

NEGATIVE AND FAILED CLINICAL TRIAL REPORTS

Key Words: antidepressive agents [pharmacological action]; antipsychotic agents; clinical trial; sustained-release preparations; treatment efficacy; clinical trial, Phase III; controlled clinical trial; multicenter study

A Randomized, Double-blind Study of the Efficacy and Tolerability of Extended Release Quetiapine Fumarate (Quetiapine XR) Monotherapy in Patients with Major Depressive Disorder

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ABSTRACT ~ Objectives: Evaluate the efficacy and tolerability of once-daily extended release quetiapine fumarate (quetiapine XR) monotherapy in patients with major depressive disorder (MDD). **Methods:** 10-week (8-week active-treatment/2-week post-treatment), randomized, double-blind, placebo- and active-controlled study (D1448C00004). Patients received quetiapine XR 150 mg/day, escitalopram 10 mg/day, or placebo; patients with an inadequate response (<20% improvement in MADRS total score) at Week 2 received double-treatment dose. Primary endpoint: Week 8 change from randomization in MADRS total score. Secondary endpoints included: MADRS response ($\geq 50\%$ improvement) and remission (score ≤ 8), HAM-D total and Item 1, HAM-A total, psychic and somatic, CGI-S total, PSQI global, and Q-LES-Q-SF% maximum total scores; tolerability was assessed throughout. **Results:** 471 patients were randomized. No significant improvements in MADRS total score were observed at Week 8 (LOCF) with either active treatment (quetiapine XR, -17.21 [$p=0.174$]; escitalopram, -16.73 [$p=0.346$]) versus placebo (-15.61). There were no significant differences in secondary endpoints versus placebo, with the exception of Week 8 change in PSQI global score (quetiapine XR, -4.96 [$p < 0.01$] versus placebo, -3.37). MMRM analysis of observed cases data suggested that the primary analysis may not be robust. Most commonly reported AEs included: dry mouth, somnolence, and dizziness for quetiapine XR; headache and nausea for escitalopram. **Conclusions:** In this study, neither quetiapine XR (150/300 mg/day) nor escitalopram

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(10/20 mg/day) showed significant separation from placebo. Both compounds have been shown previously to be effective in the treatment of MDD; possible reasons for this failed study are discussed. Quetiapine XR was generally well tolerated with a profile similar to that reported previously. Psychopharmacology Bulletin. 2012;45(1):5–30.

INTRODUCTION

Despite the plethora of available antidepressants (>25 agents are currently approved for major depressive disorder [MDD]), many patients discontinue treatment due to side effects.¹ Furthermore, a considerable proportion of patients fail to achieve remission following initial treatment; for example, only 28% of patients in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study achieved remission following treatment with citalopram.² Those patients who do not respond to their treatment, or are unable to tolerate it, may receive a number of different pharmacotherapies until the optimum one is identified. This suggests a need for new treatment options for patients with MDD.

Once-daily extended release quetiapine fumarate (quetiapine XR) is approved in the USA and Europe for the treatment of schizophrenia, bipolar disorder (both bipolar mania and bipolar depression), and, more recently, as adjunctive treatment for patients with MDD who have had suboptimal response to antidepressant monotherapy.^{3,4} It is also licensed as a monotherapy for the treatment of MDD in some countries. The present randomized, placebo-controlled study is part of the clinical development program investigating quetiapine XR in patients with MDD. To date, three acute monotherapy studies,^{5–7} two acute adjunct studies,^{8,9} one maintenance study,¹⁰ and one acute monotherapy study in the elderly¹¹ have reported positive efficacy and acceptable tolerability of quetiapine XR in patients with MDD.

The design of the current study (Study D1448C00004) was identical to Study D1448C00003⁵—a modified fixed-dose design consisting of a fixed initial dose for 2 weeks followed by a doubling of the dose of randomized treatment for those patients not responding to therapy at Week 2. The modified fixed-dose design was intended to reflect both clinical practice and the recommendation that non-responsive patients receive an increase in their medication dose.¹²

The primary hypothesis of the current study was that quetiapine XR would be more effective than placebo in reducing Montgomery Åsberg Depression Rating Scale (MADRS) total score from randomization to Week 8 in adult patients with MDD. However, in the primary analysis, neither quetiapine XR nor the active control escitalopram separated from placebo, which is an unexpected result, as both agents have

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demonstrated efficacy in this indication. In addition to presenting the results of the study, this article also discusses the most likely explanations for this failed study.

METHODS

Study Design

This 10-week, multicenter, parallel-group, placebo- and active-controlled, double-blind, randomized, Phase III study (D1448C00004, Amber; ClinicalTrials.gov Identifier: NCT00351169) consisted of a 1- to 4-week enrollment/wash-out period, an 8-week randomized treatment period, and a 2-week drug-discontinuation/tapering follow-up period.

The study was performed in accordance with the Declaration of Helsinki and International Conference on Harmonisation/Good Clinical Practice guidelines. All patients provided written, informed consent.

Patients

Male or female outpatients (18–65 years) with a documented diagnosis meeting the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for MDD (single episode/recurrent) and confirmed by Mini-International Neuropsychiatric Interview¹³ were eligible for inclusion in the study. Patients were required to have a Hamilton Rating Scale for Depression (HAM-D)¹⁴ 17-item total score ≥ 22 and HAM-D Item 1 (depressed mood) score ≥ 2 at both enrollment and randomization.

Exclusion criteria included: diagnosis of any DSM-IV Axis I disorder other than MDD within 6 months prior to enrollment or any DSM-IV Axis II disorder impacting on the patient's current psychiatric status; a current depressive episode lasting >12 months or <4 weeks in duration; a history of inadequate response to treatment (≥ 2 classes of antidepressants each for ≥ 6 weeks) during the current depressive episode; a DSM-IV diagnosis of substance or alcohol abuse within 6 months prior to enrollment; a current serious suicidal or homicidal risk; a HAM-D Item 3 (suicide) score ≥ 3 or a suicide attempt within the past 6 months; or a clinically relevant medical illness or clinically relevant findings (including laboratory tests, or electrocardiogram [ECG]).

Randomization

Randomization was neither site- nor country-specific and was generated using a computer-based system. Randomization numbers were

allocated via a computer-based randomization system in a strictly sequential manner to assign patients to either quetiapine XR, escitalopram, or placebo in a ratio of 1:1:1. To ensure blinding, placebo tablets/capsules were identical in appearance, smell, and taste to their respective active treatment (quetiapine XR or escitalopram) tablets/capsules. A double-dummy method was used and the number of tablets/capsules dispensed was the same across all treatment groups. All study medication was administered orally, once-daily, in the evening.

Study Medication and Dosing Schedule

Dose titration for quetiapine XR was 50 mg on Days 1–2, increasing to 150 mg on Days 3–14. Escitalopram was dosed at 10 mg/day on Days 1–14. At Day 15 (Week 2), all patients with an inadequate response (<20% reduction from randomization in MADRS¹⁵ total score) had their dose doubled (quetiapine XR 300 mg/day; escitalopram 20 mg/day). Investigators were not informed of the criteria for dose increase and an Interactive Voice Response System (IVRS) was used to blind dose increases. After Week 2, patients continued to receive their assigned doses for the remaining randomized treatment period. The initial dosage and up-titration of escitalopram was in accordance with the prescribing information.¹⁶

At the end of Week 8 (Day 57), patients receiving quetiapine XR 150 mg/day or escitalopram 10 mg/day discontinued active treatment and took placebo until Day 63 (post-treatment Day 6) to maintain the study blinding. Patients receiving quetiapine XR 300 mg/day or escitalopram 20 mg/day had their dose down-titrated to 150 mg/day or 10 mg/day, respectively, from Day 57 until Day 63. From Day 64, patients received no treatment.

Prior and Concomitant Treatment

Prior to randomization, patients were not permitted to receive antipsychotics, mood stabilizers, or antidepressants within 7 days, monoamine oxidase inhibitors, anxiolytics, drugs that induce or inhibit the hepatic metabolizing cytochrome P450 3A4 enzymes, or hypnotics within 14 days, fluoxetine within 28 days, a depot antipsychotic injection within two dosing intervals prior to randomization, or electroconvulsive therapy within 90 days.

During the study, lorazepam (2 mg/day or equivalent), zolpidem tartrate (10 mg/day), zaleplon (20 mg/day), zopiclone (7.5 mg/day), or chloral hydrate (1 g/day) were permitted for insomnia if treatment had been ongoing for 28 days prior to enrollment. Anticholinergics could be

used to treat emergent extrapyramidal symptoms (EPS), but not prophylactically. Patients were permitted to receive psychotherapy during the study if it had been ongoing for ≥ 3 months prior to randomization. During the active treatment period of the study, other psychoactive medications were not permitted. During the second week of the follow-up period (Days 64–71), physicians could prescribe other medications, including alternative antidepressants, if clinically warranted.

