Extended-Release Quetiapine as Adjunct to an Antidepressant in Patients With Major Depressive Disorder: Results of a Randomized, Placebo-Controlled, Double-Blind Study

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Objective: This 6-week, randomized, double-blind study evaluated efficacy and safety of adjunctive extended-release (XR) quetiapine in patients with major depressive disorder (MDD) and an inadequate response to ≥ 1 antidepressant.

Method: Male or female patients aged 18 to 65 years with DSM-IV-TR MDD were randomly assigned to receive quetiapine XR (150 or 300 mg/day) or placebo adjunctive to continuing antidepressant. Primary endpoint was change from randomization to week 6 in Montgomery-Asberg Depression Rating Scale (MADRS) total score. Secondary variables included MADRS response (≥ 50% reduction in score from randomization) at weeks 1 and 6, MADRS remission (≤ 8 total score) at week 6, and week 6 change in Hamilton Rating Scale for Depression and Hamilton Rating Scale for Anxiety total scores. Safety was assessed throughout the study. The study was conducted between May 8, 2006, and April 7, 2007.

Results: Four hundred ninety-three patients were randomly assigned. Mean change from randomization to week 6 in MADRS score was –15.26 and –14.94 for quetiapine XR 150 mg/day and 300 mg/day, respectively (both $p < .01$ vs. placebo [–12.21]). Quetiapine XR showed separation from placebo in MADRS score from week 1 ($p < .001$) onward. The MADRS response rates were 55.4%, 57.8%, and 46.3% for quetiapine XR 150 mg/day ($p = .107$ vs. placebo), 300 mg/day ($p < .05$), and placebo, respectively; MADRS remission rates were 36.1% ($p < .05$ vs. placebo), 31.1% ($p = .126$), and 23.8% for quetiapine XR 150 mg/day, 300 mg/day, and placebo, respectively. Withdrawal rates due to adverse events were 6.6%, 11.7%, and 3.7% with quetiapine XR 150 mg/day, 300 mg/day, and placebo, respectively. The most common adverse events were dry mouth (20.4%, 35.6%, and 6.8%) and somnolence (16.8%, 23.3%, and 3.1%).

Conclusions: Adjunctive quetiapine XR (150 mg/day and 300 mg/day) was effective in patients with MDD who had shown an inadequate response to antidepressant treatment. Significant reduction of depressive symptoms occurred as early as week 1. Findings were consistent with the known safety and tolerability profile of quetiapine.

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Patients with major depressive disorder (MDD) require effective treatment to reduce symptoms and improve functional disability. However, achieving an adequate response in patients with MDD continues to be a challenge; existing antidepressants are not effective at achieving an adequate initial response in many patients with MDD, with around 50% of patients not achieving a response and 60% to 70% not achieving full remission of symptoms.[1,2] Possible treatment strategies for patients with MDD who are nonresponsive to an adequate trial of a standard antidepressant include switching, combination with another antidepressant with a different mechanism of action, or augmentation with a nonantidepressant drug.[3] Augmentation options include lithium[4] and benzodiazepines, and, recently, attention has turned to the atypical antipsychotics.[5,6]

Previously reported studies have shown that quetiapine may provide clinical benefits as an adjunct to

antidepressants for the treatment of MDD. Yargic and colleagues[7] found that quetiapine as adjunct therapy to paroxetine led to significantly greater improvements in symptoms compared with paroxetine alone. McIntyre and colleagues[8] showed that quetiapine augmentation of venlafaxine or a selective serotonin reuptake inhibitor (SSRI) led to significantly greater improvements in efficacy from week 1 onward in patients with MDD and comorbid anxiety and residual depressive symptoms. Also in patients with treatment-resistant depression, Doree and colleagues[9] conducted an open-label comparative study of quetiapine and lithium as adjunct therapy to antidepressant therapy and found that quetiapine-treated patients showed significantly greater improvements in assessments of efficacy compared with lithium-treated patients. Quetiapine has been shown to have antidepressant effects; in 2 large, double-blind, randomized, phase III, placebo-controlled studies, quetiapine was effective as a monotherapy in the acute treatment of patients with depression associated with bipolar I or II disorder.[10,11] This evidence provides the rationale for investigating extended-release (XR) quetiapine as adjunct therapy in MDD. Furthermore, recent preclinical data have highlighted that the metabolite of quetiapine, norquetiapine, inhibits norepinephrine reuptake by blocking the norepinephrine transporter.[12] Antagonism of the norepinephrine transporter is a common pathway affected by many antidepressants.

This study (ONYX: D1448C00007) evaluated quetiapine XR as an adjunct to antidepressant therapy. The primary hypothesis was that quetiapine XR 150 mg/day and 300 mg/day plus antidepressant would be more effective than an antidepressant alone in reducing symptoms of depression following 6 weeks of treatment in patients with MDD who had an inadequate response to their antidepressant therapy.

