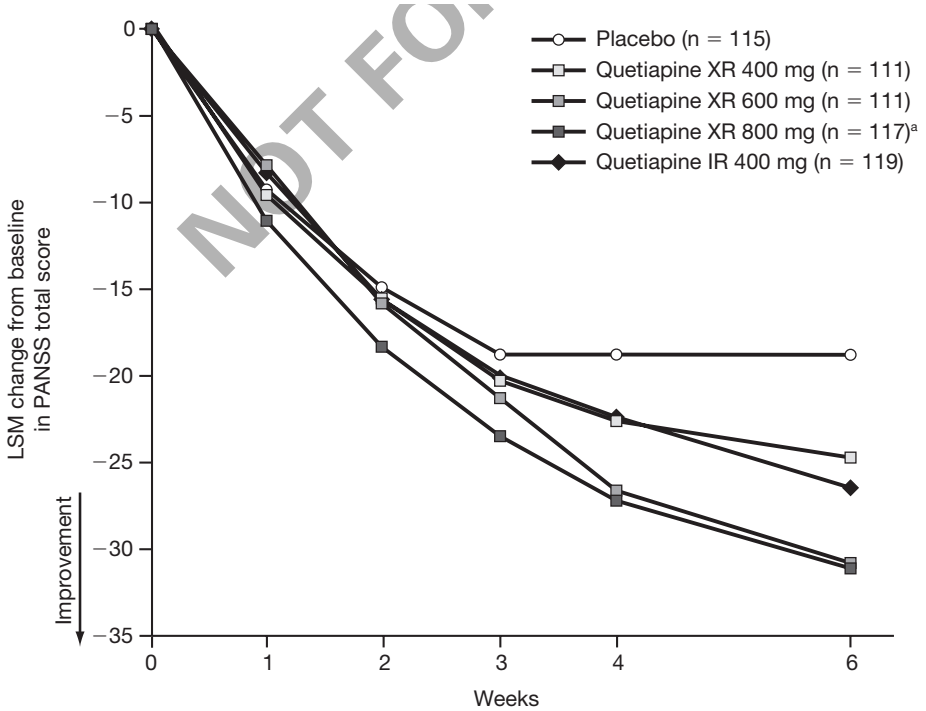
LDL, low-density lipoprotein; HDL, high-density lipoprotein.

chronic or subchronic schizophrenia (−18.7).[24] In addition, a meta-analysis of short-term studies of atypical antipsychotics in patients with schizophrenia or schizoaffective disorder reported mean improvements in PANSS total scores of −13.8 for aripiprazole, −18.2 for olanzapine, −18.5 for quetiapine IR, −18.8 for risperidone, and −14.8 for ziprasidone.[25] The lack of statistical separation of quetiapine IR from placebo in the present study is remarkable, since the efficacy of this agent in the treatment of schizophrenia is well established.[1–3,24] The fact that quetiapine IR did not separate from placebo by a statistically significant margin in the present study suggests a failed study rather than lack of efficacy of quetiapine XR.

The efficacy results presented here conflict with those reported in a previous study of identical design (Study 132) that found quetiapine XR (400, 600, and 800 mg/day) to be statistically superior to placebo in improving PANSS total scores at Week 6[15] (Figure 7).[26] Study 132 also found quetiapine IR to be statistically superior to placebo in improving PANSS total scores at Week 6. Furthermore, in another study, quetiapine XR was statistically superior to placebo in the prevention of relapse.[27]

FIGURE 7

STUDY 132: CHANGE IN PANSS TOTAL SCORE FROM BASELINE AT EACH ASSESSMENT (LOCF; MITT POPULATION)



[a]n = 116 at Week 1

The FDA reports that 4/16 (25%) short-term, well-designed, placebo-controlled studies in patients with schizophrenia failed to distinguish the active treatment from placebo even though these agents were known to be effective in this indication.[28] Thus, the non-significant outcome of our study, although surprising in light of the Study 132 results and established efficacy in this population, is not necessarily unusual.