Efficacy Evaluations

The primary efficacy variable was the change from randomization to Week 8 in MADRS total score. To reduce the likelihood of rater-associated inflation of primary efficacy scale scores, HAM-D assessments comprised part of the inclusion criteria but the primary efficacy endpoint utilized the MADRS scale.

Additional efficacy evaluations included: change from randomization to each assessment in MADRS total score; change in individual MADRS items at Week 8; MADRS response ($\geq 50\%$ reduction from randomization in MADRS total score) at Weeks 1 and 8; the proportion of patients with a Clinical Global Impressions-Improvement (CGI-I)¹⁷ score of 1 ('very much improved') or 2 ('much improved'), and MADRS remission (total score ≤ 8) rates at Week 8. Additional definitions of remission were MADRS total scores of ≤ 10 and ≤ 12 (analyzed post hoc). Changes from randomization at Week 8 in HAM-D total and Item 1 (depressed mood) scores, Hamilton Rating Scale for Anxiety (HAM-A)¹⁸ total, and psychic and somatic cluster scores, and CGI-Severity of Illness [CGI-S] score¹⁷ were also evaluated.

Clinical assessments of MADRS, HAM-A, and CGI-S total scores were conducted on Day 1 (randomization), and at Weeks 1, 2, 4, 6, and 8. In addition, CGI-S total score was also assessed at enrollment (baseline). HAM-D scores were determined at enrollment, Day 1, and Week 8. CGI-I scores were recorded at Weeks 1, 2, 4, 6, and 8. Where possible, the same trained rater conducted all assessments for a given patient for a specific scale, to reduce scoring variability among raters. Raters received computer-based training (provided by PharmaStar/UBC) and needed to be certified as a qualified rater by the sponsor. High levels of inter-rater agreement were demonstrated for MADRS baseline ($\kappa = 0.826$) and follow-up ($\kappa = 0.861$) assessments.

Patient-reported Outcomes

Quality of Life Enjoyment and Satisfaction [Q-LES-Q]¹⁹ short form (SF) and Pittsburgh Sleep Quality Index (PSQI)²⁰ were assessed at randomization and Weeks 4 and 8. Change from randomization to

Week 8 in Q-LES-Q (Items 1–14) % maximum total, Item 15 (satisfaction with medication), and Item 16 (overall quality of life) scores were reported.

Changes in PSQI were used to assess several dimensions of sleep, including quality, latency, duration, efficiency, sleep disturbances, use of medication, and daytime dysfunction.

Analysis of Primary Efficacy Variable by Age, Gender, Ethnicity, Disease Severity, and Continent

To examine whether the outcome of the study was affected by various factors, analyses of the primary endpoint were carried out for patient subgroups, including age, gender, ethnicity, disease severity, and region. Response rates at Week 8 were also analyzed by region (Asia, Europe, North America, and South Africa).

Safety and Tolerability

The incidence, severity of, and withdrawal due to adverse events (AEs) were recorded throughout the study. Assessment of serum glucose (fasting), lipid (fasting), and prolactin levels, and 12-lead ECG recordings were performed at enrollment and Week 8 (fasting serum glucose was also assessed at Week 4). Body weight and vital signs were measured at enrollment and all subsequent visits up to Week 8.

The Simpson-Angus Rating Scale (SAS)²¹ and Barnes Akathisia Rating Scale (BARS)²² were used to assess EPS at randomization, Week 4, and Week 8. The self-administered, 14-item Changes in Sexual Functioning Questionnaire (CSFQ) was assessed at randomization, Week 4, and Week 8, and was used to measure illness- and medication-related changes in sexual functioning, with males and females completing separate versions.²³

During the 2-week, post-treatment, drug-discontinuation follow-up phase, treatment discontinuation signs and symptoms (TDSS) were assessed using an 18-item TDSS scale, which was developed by AstraZeneca as a hybrid of the 17-item discontinuation AE scale²⁴ and the 43-item discontinuation emergent signs and symptoms scale.²⁵ Patients completing the randomized period were asked to rate discontinuation symptoms using the TDSS scale. Patients completed the TDSS by IVRS at the study center during the final randomized treatment period visit (Day 57) and on post-treatment Days 7 and 14, and by telephone at home on post-treatment Days 1, 3, and 5. Patients were asked whether the symptom was 'present' or 'absent'. TDSS total scores were calculated for each visit by summing the number of patient-reported treatment-emergent symptoms (TDSS items) present.

Statistical Analyses

The modified intent-to-treat (MITT) population (randomized patients who received ≥ 1 dose of study treatment and had randomization and ≥ 1 post-randomization MADRS total score assessments) was used for the analysis of primary and secondary efficacy variables. The safety population included patients who received ≥ 1 dose of study treatment. The TDSS population included patients who completed 8 weeks of double-blind treatment and had baseline (Week 8) and ≥ 1 post-baseline TDSS assessments.

Sample size was calculated to allow demonstration of a significant difference between quetiapine XR and placebo for the primary efficacy variable and was achieved by assuming an anticipated difference of 3.5 units from placebo and a standard deviation (SD) of 9 for the change in MADRS total score from randomization at Week 8. For a two-sided hypothesis test with a 5% significance level ($\alpha = 0.05$), a sample size of 140 evaluable patients per treatment group was required to ensure 90% power. Escitalopram was included as an active control for the purpose of assay sensitivity (i.e. for comparison with placebo); the study was not powered to make any direct comparisons between quetiapine XR and escitalopram.

Analysis of the change from randomization at Week 8 in MADRS total score (primary efficacy variable) and Q-LES-Q-SF% maximum total score (secondary efficacy variable of particular interest) was conducted using an analysis of covariance (ANCOVA) model, including treatment (fixed effect), center (random effect), and baseline MADRS total score (covariate) as explanatory variables. A last observation carried forward (LOCF) approach was used for imputation of missing data. To assess the robustness of the primary analysis results, point estimates for the changes in MADRS total score were calculated at each time point for observed cases (OC) data using a mixed model repeated measures (MMRM) analysis, which included center, treatment, baseline MADRS total score, visit, and treatment-by-visit interaction terms.

Type-I error ($\alpha = 0.05$) was controlled using a sequential testing procedure for the two comparisons of primary interest. If the reduction in MADRS total score from randomization at Week 8 with quetiapine XR was significantly greater than with placebo, then the hypothesis relating to the change in Q-LES-Q-SF% maximum total score from randomization to Week 8 was to be tested. Any comparisons between escitalopram and placebo were not adjusted for multiplicity.

All other continuous efficacy variables were analyzed using the same ANCOVA model as the primary efficacy variable. MADRS response and remission rates were analyzed using logistic regression models, which included terms for center, treatment, and baseline MADRS total

score. Model-based point estimates of odds ratios and 95% confidence intervals were reported. The number needed to treat (NNT) for MADRS responders was calculated using the formula:

$$\text{NNT} = 100 / (\% \text{ responders with quetiapine XR} - \% \text{ responders with placebo}).$$

Changes in Q-LES-Q overall quality of life (Item 16) and satisfaction with medication (Item 15) scores from randomization to Week 8 were presented by descriptive statistics. All statistical tests were two-sided with a significance level of 5% (unless otherwise specified) and, with the exception of the primary efficacy variable and secondary efficacy variable of particular interest, were reported as nominal p-values.

RESULTS

Patient Population

This study was conducted at 54 centers in Canada, China, Finland, Korea, Malaysia, Mexico, the Philippines, South Africa, and Spain between May 2006 and June 2007. In total, 660 patients were screened and 471 eligible patients with MDD were randomized to receive quetiapine XR, escitalopram, or placebo. Of those randomized, 468 patients received treatment and were included in the safety analysis set; the MITT population comprised 459 patients (nine patients were excluded due to missing randomization or post-randomization MADRS scores) (Figure 1).