METHOD

Study Design

This was a 6-week, randomized, double-blind, parallel-group, placebo-controlled, phase III, double-dummy study conducted between May 8, 2006, and April 7, 2007, in 87 centers in Australia, Canada, Europe, and South Africa. The study was performed in accordance with the Declaration of Helsinki, the International Conference of Harmonisation, Good Clinical Practice guidelines, and applicable regulatory requirements. At each study center, institutional review board or independent ethics committee approval was obtained. Following randomization, study visits occurred at weeks 1, 2, 4, and 6.

Patients

Male or female patients aged 18 to 65 years with a documented *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR)[13] diagnosis of MDD (single episode [296.2x] or recurrent [296.3x]) were eligible for inclusion in this study. Patients' diagnoses were confirmed by the Mini-International Neuropsychiatric Interview.[14]

Patients were outpatients at enrollment and met the following criteria: a Hamilton Rating Scale for Depression (HAM-D)[15] 17-item total score ≥ 20 and a HAM-D item 1 (depressed mood) score ≥ 2 at enrollment and randomization and a history of an inadequate response during the current episode to amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline, or venlafaxine, which were given for ≥ 6 weeks at adequate doses (minimum effective dose according to label and including at least 1 dose increase as permitted by label).

Exclusion criteria included any DSM-IV Axis I disorder other than MDD within 6 months prior to enrollment; any DSM-IV Axis II disorder significantly impacting the patient's current psychiatric status; duration of current MDD episode > 12 months or < 4 weeks from enrollment; substance or alcohol abuse or dependence, as defined by DSM-IV criteria, within 6 months prior to enrollment; any clinically significant medical illness, such as renal or hepatic impairment, or coronary artery disease; conditions that could affect absorption or metabolism of study medication; risk of suicide or homicide (in the investigator's opinion); a HAM-D item 3 score of ≥ 3; or a suicide attempt within the past 6 months. Patients requiring psychotherapy (other than supportive psychotherapy) during the study were also excluded, unless psychotherapy had been ongoing for ≥ 3 months before randomization. In addition, the use of drugs that induce or inhibit the hepatic metabolizing cytochrome P450 3A4 enzymes (for example, fluvoxamine) was not permitted within 2 weeks prior to randomization. Patients were excluded from the study if they had received quetiapine > 25 mg/day for insomnia within 7 days before randomization, had a known lack of response following 4 weeks' treatment with quetiapine ≥ 50 mg/day for depression, or were receiving quetiapine ≥ 50 mg/day at enrollment.

After complete description of the study to the patients, written informed consent was obtained.

Treatment

Following a 14-day washout period for the discontinuation of prohibited medications, eligible patients were maintained on the antidepressant dose with which they had entered the study and then were randomly assigned (1:1:1 ratio) to receive 6 weeks of double-blind treatment with 1 of 3 treatment regimens as adjunctive therapy to ongoing antidepressant treatment: quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, or placebo. Quetiapine XR or placebo were administered orally once daily in the evening.

Titration of quetiapine XR to target dose was 50 mg/day on days 1 and 2, 150 mg/day on days 3 and 4, and

300 mg/day on day 5. Ongoing antidepressant treatment was maintained at the same dose throughout the study.

Use of other psychoactive medication was not allowed, with the exception of hypnotics to treat insomnia. Sleep medication, including benzodiazepines (≤ 2 mg/day lorazepam equivalent), could be continued if it had been used consistently for ≥ 28 days before enrollment. Anticholinergics were permitted for the treatment of extrapyramidal symptoms (EPS) but not prophylactically.

Efficacy Evaluations

The primary endpoint was change from randomization to week 6 in Montgomery-Asberg Depression Rating Scale (MADRS)[16] total score. Efficacy change data were calculated as least squares means change unless otherwise specified.

Secondary endpoints included change in MADRS total score from randomization to each assessment starting at week 1 (day 8); MADRS response rates (≥ 50% reduction in score from randomization) at week 1 and week 6; MADRS remission rates (MADRS total score ≤ 8) at week 6 (post hoc analyses using remission definitions of MADRS total score ≤ 10 and ≤ 12 at week 6 were also conducted); change from randomization to week 6 in HAM-D scores (total, item 1, anxiety items, and sleep disturbance items), Hamilton Rating Scale for Anxiety (HAM-A)[17] scores (total score and psychic and somatic anxiety subscale), and Clinical Global Impressions-Severity of Illness scale (CGI-S)[18] scores; and the proportion of patients with a CGI-Improvement scale (CGI-I)[18] score of 1 ("very much improved") or 2 ("much improved") at week 6. Additional secondary endpoints were change from randomization to week 6 in Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)[19] short form percent maximum total score, overall quality of life (item 16) score, and satisfaction with medication (item 15) score and change from randomization to week 6 in Pittsburgh Sleep Quality Index (PSQI)[20] total score.