There are many possible reasons for failure of active treatments to separate from placebo in a clinical study. In our study, the failure to separate from placebo was clearly not due to an unusually high placebo response per se, since the magnitude of improvement for the primary efficacy endpoint in the placebo group of 12.1 is less than that seen in Study 132 (18.8). Rather, it is likely that failure in this study was due to an attenuated drug response, which became apparent at around Week 3; PANSS change data show that from Week 3 the response to active treatment tapered off. Many factors could have contributed to this attenuated response (discussed in more depth below), but we believe that it is most likely related to two key factors. Firstly, patients were allowed to be out-patients throughout the study. As a result, patients were probably less acutely ill and less closely monitored, with fewer external variables controlled for, resulting in a higher attrition rate. Secondly, the studies were geographically different; Study 133 was performed in the US only, while Study 132 had no US study centers. There were clear resultant differences in demography (for example, age, ethnicity, and prior exposure to atypical antipsychotics), as well as duration of hospitalization and study completion rates. This may have been due to cultural or other factors that impacted on the actual conduct of and populations included in the two studies.

Although designed as an acute schizophrenia study, hospitalization of patients was not a requirement at any point and the study enrolled both in-patients and out-patients. Hospital discharge was encouraged if clinically feasible after Week 2. At enrollment, the proportion of out-patients was approximately 19–27% and at Week 1 this had increased to 26–33%. At Week 2, the proportion of out-patients had doubled from that observed at Week 1 and the proportion again increased markedly at Week 3. It is from this timepoint that the attenuation of drug response was observed.

Hospitalized patients are regularly monitored and as a consequence are more likely to adhere to medication, and more accurate observational data would be available to enhance the precision of rating scales. Furthermore, patients who initially respond well and are then released from a controlled hospital environment experience a reduction in their level of care, as well as additional life stressors, and these factors may

result in treatment non-adherence and/or a worsening of the patient's symptoms following discharge. Therefore, a hospitalized study population may be more likely to achieve and maintain a significant response to treatment than an out-patient population. In addition, in-patients are more likely to complete a study; thus, allowing discharge from hospital may adversely affect attrition rates, consequently weakening the effect size of the study. A considerably lower proportion of patients were hospitalized at Week 6 in this study (10%) compared with Study 132 (65%). For the reasons outlined above, this difference may explain the conflicting results of these two identically designed trials.

In clinical practice in the USA, patients are discharged relatively quickly, so in this regard the design of the present study, which allows the discharge of patients at any time during the study, closely simulated real-life clinical practice. However, this study was intended to be supportive of an FDA New Drug Application for a marketing indication, not as a naturalistic study. The lack of separation from placebo seen in this study for quetiapine IR—an agent with established efficacy in schizophrenia—suggest that for short-term, placebo-controlled studies in patients with acute schizophrenia conducted in the US, it is advisable that criteria for release from hospital are made more stringent, so that patients remain hospitalized for as long as required.

The withdrawal rate in the present study was high (41.1%); reasons for withdrawals were similar across treatment groups with the exception of 'lack of therapeutic response', which was higher in the placebo group. A high drop-out rate directly affects the power of the study; as patients drop out the standard deviation is expected to increase, which decreases the effect size and, consequently, reduces the power to detect a predefined difference. This issue is particularly relevant in studies with a higher number of treatment arms because more patients are needed to overcome the loss of statistical power. The withdrawal rate in Study 132 was much lower (24%) than in the present study and this factor may have contributed to the difference in the outcomes of these two studies as these studies both included five treatment arms. Furthermore, discontinuations occurred early in the present study, so many patients discontinued before they had an opportunity to improve, and the use of LOCF analysis resulted in scores closer to baseline values being carried forward.