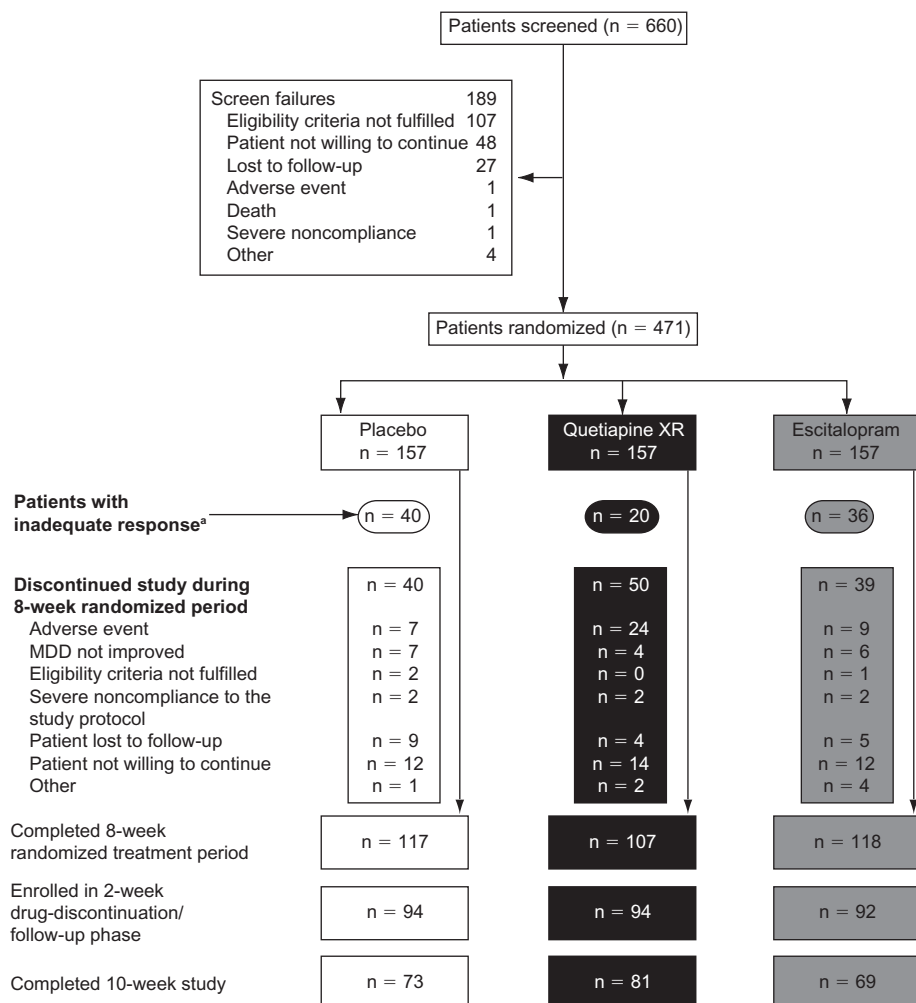
The treatment groups were generally well balanced with respect to demographic and clinical characteristics (Table 1). Overall, 68.2%, 75.2%, and 74.5% of patients in the quetiapine XR, escitalopram, and placebo groups completed the randomized treatment phase; of these, 75.7%, 58.5%, and 62.4%, respectively, completed the 2-week follow-up period. The most common reasons for withdrawal during the randomized treatment period were an AE in the quetiapine XR group and 'patient not willing to continue' in the escitalopram and placebo groups.

In the quetiapine XR (150 mg/day), escitalopram (10 mg/day), and placebo groups, 13.0% (20/154), 23.7% (36/152), and 26.1% (40/153) of patients, respectively, met the criteria for inadequate response at Week 2, and were up-titrated to double their initial randomized dose (MITT population). The mean (SD) daily dose was 150.1 (42.7) mg/day for quetiapine XR and 11.3 (2.9) mg/day for escitalopram during the randomized treatment period (MITT population).

High levels of adherence to study medication (based on tablet counts consistent with $\geq 80\%$ and $\leq 120\%$ consumption of doses) were observed

FIGURE 1

PATIENT DISPOSITION



^aPatients who failed to meet the criterion of adequate response ($\geq 20\%$ reduction in MADRS total score after 2 weeks of treatment) were up-titrated to double the initial randomized dose for the remaining 6 weeks of randomized treatment.

MADRS = Montgomery Åsberg Depression Rating Scale; MDD = major depressive disorder.

in each treatment cohort (97.4%, 96.7%, and 99.7% in the quetiapine XR, escitalopram, and placebo groups, respectively [MITT population]).

Prior and Concomitant Medication

Prior to randomization, 21.6% of patients were receiving benzodiazepines, 11.3% were receiving selective serotonin reuptake inhibitors, and 4.9% were receiving nonselective monoamine reuptake inhibitors.

TABLE 1

DEMOGRAPHIC AND BASELINE CLINICAL CHARACTERISTICS
(MITT POPULATION)

| | PLACEBO (n = 153) | QUETIAPINE XR (n = 154) | ESCITALOPRAM (n = 152) |
|---|----------------------|----------------------------|---------------------------|
| Gender, n (%) | | | |
| Male | 50 (32.7) | 44 (28.6) | 37 (24.3) |
| Female | 103 (67.3) | 110 (71.4) | 115 (75.7) |
| Age, years | | | |
| Mean (SD) | 39.7 (11.1) | 40.1 (11.6) | 40.3 (12.5) |
| Ethnicity, n (%) | | | |
| White | 84 (54.9) | 86 (55.8) | 80 (52.6) |
| Asian | 41 (26.8) | 43 (27.9) | 45 (29.6) |
| Black | 25 (16.3) | 20 (13.0) | 22 (14.5) |
| Other | 3 (2.0) | 5 (3.2) | 5 (3.3) |
| Weight, kg | | | |
| Mean (SD) | 70.2 (19.2) | 73.2 (21.1) | 72.1 (17.9) |
| BMI, kg/m² | | | |
| Mean (SD) | 25.8 (6.1) | 27.2 (7.7) | 26.8 (6.1) |
| DSM-IV diagnosis, n (%) | | | |
| MDD, recurrent | 116 (75.8) | 114 (74.0) | 120 (79.0) |
| MDD, single episode | 37 (24.2) | 40 (26.0) | 32 (21.0) |
| DSM-IV diagnosis by region, n (%) | | | |
| MDD, recurrent | | | |
| North America | 49 (32.0) | 50 (32.5) | 45 (29.6) |
| South Africa | 24 (15.7) | 28 (18.2) | 35 (23.0) |
| Asia | 28 (18.3) | 23 (14.9) | 26 (17.1) |
| Europe | 15 (9.8) | 13 (8.4) | 14 (9.2) |
| MDD, single episode | | | |
| North America | 8 (5.2) | 12 (7.8) | 5 (3.3) |
| South Africa | 11 (7.2) | 4 (2.6) | 4 (2.6) |
| Asia | 13 (8.5) | 20 (13.0) | 18 (11.8) |
| Europe | 5 (3.3) | 4 (2.6) | 5 (3.3) |
| Time since first onset of depressive symptoms, years | | | |
| Mean (SD) | 9.4 (10.0) | 10.1 (11.1) | 8.8 (9.0) |
| Disease severity at baseline by region, n (%) | | | |
| HAM-D total score <28 | | | |
| North America | 36 (23.5) | 39 (25.3) | 35 (23.0) |
| South Africa | 18 (11.8) | 16 (10.4) | 16 (10.5) |
| Asia | 31 (20.3) | 32 (20.8) | 28 (18.4) |
| Europe | 14 (9.2) | 11 (7.1) | 17 (11.2) |
| Total | 99 (64.7) | 98 (63.6) | 96 (63.2) |

(continued)

QUETIAPINE XR MONOTHERAPY IN MDD

TABLE 1 (CONTINUED)

| | PLACEBO (n = 153) | QUETIAPINE XR (n = 154) | ESCITALOPRAM (n = 152) |
|---------------------------------------|----------------------|----------------------------|---------------------------|
| HAM-D total score ≥ 28 | | | |
| North America | 21 (13.7) | 23 (14.9) | 15 (9.9) |
| South Africa | 17 (11.1) | 16 (10.4) | 23 (15.1) |
| Asia | 10 (6.5) | 11 (7.1) | 16 (10.5) |
| Europe | 6 (3.9) | 6 (3.9) | 2 (1.3) |
| Total | 54 (35.3) | 56 (36.4) | 56 (36.8) |
| Rating scale scores, mean (SD) | | | |
| MADRS total | 31.6 (5.4) | 32.2 (5.6) | 32.0 (5.6) |
| HAM-D total | 26.6 (3.7) | 27.1 (4.0) | 27.2 (4.1) |
| HAM-D Item 1 | 3.0 (0.5) | 3.0 (0.5) | 3.0 (0.5) |
| HAM-A total | 19.8 (7.0) | 20.8 (7.0) | 20.6 (7.4) |
| HAM-A psychic | 12.5 (3.7) | 13.0 (3.6) | 13.0 (4.0) |
| HAM-A somatic | 7.3 (4.3) | 7.8 (4.9) | 7.6 (4.4) |
| CGI-S | 4.8 (0.9) | 4.9 (0.8) | 5.0 (0.9) |
| Q-LES-Q-SF% maximum total | 38.6 (14.3) | 35.3 (16.0) | 38.3 (14.3) |
| PSQI global | 12.8 (4.3) | 12.5 (4.0) | 12.3 (3.9) |

BMI = body mass index; CGI-S = Clinical Global Impressions-Severity of Illness; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression; MADRS = Montgomery Åsberg Depression Rating Scale; MDD = major depressive disorder; MITT = modified intent-to-treat; PSQI = Pittsburgh Sleep Quality Index; Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form; SD = standard deviation.