High attrition rates are a common problem in studies in patients with schizophrenia, particularly in placebo-controlled trials.[29] A recent iloperidone study[30] employed several features to counteract potential factors that may have otherwise led to a failed study; these include hospitalization of patients throughout the study, less stringent criteria for concomitant medication (zolpidem for insomnia, lorazepam for agitation, and benztropine for EPS were all permitted), and the use of

mixed-effects model repeated measures (MMRM) analysis. These design elements should be considered when undertaking a study of antipsychotic medication in patients with schizophrenia. In the present study, it is possible that the requirement to discontinue lorazepam at Day 6 irrespective of patients' clinical status may have introduced a bias towards early discontinuation because patients would no longer have benefitted from any effects of receiving lorazepam and, consequently, this may have affected their willingness to continue in the study.

The patient populations of Studies 133 and 132 were different in terms of baseline severity: PANSS total score was lower (by about 4–5 points) in Study 133 than in Study 132. Another key difference between the populations of Studies 133 and 132 was that the mean age of patients at randomization was lower in Study 132 than Study 133 (34.2 versus 41.4 years). It is possible that younger patients may have greater capacity for improvement in symptoms than older patients. This difference in the average age of patients may or may not have contributed to the difference in the efficacy outcomes of the two studies. However, as well as being older, patients in this study had a longer mean time since first diagnosis (18 versus 8 years) and had experienced more psychotic episodes (average of 12 versus 5 episodes) compared with Study 132 patients. There is evidence that molecular changes occur during the progression from early to chronic phases of schizophrenia and so the nature of the disease also changes with time.[31] It is, also, more likely that patients in the US study (Study 133) had been treated with more antipsychotics and had been previously exposed to atypical antipsychotics (as these are more commonly used in the US than in the rest of the world), compared with patients in Study 132. Patients who are more chronically ill and have received more treatments may respond less well to subsequent therapy. In the USA, polypharmacy is widely used for the treatment of patients with schizophrenia.[32] These differences in study populations may reflect the geographical differences between the two studies.

The reduction in PANSS scores in the placebo group in the present study indicates that placebo-treated patients were benefiting from non-treatment-related interventions. Also, the proportions of hospitalized patients were similar in the placebo and active treatment groups at all timepoints. This suggests that for this patient population there was little difference in the therapeutic benefit experienced by patients on active treatment and those on placebo. The fact that the discontinuation rates in the placebo and active treatment groups were similar supports this theory.

Other possible reasons for the failure of this study to achieve separation from placebo were explored using post hoc analyses. The inclusion

of less severely ill patients in a study means that there is less scope for improvement; thus the difference between active treatment and placebo may be smaller. The risperidone study in patients with bipolar mania by Khanna, et al.[33] is an example of a large improvement versus placebo occurring in patients who were more severely ill. Patients enrolled into the present study were less ill than those entered into Study 132; as demonstrated by PANSS total scores at baseline of 90.8–93.1 in the present study and 95.8–97.3 in Study 132, and >50% of patients in the present study had a CGI-S of <5 compared with 25% in Study 132. Therefore, in theory, the margin by which patients in this study could improve was lower. This hypothesis is supported by the results of the post hoc analysis of primary efficacy variable data for patients who were markedly ill at baseline (CGI-S ≥5), which showed a statistically significant separation from placebo at Week 6 for the quetiapine XR 600 and 800 mg/day groups. The post hoc analyses of primary efficacy variable data for patients who were moderately ill at baseline highlighted the rapid and sustained placebo response that occurred in these patients. The results of this post hoc analysis suggest that baseline severity of illness may have impacted study outcome. There were considerably more moderately ill patients in the present study compared with Study 132, which may have contributed to the difference in outcome of the two studies. The inclusion of out-patients from the start of the present study may have inadvertently led to an enrollment bias favoring inclusion of a higher proportion of less severely ill patients.