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The proportions of patients who received concomitant sleep medication (hypnotics/sedatives) at some time during the randomized phase were 5.4%, 7.4%, and 7.3% in the quetiapine XR, escitalopram, and placebo groups, respectively; benzodiazepines were received at some time during the randomized phase by 15.3%, 22.2%, and 22.7% of patients, respectively. Anticholinergic use at some time during randomized treatment occurred in 5.4%, 2.8%, and 3.6% of patients in the quetiapine XR, escitalopram, and placebo groups, respectively.

Efficacy

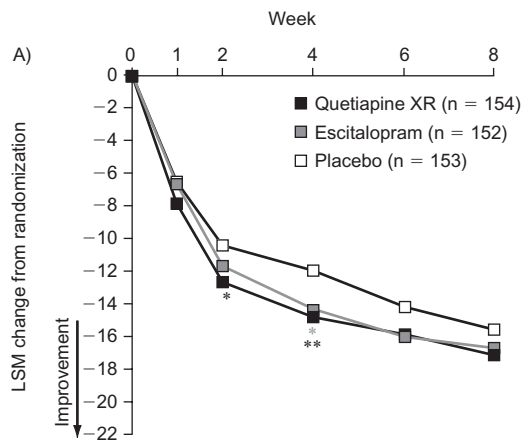
At Week 8, neither quetiapine XR nor escitalopram significantly reduced MADRS total scores from randomization (LOCF): least squares means (LSM) of -17.21 ($p = 0.174$) and -16.73 ($p = 0.346$), respectively, versus -15.61 for placebo (Figure 2A).

The mean changes from randomization to Week 8 in MADRS total score were -19.4 , -19.8 , and -18.3 for quetiapine XR, escitalopram, and placebo, respectively, for patients with adequate response at Week 2, and -13.1 , -8.3 , and -10.3 for quetiapine XR, escitalopram, and

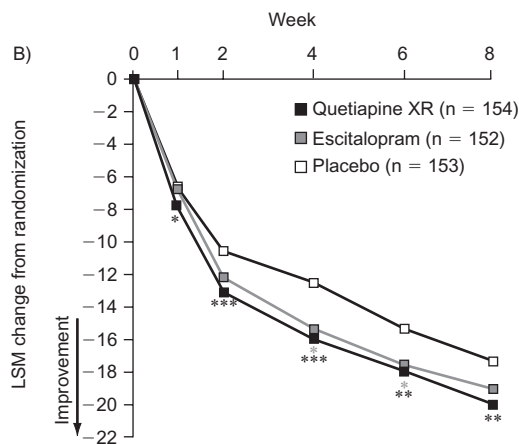
QUETIAPINE XR MONOTHERAPY IN MDD

FIGURE 2

CHANGE FROM RANDOMIZATION TO WEEK 8 IN MADRS TOTAL SCORE: A) LOCF APPROACH AND B) MMRM ANALYSIS OF OC DATA (MITT POPULATION)



* $p < 0.05$; ** $p < 0.01$ versus placebo.



Number of evaluable patients:

| | | | | | |
|---------------|-----|-----|-----|-----|-----|
| Quetiapine XR | 152 | 140 | 127 | 113 | 109 |
| Escitalopram | 149 | 144 | 127 | 124 | 114 |
| Placebo | 150 | 145 | 131 | 127 | 115 |

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

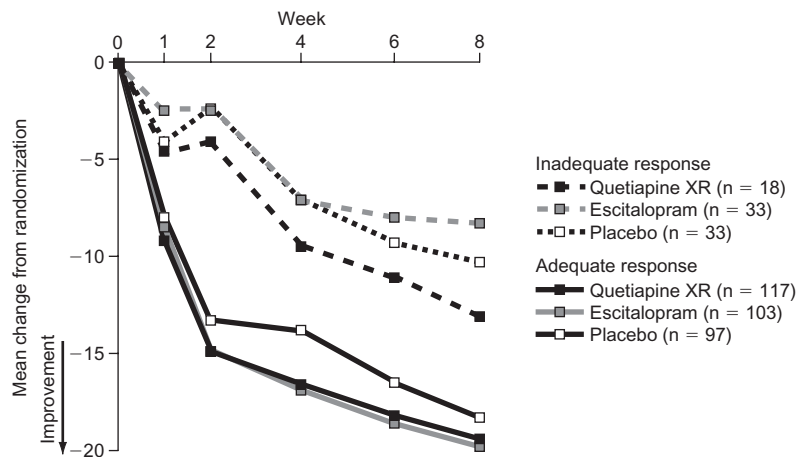
LOCF = last observation carried forward; LSM = least squares means; MADRS = Montgomery Åsberg Depression Rating Scale; MITT = modified intent-to-treat; MMRM = mixed-model repeated measures; OC = observed case.

placebo, respectively, in patients with an inadequate response at Week 2 (Figure 3).

Of the individual MADRS items, significant improvement at Week 8 was only seen in MADRS Item 4 (reduced sleep) in the quetiapine XR group (LSM change -2.77 ; $p < 0.001$) compared with placebo (-1.94) (Figure 4).

QUETIAPINE XR MONOTHERAPY IN MDD

FIGURE 3

CHANGE IN MADRS TOTAL SCORE OVER TIME IN PATIENTS WITH AN ADEQUATE AND INADEQUATE RESPONSE^{a,b} AT WEEK 2 (LOCF; MITT POPULATION)

^aInadequate response defined as <20% reduction in MADRS total score from randomization to Week 2.

^bPatients with an inadequate response at Week 2 had their dose doubled (quetiapine XR 300 mg/day; escitalopram 20 mg/day).

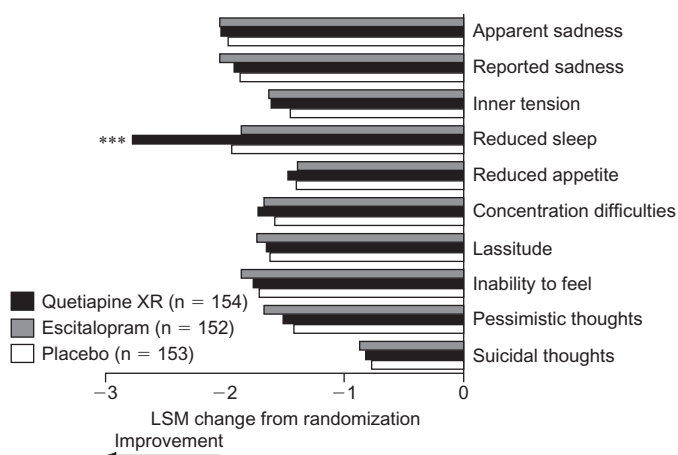
LOCF = last observation carried forward; MADRS = Montgomery Åsberg Depression Rating Scale; MITT = modified intent-to-treat.

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FIGURE 4

CHANGE IN INDIVIDUAL MADRS ITEM SCORES FROM RANDOMIZATION TO WEEK 8 (MITT POPULATION; LOCF)



***p < 0.001 versus placebo.

LOCF = last observation carried forward; LSM = least squares means; MADRS = Montgomery Åsberg Depression Rating Scale; MITT = modified intent-to-treat.

With the exception of the PSQI, there were no statistically significant differences for quetiapine XR or escitalopram compared with placebo in any of the secondary endpoints (Table 2). The NNT using MADRS response at Week 8 was 10.6 for quetiapine XR and 11.3 for escitalopram compared with placebo. Post hoc analyses of remission rates at Week 8 using the criteria of MADRS total score ≤ 10 were 44.8%

TABLE 2

CHANGE FROM RANDOMIZATION AT WEEK 1 AND AT WEEK 8 IN SECONDARY EFFICACY VARIABLES (MITT POPULATION, LOCF UNLESS OTHERWISE STATED) AND TDSS TOTAL SCORES OVER TIME DURING THE DRUG-DISCONTINUATION/TAPERING FOLLOW-UP PHASE (TDSS POPULATION; OC)

| | PLACEBO (n = 153) | QUETIAPINE XR (n = 154) | ESCITALOPRAM (n = 152) |
|--------------------------------------|----------------------|----------------------------------|----------------------------------|
| Week 1 | | | |
| MADRS total score | | | |
| LSM change | -6.65 | -7.93 | -6.69 |
| Difference (95% CI) versus placebo | | -1.27 (-2.81, 0.27) p = 0.105 | -0.04 (-1.60, 1.52) p = 0.960 |
| MADRS response rate, ^a % | 12.0 | 14.5 | 14.1 |
| Odds ratio (95% CI) ^b | | 1.22 (0.62, 2.38) p = 0.562 | 1.19 (0.60, 2.33) p = 0.620 |
| Week 8 | | | |
| MADRS response rate, ^a % | 51.0 | 60.4 | 59.9 |
| Odds ratio (95% CI) ^b | | 1.47 (0.94, 2.32) p = 0.094 | 1.44 (0.91, 2.27) p = 0.116 |
| MADRS remission rate, ^c % | 35.3 | 35.7 | 40.8 |
| Odds ratio (95% CI) ^b | | 1.05 (0.66, 1.68) p = 0.839 | 1.30 (0.81, 2.07) p = 0.276 |
| HAM-D total ^d | | | |
| LSM change | -13.75 | -14.99 | -14.70 |
| Difference (95% CI) versus placebo | | -1.25 (-3.16, 0.67) p = 0.200 | -0.95 (-2.88, 0.98) p = 0.332 |
| HAM-D Item 1 ^d | | | |
| LSM change | -1.41 | -1.57 | -1.65 |
| Difference (95% CI) versus placebo | | -0.16 (-0.42, 0.10) p = 0.230 | -0.24 (-0.50, 0.02) p = 0.074 |
| HAM-A total | | | |
| LSM change | -8.28 | -9.44 | -9.67 |
| Difference (95% CI) versus placebo | | -1.16 (-2.77, 0.44) p = 0.155 | -1.39 (-3.02, 0.24) p = 0.095 |
| HAM-A psychic cluster ^e | | | |
| LSM change | -5.54 | -6.50 | -6.21 |
| Difference (95% CI) versus placebo | | -0.96 (-1.94, 0.02) p = 0.055 | -0.67 (-1.67, 0.32) p = 0.185 |

(continued)

QUETIAPINE XR MONOTHERAPY IN MDD

TABLE 2 (CONTINUED)

| | PLACEBO (n = 153) | QUETIAPINE XR (n = 154) | ESCITALOPRAM (n = 152) |
|---|----------------------|----------------------------------|----------------------------------|
| HAM-A somatic cluster ^f | | | |
| LSM change | -2.75 | -2.93 | -3.44 |
| Difference (95% CI) versus placebo | | -0.18 (-0.95, 0.59) p = 0.647 | -0.69 (-1.47, 0.09) p = 0.081 |
| CGI-S | | | |
| LSM change | -1.76 | -1.83 | -1.85 |
| Difference (95% CI) versus placebo | | -0.07 (-0.37, 0.23) p = 0.641 | -0.09 (-0.39, 0.21) p = 0.554 |
| CGI-I score 'much'/'very much' improved, % | 58.8 | 61.4 | 64.2 |
| Odds ratio (95% CI) ^b | | 1.11 (0.70, 1.75) p = 0.664 | 1.24 (0.78, 1.97) p = 0.372 |
| Q-LES-Q-SF% maximum total | | | |
| LSM change | 13.55 | 13.46 | 16.00 |
| Difference (95% CI) versus placebo | | -0.09 (-4.04, 3.86) p = 0.964 | 2.45 (-1.50, 6.39) p = 0.223 |
| Q-LES-Q-SF Satisfaction with medication (Item 15) | | | |
| Mean change | 0.2 | 1.0 | 0.4 |
| Q-LES-Q-SF Overall quality of life (Item 16) | | | |
| Mean change | 0.9 | 1.1 | 1.2 |
| PSQI global | | | |
| LSM change | -3.37 | -4.96 | -3.32 |
| Difference (95% CI) versus placebo | | -1.59 (-2.57, -0.61) p < 0.01 | 0.05 (-0.94, 1.04) p = 0.918 |
| TDSS total score, mean (SD)^d | N = 88 | N = 91^g | N = 92^g |
| Post-treatment Day 1 | 1.7 (1.8) | 3.1 (3.4) | 2.0 (2.8) |
| Post-treatment Day 3 | 2.2 (2.1) | 4.9 (4.0) | 3.4 (3.8) |
| Post-treatment Day 5 | 2.7 (2.8) | 3.7 (3.4) | 3.8 (3.5) |
| Post-treatment Day 7 | 2.7 (2.7) | 3.4 (3.6) | 4.0 (3.6) |
| Post-treatment Day 14 | 2.9 (3.4) | 3.2 (3.3) | 4.3 (3.9) |

CI = confidence interval; CGI-I = Clinical Global Impressions-Improvement; CGI-S = CGI-Severity of Illness; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression; LOCF = last observation carried forward; LSM = least squares means; MADRS = Montgomery Åsberg Depression Rating Scale; MITT = modified intent-to-treat; PSQI = Pittsburgh Sleep Quality Index; Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form; SD = standard deviation; TDSS = treatment discontinuation signs and symptoms.

p-values are versus placebo.

^aResponse defined as $\geq 50\%$ reduction from randomization in MADRS total score.

^b95% CI for odds ratio for difference versus placebo.

^cRemission defined as MADRS total score ≤ 8 .

^dObserved cases data.

^eEncompassing anxious mood, behavior at interview, depressed mood, fears, insomnia, intellectual changes, and tension.

^fEncompassing autonomic systems, cardiovascular, gastrointestinal, genitourinary, respiratory, somatic muscular, and somatic sensory.

^gPatients receiving a dose of quetiapine XR 300 mg/day or escitalopram 20 mg/day received 150 mg/day of quetiapine XR and 10 mg/day of escitalopram, respectively, from Day 57 to Day 63/post-treatment Day 7.

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($p = 0.376$) for quetiapine XR, 48.0% ($p = 0.157$) for escitalopram, and 40.5% for placebo; for MADRS total score ≤ 12 , remission rates were 55.2% ($p < 0.05$), 52.0% ($p = 0.146$), and 44.4%, respectively.

Analysis of Primary Efficacy Variable by MMRM Analysis, Patient Subgroups, and Region

Using the MMRM analysis of OC data, LSM reductions in MADRS total score at Week 8 were: quetiapine XR -20.00 ($p < 0.01$) and escitalopram -19.03 ($p = 0.189$) versus -17.34 (placebo) (Figure 2B).

Subgroup analyses of the primary efficacy variable did not reveal any discernible effects for age, gender, or disease severity (Table 3); the only statistically significant change in MADRS total score at Week 8 was for patients from Asia receiving escitalopram (-20.68 ; $p < 0.05$ versus -15.57 [placebo]). Analysis of the response rate at Week 8 by region provided similar results to those for the change in the primary efficacy variable by region at Week 8 (Table 3).

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TABLE 3

LSM CHANGE IN MADRS TOTAL SCORE FROM RANDOMIZATION TO WEEK 8 BY AGE, GENDER, ETHNICITY, DISEASE SEVERITY, AND REGION, AND MADRS RESPONSE RATES BY REGION (LOCF; MITT POPULATION^a)

| | PLACEBO (n = 153) | QUETIAPINE XR (n = 154) | ESCITALOPRAM (n = 152) |
|---|----------------------|----------------------------|---------------------------|
| Age, years | | | |
| 18–39 | -16.65 (n = 74) | -20.06 (n = 69) | -19.52 (n = 76) |
| 40–65 | -15.48 (n = 79) | -16.14 (n = 85) | -14.60 (n = 76) |
| Gender | | | |
| Male | -14.76 (n = 50) | -17.85 (n = 44) | -16.18 (n = 37) |
| Female | -16.68 (n = 103) | -17.90 (n = 110) | -17.36 (n = 115) |
| Disease severity, baseline HAM-D score | | | |
| <28 | -14.70 (n = 99) | -16.42 (n = 98) | -14.69 (n = 96) |
| ≥ 28 | -18.46 (n = 54) | -20.55 (n = 56) | -21.11 (n = 56) |
| Ethnicity | | | |
| White | -14.48 (n = 84) | -15.95 (n = 86) | -13.76 (n = 80) |
| Asian | -15.57 (n = 41) | -19.07 (n = 43) | -20.68* (n = 45) |
| Black | -21.69 (n = 25) | -22.64 (n = 20) | -21.59 (n = 22) |
| Other | -23.79 (n = 3) | -23.34 (n = 5) | -13.78 (n = 5) |

(continued)

QUETIAPINE XR MONOTHERAPY IN MDD

TABLE 3 (CONTINUED)

| | PLACEBO (n = 153) | QUETIAPINE XR (n = 154) | ESCITALOPRAM (n = 152) |
|---|----------------------|----------------------------|---------------------------|
| Region | | | |
| North America | -13.21 (n = 49) | -15.76 (n = 53) | -13.10 (n = 42) |
| South Africa | -21.21 (n = 29) | -22.20 (n = 31) | -20.06 (n = 34) |
| Asia | -15.54 (n = 36) | -19.03 (n = 37) | -21.06* (n = 42) |
| Europe | -15.70 (n = 16) | -15.20 (n = 14) | -12.14 (n = 18) |
| MADRS response rate by region, % | | | |
| North America | 38.6 (n = 57) | 50.0 (n = 62) | 42.0 (n = 50) |
| South Africa | 74.3 (n = 35) | 78.1 (n = 32) | 71.8 (n = 39) |
| Asia | 48.8 (n = 41) | 67.4 (n = 43) | 79.5** (n = 44) |
| Europe | 50.0 (n = 20) | 47.1 (n = 17) | 36.8 (n = 19) |

HAM-D = Hamilton Rating Scale for Depression; LOCF = last observation carried forward;
LSM = least squares means; MADRS = Montgomery Åsberg Depression Rating Scale;
MITT = modified intent-to-treat.