Placebo response is common in studies in patients with psychiatric disorders, such as major depressive disorder (MDD).[34] Various strategies have been employed to address this phenomenon, such as a single-blind placebo run-in period with removal of early high placebo responders; a technique that has been used in MDD studies. Since the present study did not include a run-in period, a post hoc analysis of the primary efficacy endpoint data was conducted on a subset of the MITT population with initial outliers excluded (the modified analysis population) as a method of retrospectively eliminating the effect of initial placebo response (Figure 6). A literature review and data from earlier quetiapine studies suggest that it would be unusual to see a reduction of more than 20 points on the PANSS total score during the first week of a study in patients with schizophrenia. For the post hoc analysis, initial outliers were arbitrarily defined as having a decrease of ≥20 in PANSS total score by the end of Week 1. This post hoc analysis found that all three quetiapine XR arms separated from placebo ($p = 0.043$, 0.026, and 0.020 for quetiapine XR 400 mg, 600 mg and 800 mg, respectively); however, separation from placebo was not achieved for quetiapine IR although it approached statistical significance ($p = 0.065$).

Another possible limitation of the present study related to illness severity could be the inclusion criteria of a score of ≥4 at randomization for at least one of the PANSS items of delusions, conceptual disorganization, hallucinatory behavior, or suspiciousness/persecution; it is more typical to use the inclusion criteria of a score of ≥4 at both screening and randomization for at least two of the four positive PANSS items. Another limitation could be that compared with other studies, the present study had overly strict restrictions regarding prior psychoactive medication usage and these, again, may have introduced a selection bias favoring recruitment of less severely ill patients.

To summarize, we propose several possible explanations as to why this study—in contrast to Study 132[15]—failed to demonstrate a statistical separation of any active treatment from placebo for the reduction in PANSS total score. The most likely reasons are: 1) the lack of requirement for hospitalization and other factors biasing towards the selection of a less acutely ill patient population and 2) geographic differences resulting in key differences between the two study populations (including age, duration of hospitalization, and study completion rates).

The safety profile of quetiapine XR reported here was similar to the known safety profile of quetiapine. Furthermore, the tolerability data demonstrate that quetiapine XR 400, 600, and 800 mg/day was generally well tolerated in patients with schizophrenia over the 6-week treatment period. Dry mouth, sedation, and somnolence were the three most common AEs seen with quetiapine XR, occurring at a higher incidence than in the placebo group, a finding that is consistent with previous quetiapine IR studies.[35,36]

The incidence of AEs associated with EPS was low in the placebo group (4.3%) and in all quetiapine groups (5.7%–9.7%), with the two 800 mg/day dosage groups having a similar incidence (9.7%, quetiapine XR 800 mg/day; and 7.8%, quetiapine IR 800 mg/day). At Week 6 there were reductions in mean SAS and BARS scores in all treatment groups. The use of anticholinergic medication in the quetiapine XR and IR groups was low, although it was slightly higher versus placebo. Increases in mean body weight with quetiapine XR 400 mg and 800 mg/day were similar to the mean increase seen with quetiapine IR; for the quetiapine XR 600 mg/day group the body weight increase was higher than with quetiapine IR.

In conclusion, both quetiapine XR and quetiapine IR were not statistically superior to placebo at study endpoint (Week 6), though numerical improvements were observed with both active treatments. The numerical improvement with quetiapine XR was similar to that with quetiapine IR, an agent with established efficacy in the treatment of acute schizophrenia.[1]

Many factors may have contributed to the non-significant outcome in this study, but as discussed above, the most likely causes relate to two main issues: lack of requirement for hospitalization and geographic differences in the patient population included in this study versus the successful Study 132, which was performed outside of the US. Further work is needed to understand the reasons why drugs with proven efficacy fail to separate from placebo in some controlled clinical trials. 'Failed' studies such as this one warrant close attention so that important lessons in study design and conduct may be learned. ✤

ACKNOWLEDGEMENTS

This study was funded by AstraZeneca. We thank Robin McCoy (AstraZeneca) for her contribution to the execution of the study. We thank Jocelyn Woodcock, MPhil, from Complete Medical Communications, who provided medical writing support funded by AstraZeneca.