*p < 0.05; **p < 0.01 versus placebo for that subgroup.

ⁿ in parenthesis refers to the number of patients assessed.

Safety and Tolerability

The overall incidence of AEs was 86.6% (quetiapine XR), 81.4% (escitalopram), and 73.5% (placebo); serious AEs (SAEs) were reported by four (2.5%), three (1.9%), and one (0.6%) patients, respectively. Two SAEs were considered treatment related by the study investigator (depression and suicide attempt) and occurred in one patient (who had not received a dose increase) in the quetiapine XR group and led to withdrawal of the patient from the study. Treatment-related AEs were reported by 79.6%, 67.9%, and 52.3% of patients in the quetiapine XR, escitalopram, and placebo treatment groups, respectively. There were no deaths in this study.

The percentages of patients who discontinued due to an AE were 15.9%, 7.1%, and 4.5% for quetiapine XR, escitalopram, and placebo, respectively. The most frequently reported AEs leading to discontinuation were: sedation and dizziness (each n = 5) with quetiapine XR; nausea (n = 3), dizziness, and depressed mood (each n = 2) with escitalopram; and palpitations and insomnia (each n = 3) with placebo. The most common AEs (>5% in any group) and AEs of special interest (EPS, sexual dysfunction, suicidality, somnolence, and nausea and vomiting) are shown in Table 4.

QUETIAPINE XR MONOTHERAPY IN MDD

TABLE 4

MOST FREQUENTLY REPORTED AEs (OCCURRING AT AN INCIDENCE OF >5% IN ANY GROUP) AND AEs OF SPECIAL INTEREST (SAFETY POPULATION)

| | PLACEBO (n = 155) | QUETIAPINE XR (n = 157) | ESCITALOPRAM (n = 156) |
|---|----------------------|----------------------------|---------------------------|
| Most frequently reported AEs, MedDRA preferred term, n (%) | | | |
| Any AE | 114 (73.5) | 136 (86.6) | 127 (81.4) |
| Dry mouth | 13 (8.4) | 60 (38.2) | 22 (14.1) |
| Somnolence ^a | 6 (3.9) | 56 (35.7) | 13 (8.3) |
| Dizziness | 22 (14.2) | 53 (33.8) | 29 (18.6) |
| Headache | 49 (31.6) | 41 (26.1) | 49 (31.4) |
| Nausea | 30 (19.4) | 34 (21.7) | 47 (30.1) |
| Insomnia | 22 (14.2) | 22 (14.0) | 23 (14.7) |
| Constipation | 7 (4.5) | 20 (12.7) | 13 (8.3) |
| Diarrhea | 11 (7.1) | 19 (12.1) | 19 (12.2) |
| Fatigue | 8 (5.2) | 19 (12.1) | 14 (9.0) |
| Sedation | 5 (3.2) | 17 (10.8) | 8 (5.1) |
| Anxiety | 4 (2.6) | 12 (7.6) | 7 (4.5) |
| Dyspepsia | 9 (5.8) | 12 (7.6) | 5 (3.2) |
| Increased appetite | 6 (3.9) | 11 (7.0) | 3 (1.9) |
| Myalgia | 6 (3.9) | 11 (7.0) | 12 (7.7) |
| Abdominal pain upper | 6 (3.9) | 9 (5.7) | 5 (3.2) |
| Hypersomnia | 1 (0.6) | 9 (5.7) | 2 (1.3) |
| Irritability | 8 (5.2) | 9 (5.7) | 8 (5.1) |
| Vomiting | 3 (1.9) | 9 (5.7) | 6 (3.8) |
| Arthralgia | 5 (3.2) | 8 (5.1) | 1 (0.6) |
| Hyperhidrosis | 9 (5.8) | 8 (5.1) | 12 (7.7) |
| Influenza | 4 (2.6) | 8 (5.1) | 3 (1.9) |
| Palpitations | 6 (3.9) | 6 (3.8) | 8 (5.1) |
| Nasopharyngitis | 9 (5.8) | 2 (1.3) | 7 (4.5) |
| AEs of special interest, n (%) | | | |
| EPS ^{b,c} | 8 (5.2) | 13 (8.3) | 15 (9.6) |
| Sexual dysfunction ^{d,e} | 3 (1.9) | 1 (0.6) | 4 (2.6) |
| Suicidality ^f | 0 (0.0) | 2 (1.3) | 2 (1.3) |
| Somnolence ^{g,h} | 11 (7.1) | 72 (45.9) | 23 (14.7) |
| Nausea and vomiting ^{i,j} | 32 (20.6) | 41 (26.1) | 48 (30.8) |

AE = adverse event; EPS = extrapyramidal symptoms; MedDRA = Medical Dictionary for Regulatory Affairs.

^aThe median times to first onset of somnolence were 2.0, 2.0, and 4.0 days for placebo, quetiapine XR, and escitalopram, respectively.

^bIncludes AEs with the MedDRA terms akathisia, bradykinesia, dyskinesia, dystonia, extrapyramidal disorder, hypertonia, hypokinesia, muscle rigidity, psychomotor hyperactivity, restlessness, and tremor.

^cOf these AEs, one was severe in intensity: restlessness in the quetiapine XR group.

^dIncludes AEs with the MedDRA terms anorgasmia, ejaculation failure, erectile dysfunction, libido decreased, and loss of libido.

^eOf these AEs (all occurred in male patients), two were severe in intensity: libido decreased and ejaculation failure, both in the escitalopram group.

^fIncludes AEs with the MedDRA preferred terms: suicidal behavior, suicidal ideation, and suicide attempt.

^gIncludes AEs with the MedDRA preferred terms: lethargy, sedation, sluggishness, and somnolence.

^hMajority of AEs were mild/moderate in intensity; there were eight AEs in the quetiapine XR group, three in the escitalopram group, and one in the placebo group that were of severe intensity.

ⁱIncludes AEs with the MedDRA preferred terms: nausea, regurgitation, and vomiting.

^jOf these AEs, six each in the quetiapine XR and escitalopram groups and two in the placebo group were of severe intensity.

EPS

At the end of treatment, 87.6%, 91.7%, and 91.1% of patients in the quetiapine XR, escitalopram, and placebo groups, respectively, experienced an improvement/no change in SAS total scores; 96.6%, 94.5%, and 95.9% of patients, respectively, experienced an improvement/no change in BARS global scores.

Sexual Dysfunction

For males, mean improvement from randomization in CSFQ total score at end of treatment was 2.5 with quetiapine XR, 2.4 with escitalopram, and 0.6 with placebo; for females, these changes were 2.4, 1.4, and 1.6, respectively.

Suicidality

AEs potentially related to suicidality were reported in four patients; two in the quetiapine XR group (suicide attempt [SAE] and suicide ideation), which were considered treatment related, and two in the escitalopram group (suicidal behavior [SAE] and suicide ideation), which were considered not to be treatment related. All four patients were withdrawn from the study. The proportions of patients with a MADRS Item 10 (suicidal thought) score ≥ 4 at any time following randomization were 2.7%, 4.8%, and 1.4% for quetiapine XR, escitalopram, and placebo, respectively (OC data).

Somnolence

The majority of AEs potentially related to somnolence occurred within the first 4 days of treatment and were generally mild or moderate in intensity (87.0% to 90.9%). Of the total number of patients reporting somnolence, 52.1%, 50.0%, and 40.0% reported this as an ongoing AE on the last day of treatment in the quetiapine XR, escitalopram, and placebo groups, respectively. The incidence of hypersomnia was higher in the quetiapine XR (5.7%) and escitalopram groups (1.3%) compared with placebo (0.6%) (Table 4).

Vital Signs

Two patients each in the quetiapine XR and placebo groups had AEs of syncope; all AEs, except one in the quetiapine XR group, were considered treatment related. There were no notable differences in the mean changes from randomization to end of treatment in vital signs (including orthostatic changes) or ECG results between treatment groups. Mean changes at end of treatment in supine pulse were +1.7,

−3.0, and −2.0 bpm in the quetiapine XR, escitalopram, and placebo groups; mean changes in the QTc (Fridericia) interval at Week 8 were −0.5, +4.0, and −1.1 msec, respectively.

Clinical Laboratory Parameters

One patient in the escitalopram group experienced an AE of neutrophil count decreased ($<0.8 \times 10^9$ cells/L), which was neither serious nor considered related to study treatment.

Eight AEs potentially related to diabetes mellitus (Medical Dictionary for Regulatory Affairs [MedDRA] preferred terms: thirst, polyuria, and blood glucose increased) were reported during the study: thirst (4 [2.5%]) and polyuria (1 [0.6%]) in the quetiapine XR group; thirst and polyuria (1 [0.6%] each) in the escitalopram group; and blood glucose increased (1 [0.6%]) in the placebo group; of these, one AE (polyuria) in the escitalopram group was severe in intensity.

Table 5 shows mean changes and clinically important shifts from normal to clinically important values (randomization to end of treatment) for clinical laboratory parameters, including glucose, lipid, and prolactin data. Mean changes (randomization to end of treatment) in confirmed fasting glucose were +0.4, +0.3, and +1.2 mg/dL in the quetiapine XR, escitalopram, and placebo groups, respectively; one (0.8%), three (2.4%), and three (2.5%) patients, respectively, had a clinically relevant increase in fasting glucose at treatment end. At treatment end, clinically relevant increases in total cholesterol were reported for four (3.7%), five (5.0%), and three (3.1%) patients, respectively, and clinically relevant increases in low-density lipoprotein (LDL)-cholesterol were reported for three (2.8%), four (3.9%), and four (3.9%) patients, respectively. Clinically relevant decreases in high-density lipoprotein (HDL)-cholesterol at treatment end occurred in eight (8.5%), six (6.3%), and three (3.2%) patients, respectively. The mean changes in triglyceride levels (randomization to treatment end) were +8.4, +3.6, and +3.6 mg/dL in the quetiapine XR, escitalopram, and placebo groups, respectively (Table 5); clinically important increases occurred in 14 (13.1%), eight (7.8%), and five (5.0%) patients, respectively.

Body Weight

At the end of treatment, patients in the quetiapine XR, escitalopram, and placebo groups experienced a mean (SD) weight change of +0.6 (2.4), −0.1 (2.0), and −0.1 (1.9) kg (Table 5); the proportion of patients experiencing a $\geq 7\%$ increase in weight was 1.9%, 3.2%, and 0.6%, respectively.

TABLE 5

CHANGES IN CLINICAL LABORATORY PARAMETERS AND BODY WEIGHT AND PROPORTION OF PATIENTS WITH CLINICALLY RELEVANT SHIFTS (DEFINED WITHIN THE TABLE) FROM RANDOMIZATION TO END OF TREATMENT (SAFETY POPULATION; LOCF)

| | PLACEBO (n = 155) | QUETIAPINE XR (n = 157) | ESCITALOPRAM (n = 156) |
|--|----------------------|----------------------------|---------------------------|
| Glucose (mg/dL)^a | | | |
| Mean (SD) at randomization | 92.0 (11.9) | 92.7 (10.9) | 93.0 (13.8) |
| Mean (SD) change | 1.2 (11.4) | 0.4 (9.6) | 0.3 (14.4) |
| Total cholesterol (mg/dL)^a | | | |
| Mean (SD) at randomization | 195.3 (41.1) | 192.8 (40.1) | 194.7 (40.2) |
| Mean (SD) change | -4.5 (26.1) | -4.0 (26.2) | -3.0 (27.4) |
| HDL-cholesterol (mg/dL)^a | | | |
| Mean (SD) at randomization | 54.2 (15.0) | 53.6 (17.0) | 54.1 (14.4) |
| Mean (SD) change | -0.9 (8.5) | -1.1 (11.0) | -1.1 (8.3) |
| LDL-cholesterol (mg/dL)^a | | | |
| Mean (SD) at randomization | 116.8 (33.6) | 113.4 (34.8) | 116.6 (36.4) |
| Mean (SD) change | -3.7 (22.0) | -4.6 (23.7) | -2.5 (26.2) |
| Triglycerides (mg/dL)^a | | | |
| Mean (SD) at randomization | 122.3 (71.4) | 131.0 (72.3) | 122.2 (70.6) |
| Mean (SD) change | 3.6 (52.6) | 8.4 (62.7) | 3.6 (51.6) |
| Prolactin (ng/mL)^b | | | |
| Mean (SD) at randomization | 9.2 (11.4) | 9.4 (7.2) | 10.0 (12.3) |
| Mean (SD) change | 0.3 (5.2) | -0.4 (7.7) | -0.6 (6.1) |
| Weight (kg) | | | |
| Mean (SD) at randomization | 70.4 (19.3) | 73.3 (21.3) | 72.0 (18.0) |
| Mean (SD) change | -0.1 (1.9) | 0.6 (2.4) | -0.1 (2.0) |
| Clinically relevant shifts at end of treatment, n (%) | | | |
| Glucose ≥ 126 mg/dL ^a | 3 (2.5) | 1 (0.8) | 3 (2.4) |
| Total cholesterol ≥ 240 mg/dL ^a | 3 (3.1) | 4 (3.7) | 5 (5.0) |
| LDL-cholesterol ≥ 160 mg/dL ^a | 4 (3.9) | 3 (2.8) | 4 (3.9) |
| HDL-cholesterol ≤ 40 mg/dL ^a | 3 (3.2) | 8 (8.5) | 6 (6.3) |
| Triglycerides ≥ 200 mg/dL ^a | 5 (5.0) | 14 (13.1) | 8 (7.8) |
| Weight $\geq 7\%$ increase | 1 (0.6) | 3 (1.9) | 5 (3.2) |

HDL = high-density lipoprotein; LDL = low-density lipoprotein; LOCF = last observation carried forward; SD, standard deviation.

^aFasting status was determined based upon a documented report from the patient that last meal was ≥ 8 hours before blood sample taken for baseline and post-randomization laboratory measurements. However, not all samples could be confirmed as fasted despite there being an 8-hour interval since the last meal, as patients could have had caloric intake.

^bNormal prolactin range: 2–20 ng/mL (males); 2–29 ng/mL (females).

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Two-week Drug-Discontinuation/Tapering Follow-up Phase

The most common AEs (>2 patients) during the drug-discontinuation/tapering follow-up phase were: headache (n = 6) in the quetiapine XR group; insomnia and nausea (each n = 4), headache, dizziness, and irritability (each n = 3) in the escitalopram group. No AEs were reported by >2 patients in the placebo group.

Mean TDSS total scores are shown in Table 2. The most pronounced signs and symptoms following quetiapine XR discontinuation related to insomnia, nausea, chills, headache, and muscle aches; other signs and symptoms noted for quetiapine XR were crying, agitation, sweating, muscle tension, fatigue, and vomiting. After discontinuation of escitalopram, signs and symptoms included crying, agitation, mood swings, vivid and unusual dreams, sweating, muscle aches, muscle tension, fatigue, and diarrhea.

DISCUSSION

This study assessed the efficacy and tolerability of quetiapine XR monotherapy in patients with MDD. Although quetiapine XR (150/300 mg/day) monotherapy and escitalopram (10/20 mg/day) monotherapy both reduced depressive symptoms, significantly superior efficacy over placebo was not established for either agent for the primary efficacy analysis or for most secondary efficacy endpoints. Lack of superior efficacy over placebo with escitalopram at clinically efficacious doses indicates a lack of assay sensitivity in this study and, coupled with lack of separation from placebo with quetiapine XR, means that this is a failed study rather than a negative study (the latter being characterized by the study drug not separating from placebo while the other active treatment does). In addition, the discrepancy between the primary LOCF analysis and the OC data suggests that the primary analysis may not be robust.

Failure to demonstrate statistical difference from placebo in antidepressant trials is not uncommon, with failure rates of up to 60% being reported.²⁶⁻²⁹ However, it is of note that of eight studies from a clinical development program evaluating the effectiveness of quetiapine XR in patients with MDD, this is the only failed study.⁵⁻¹¹ It is important that findings from negative/failed studies are reported and that the reasons underlying such outcomes are considered, as this may aid the design of future clinical studies.

The results from this failed international study are inconsistent with a previously reported US study of quetiapine XR (150/300 mg/day; D1448C00003) that used an identical modified fixed-dose design, but had no active control.⁵ Bortnick et al reported that quetiapine XR

(150/300 mg/day) significantly improved depressive symptoms from Week 1 onwards. The improvement in MADRS total score at Week 8 in quetiapine XR-treated patients was similar across the two studies (-17.21 and -16.49). However, the improvement in placebo-treated patients was larger in our study (-15.61) than in Study D1448C00003 (-13.10), suggesting that placebo response may have accounted for the difference in outcomes. Similar improvements were observed in placebo-treated patients at Weeks 1 to 4 across the two studies, including similar rates of placebo-treated patients requiring dose increases (approximately 26%). This observation suggests that any increases in placebo response for the current study occurred after the Week 4 assessment.