Dr. Brecher is a former employee of AstraZeneca.

The investigators involved in this study were Mohammed Bari, Jason Baron, Ronald Brenner, David Brown, Robert Dahmes, Himasiri De Silva, Juan Espinosa, Carlos Figueroa, Donald Garcia, John Gilliam, Richard Josiassen, Mary Knesevich, James Knutson, Joseph Kwentus, David Linden, Robert Litman, Edward Logue, Raymond Manning, Michael Plopper, David Sack, Stephen Saklad, Adam Sky, Tram Tran-Johnson, Madeleine Valencerina, Rakesh Ranjan, Stephen Peterson, Michael Levy, William Fuller, Jeffrey Borenstein, Richard Jaffe, Adam Lowry, Andrew Cutler, Steven Glass, Mark Lerman, Stephen Mohaupt, Murray Rosenthal, Carlos Collin, Raj Rajini, Rajinder Shiwach, David Walling, Arthur Freeman. Clinicaltrials.gov NCT identifier number: NCT 00085891.

REFERENCES

1. Arvanitis LA, Miller BG, the Seroquel Trial 13 study group. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. *Biol Psychiatry*. 1997;42:233–246.
2. Buckley PF. Efficacy of quetiapine for the treatment of schizophrenia: a combined analysis of three placebo-controlled trials. *Curr Med Res Opin*. 2004;20:1357–1363.
3. Hellewell JSE, Cameron-Hands D, Cantillon M. Seroquel®: evidence for efficacy in the treatment of hostility and aggression. *Schizophr Res*. 1998;29:154–155.
4. Vieta E, Mullen J, Brecher M, et al. Quetiapine monotherapy for mania associated with bipolar disorder: combined analysis of two international, double-blind, randomised, placebo-controlled studies. *Curr Med Res Opin*. 2005;21:923–934.
5. Calabrese JR, Keck Jr. PE, Macfadden W, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *Am J Psychiatry*. 2005;162:1351–1360.
6. Thase ME, Macfadden W, Weisler RH, et al. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). *J Clin Psychopharmacol*. 2006;26:600–609.