Literature suggests that study design and disease characteristics may play a part in increased placebo response. While the study designs were nearly identical, the probability of receiving placebo was lower (33%) in the current study compared to D1448C00003 (50%). Trials with a lower probability of receiving placebo have been reported to have higher placebo response rates.³⁰ Disease characteristics in the present study signaled a lack of depressive chronicity that (given shorter illness duration) has been associated with an increased placebo response in patients with MDD.^{31,32} As compared with Study D1448C00003, more patients in the present study were experiencing single (first) MDD episode (23.7% versus 10.0%, respectively), and patients had more recently experienced their first depressive episode (9.4 versus 13.6 years).

Analyses of the primary endpoint by age, gender, baseline disease severity, and ethnicity did not reveal any discernible effects for these variables.

Quetiapine XR monotherapy was generally well tolerated in this study; the pattern of AEs was consistent with the known pharmacological profile of quetiapine.^{3,4} No new safety findings were noted for escitalopram.¹⁶ Quetiapine XR was not associated with an increased incidence of AEs related to sexual dysfunction, QT prolongation, syncope, or neutropenia compared with placebo, nor with any notable changes in vital signs. A relationship between either quetiapine XR or escitalopram and increased suicidality could not be established in this study; black box warnings about suicidality are required on package inserts for antidepressants.³³

There were no notable differences between treatment groups in mean changes from randomization for any clinical laboratory parameters in this study; however, there was a greater incidence in shifts to clinically important high triglycerides levels in the quetiapine XR group compared with placebo and escitalopram. In the quetiapine XR group, body weight changes were consistent with those reported previously in patients with MDD receiving quetiapine XR as acute monotherapy.⁵⁻⁷

Clinical recommendations advise serum glucose, lipid, and insulin levels and body weight/body mass index are assessed during antipsychotic treatment.³⁴

Study limitations include the short study duration and exclusion of patients with comorbidities. Furthermore, the study design precluded comparison of quetiapine XR 150 versus 300 mg/day, as it mimicked medication titration used in clinical practice when a patient does not respond to the initial treatment dose. However, patients in the study may have required different dose adjustments than those allowed by the modified fixed-dose study design. Furthermore, restrictions on concomitant medications are not reflective of clinical practice. The discrepancy between LOCF and OC analyses may be due to a possible bias of the LOCF analysis towards initial values at randomization; however, an analysis to investigate this further was beyond the scope of this report.

In summary, neither quetiapine XR (150/300 mg/day) nor the active comparator escitalopram (10/20 mg/day) demonstrated statistically significant separation from placebo in the primary efficacy outcome variable in this study. The placebo response observed here may have contributed to the lack of significant differences for quetiapine XR and the active control escitalopram compared with placebo. ❖

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REFERENCES

1. Masand PS. Tolerability and adherence issues in antidepressant therapy. *Clin Ther.* 2003; 25:2289–2304.
2. Howland RH. Sequenced Treatment Alternatives to Relieve Depression (STAR*D). Part 2: Study outcomes. *J Psychosoc Nurs Ment Health Serv.* 2008;46:21–24.
3. AstraZeneca. Seroquel XR—Summary of Product Characteristics for Ireland. Available at: <http://www.medicines.ie/medicine/13032/SPC/Seroquel+XR+50mg%2c+150mg%2c+200mg%2c+300mg%2c+400mg+prolonged-release+tablets/>. Accessed: 11/14/2011.
4. AstraZeneca. Seroquel XR (quetiapine fumarate) extended-release tablets/US prescribing information. Available at: <http://www1.astrazeneca-us.com/pi/seroquelxr.pdf>. Accessed: 11/14/2011.
5. Bortnick B, El-Khalili N, Banov M, et al. Efficacy and tolerability of extended release quetiapine fumarate (quetiapine XR) monotherapy in major depressive disorder: a placebo-controlled, randomized study. *J Affect Disord.* 2011;128:83–94.
6. Cutler AJ, Montgomery SA, Feifel D, et al. Extended release quetiapine fumarate monotherapy in major depressive disorder: a placebo- and duloxetine-controlled study. *J Clin Psychiatry.* 2009;70:526–539.
7. Weisler R, Joyce M, McGill L, et al. Extended release quetiapine fumarate monotherapy for major depressive disorder: results of a double-blind, randomized, placebo-controlled study. *CNS Spectr.* 2009;14:299–313.
8. Bauer M, Pretorius HW, Constant EL, et al. Extended-release quetiapine as adjunct to an antidepressant in patients with major depressive disorder: results of a randomized, placebo-controlled, double-blind study. *J Clin Psychiatry.* 2009;70:540–549.
9. El-Khalili N, Joyce M, Atkinson S, et al. Extended-release quetiapine fumarate (quetiapine XR) as adjunctive therapy in major depressive disorder (MDD) in patients with an inadequate response to ongoing antidepressant treatment: a multicentre, randomized, double-blind, placebo-controlled study. *Int J Neuropsychopharmacol.* 2010;13:917–932.

10. Liebowitz M, Lam RW, Lepola U, et al. Efficacy and tolerability of extended release quetiapine fumarate monotherapy as maintenance treatment of major depressive disorder: a randomized, placebo-controlled trial. *Depress Anxiety*. 2010;27:964–976.
11. Katila H, Mezhebovsky I, Mulroy A, et al. Randomized, double-blind study of the efficacy and tolerability of extended release quetiapine fumarate (quetiapine XR) monotherapy in elderly patients with major depressive disorder. *Am J Geriatr Psychiatry*. In press.
12. Glick ID, Suppes T, DeBattista C, et al. Psychopharmacologic treatment strategies for depression, bipolar disorder, and schizophrenia. *Ann Intern Med*. 2001;134:47–60.
13. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59 (Suppl 20):22–33.
14. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56–62.
15. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382–389.
16. Forest Pharmaceuticals, Inc. Escitalopram prescribing information. Available at: http://www.frx.com/pi/lexapro_pi.pdf. Accessed: 5/1/2011.
17. National Institutes of Mental Health. CGI: Clinical Global Impressions. In: Guy W, Bonato RR, eds. *Manual for the ECDEU Assessment Battery*. Chevy Chase: NIMH; 1970:1–6.
18. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. 1959;32:50–55.
19. Endicott J, Nee J, Harrison W, et al. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. *Psychopharmacol Bull*. 1993;29:321–326.
20. Buysse DJ, Reynolds CF, III, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28:193–213.
21. Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand Suppl*. 1970;212:11–19.
22. Barnes TRE. A rating scale for drug-induced akathisia. *Br J Psychiatry*. 1989;154:672–676.
23. Clayton AH, McGarvey EL, Clavet GJ. The Changes in Sexual Functioning Questionnaire (CSFQ): development, reliability, and validity. *Psychopharmacol Bull*. 1997;33:731–745.
24. Michelson D, Fava M, Amsterdam J, et al. Interruption of selective serotonin reuptake inhibitor treatment. Double-blind, placebo-controlled trial. *Br J Psychiatry*. 2000;176:363–368.
25. Rosenbaum JF, Fava M, Hoog SL, et al. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. *Biol Psychiatry*. 1998;44:77–87.
26. Khan A, Schwartz K. Study designs and outcomes in antidepressant clinical trials. *Essent Psychopharmacol*. 2005;6:221–226.
27. Yang H, Cusin C, Fava M. Is there a placebo problem in antidepressant trials? *Curr Top Med Chem*. 2005;5:1077–1086.
28. Fava M, Evins AE, Dorer DJ, et al. The problem of the placebo response in clinical trials for psychiatric disorders: culprits, possible remedies, and a novel study design approach. *Psychother Psychosom*. 2003;72:115–127.
29. Kobak KA, Kane JM, Thase ME, et al. Why do clinical trials fail? The problem of measurement error in clinical trials: time to test new paradigms? *J Clin Psychopharmacol*. 2007;27:1–5.
30. Papakostas GI, Fava M. Does the probability of receiving placebo influence clinical trial outcome? A meta-regression of double-blind, randomized clinical trials in MDD. *Eur Neuropsychopharmacol*. 2009;19:34–40.
31. Posternak MA, Zimmerman M, Keitner GI, et al. A reevaluation of the exclusion criteria used in antidepressant efficacy trials. *Am J Psychiatry*. 2002;159:191–200.
32. Stein DJ, Baldwin DS, Dolberg OT, et al. Which factors predict placebo response in anxiety disorders and major depression? An analysis of placebo-controlled studies of escitalopram. *J Clin Psychiatry*. 2006;67:1741–1746.
33. FDA. Antidepressant use in children, adolescents and adults. Available at: <http://www.fda.gov/cder/drug/antidepressants/default.htm>. Accessed: 5/1/2011.
34. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, et al. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*. 2004;27:596–601.