7. Perkins DO. Adherence to antipsychotic medications. *J Clin Psychiatry*. 1999;60(Suppl 21):25–30.
8. Byerly MJ, Nakonezny PA, Lescouflair E. Antipsychotic medication adherence in schizophrenia. *Psychiatr Clin North Am*. 2007;30:437–452.
9. Valenstein M, Ganoczy D, McCarthy JF, et al. Antipsychotic adherence over time among patients receiving treatment for schizophrenia: a retrospective review. *J Clin Psychiatry*. 2006;67:1542–1550.
10. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353:1209–1223.
11. Leucht S, Heres S. Epidemiology, clinical consequences, and psychosocial treatment of nonadherence in schizophrenia. *J Clin Psychiatry*. 2006;67(Suppl 5):3–8.
12. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353:487–497.
13. Suppes T, Earley W, Datto C, et al. Effectiveness of the extended release formulation of quetiapine as monotherapy for the treatment of acute bipolar depression. *Int J Neuropsychopharmacol*. 2008;11.
14. Cutler A, Earley W, Datto C, et al. Effectiveness of the extended release formulation of quetiapine as monotherapy for the treatment of acute bipolar mania. *Int J Neuropsychopharmacol*. 2008;11.
15. Kahn RS, Schulz SC, Palazov VD, et al. Efficacy and tolerability of once-daily extended release quetiapine fumarate in acute schizophrenia: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2007;68:832–842.
16. Bell MD, Lysaker PH, Beam-Goulet JL, et al. Five-component model of schizophrenia: assessing the factorial invariance of the positive and negative syndrome scale. *Psychiatry Res*. 1994;52:295–303.
17. Emsley RA, Buckley P, Jones AM, et al. Differential effect of quetiapine on depressive symptoms in patients with partially responsive schizophrenia. *J Psychopharmacol*. 2003;17:210–215.
18. Kane JM, Carson WH, Saha AR, et al. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. *J Clin Psychiatry*. 2002;63:763–771.
19. Lieberman J, Carson WH, Saha A, et al. Meta-analysis of the efficacy of aripiprazole in schizophrenia. *Int J Neuropsychopharmacol*. 2002;5(Suppl 1):S186.
20. Potkin SG, Saha AR, Kujawa MJ, et al. Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs placebo in patients with schizophrenia and schizoaffective disorder. *Arch Gen Psychiatry*. 2003;60:681–690.
21. Hommel G. A stagewise rejective multiple test procedure based on a modified Bonferroni test. *Biometrika*. 1988;75:383–386.
22. Kobak KA, Lipsitz JD, Williams JB, et al. A new approach to rater training and certification in a multicenter clinical trial. *J Clin Psychopharmacol*. 2005;25:407–412.
23. Krell HV, Leuchter AF, Morgan M, et al. Subject expectations of treatment effectiveness and outcome of treatment with an experimental antidepressant. *J Clin Psychiatry*. 2004;65:1174–1179.
24. Copolov DL, Link CGG, Kowalcyk B. A multicentre, double-blind, randomized comparison of quetiapine (ICI 204,636, 'Seroquel') and haloperidol in schizophrenia. *Psychol Med*. 2000;30:95–105.
25. Tandon R, Jibson MD. Comparing efficacy of first-line atypical antipsychotics: no evidence of differential efficacy between risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole. *Int J Psychiatry Clin Pract*. 2005;9:204–212.
26. AstraZeneca data on file. Seroquel DOF number 9049. 2008.
27. Peuskens J, Trivedi JK, Malyarov S, et al. Prevention of schizophrenia relapse with extended release quetiapine fumarate dosed once daily: a randomized placebo-controlled trial in clinically stable patients. *Psychiatry (Edgemont)*. 2007;4:34–50.
28. Laughren TP. The scientific and ethical basis for placebo-controlled trials in depression and schizophrenia: an FDA perspective. *Eur Psychiatry*. 2001;16:418–423.
29. Kemmler G, Hummer M, Widschwendter C, et al. Dropout rates in placebo-controlled and active-control clinical trials of antipsychotic drugs: a meta-analysis. *Arch Gen Psychiatry*. 2005;62:1305–1312.
30. Cutler AJ, Kalali AH, Weiden PJ, et al. Four-week, double-blind, placebo- and ziprasidone-controlled trial of iloperidone in patients with acute exacerbations of schizophrenia. *J Clin Psychopharmacol*. 2008;28:S20–S28.
31. Narayan S, Tang B, Head SR, et al. Molecular profiles of schizophrenia in the CNS at different stages of illness. *Brain Res*. 2008.
32. Ganguly R, Kotzan JA, Miller LS, et al. Prevalence, trends, and factors associated with antipsychotic polypharmacy among Medicaid-eligible schizophrenia patients, 1998–2000. *J Clin Psychiatry*. 2004;65:1377–1388.
33. Khanna S, Vieta E, Lyons B, et al. Risperidone in the treatment of acute mania: double-blind, placebo-controlled study. *Br J Psychiatry*. 2005;187:229–234.
34. Khan A, Bhat A. Is the problem of a high placebo response unique to antidepressant trials? *J Clin Psychiatry*. 2008;69:1979–1980.

35. Mullen J, Jibson MD, Sweitzer D, et al. A comparison of the relative safety, efficacy, and tolerability of quetiapine and risperidone in outpatients with schizophrenia and other psychotic disorders: the Quetiapine Experience with Safety and Tolerability (QUEST) study. *Clin Ther*. 2001;23:1839–1854.
36. Timdahl K, Carlsson A, Stening G. An analysis of safety and tolerability data from controlled, comparative studies of quetiapine in patients with schizophrenia, focusing on extrapyramidal symptoms. *Hum Psychopharmacol*. 2007;22:315–325.