Investigators and study personnel received central and standardized training to ensure consistency throughout the study. All raters administering the MADRS and HAM-D scales received computer-based training and were certified by AstraZeneca or their designee. To minimize scoring variability among raters, every effort was made to ensure that the same trained rater conducted all assessments for a given patient on a specific scale. For the primary efficacy measure (MADRS) and the inclusion criteria (HAM-D), 214 raters were approved and certified by the sponsor. The κ values (used to verify rater reliability) for MADRS assessments at baseline and at follow-up were 0.845 and 0.850, respectively.

Safety and Tolerability

Adverse events were reported throughout the study. In addition, unsolicited serious adverse events were recorded for up to 30 days after the last dose of study medication. Adverse events were followed up until resolution or the investigator decided this was unnecessary. Plasma samples to measure concentrations of antidepressants and their metabolites were taken predose at randomization and at weeks 2 and 4. Physical examination, laboratory measurements, and electrocardiogram were conducted at enrollment and at week 6. Body weight, vital signs, and concomitant medication were recorded at enrollment and at all subsequent visits. Barnes Akathisia Scale (BAS)[21] and Simpson-Angus Scale[22] scores (to evaluate parkinsonian symptoms and akathisia) and Changes in Sexual Functioning Questionnaire (CSFQ)[23] scores were assessed at randomization and at weeks 4 and 6.

Statistical Analysis

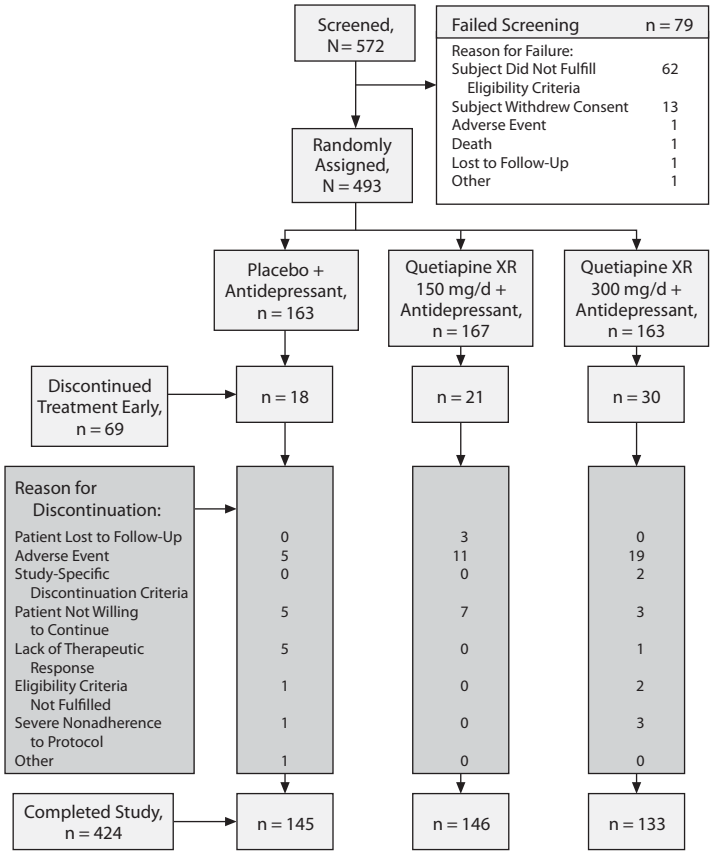
The primary efficacy analysis used an analysis of covariance (ANCOVA) model (with treatment, center, and baseline MADRS score as variables); the null hypothesis was that there was no difference between quetiapine XR and placebo in the primary efficacy endpoint. Comparisons were made between each quetiapine XR group and placebo. Point estimates, 95% confidence intervals, and p values were reported. A robustness analysis using the per-protocol population was also performed. Because 2 dose groups were compared with placebo, the primary analysis was adjusted for multiplicity using the Simes-Hommel procedure.[24]

The target sample size was based on an expected difference in the change in MADRS total score from randomization to week 6 between quetiapine XR and placebo of 3.5 points and a standard deviation (SD) of 9 points. For 90% power, 140 evaluable patients per group would be required (2-sided test at a 5% significance level, i.e., $\alpha = .05$). From earlier studies, it was expected that 93% of patients assigned to randomized treatment would be evaluable; therefore, approximately 450 patients should be assigned to randomized treatment.

Three patient populations were employed: the modified intent-to-treat (mITT) population (all patients assigned to randomized treatment who took study medication and who had a MADRS assessment at randomization and at least 1 valid MADRS assessment after randomization), the per-protocol population (a subset of the mITT population of those patients who had no significant protocol violations or deviations affecting efficacy), and the safety population (all randomized patients who received at least 1 dose of study medication).

An ANCOVA was used to assess change in the Q-LES-Q percent maximum total score from randomization to week 6 (center was included as a random effect and treatment was included as a fixed effect); baseline Q-LES-Q percent maximum total score was used as a covariate. The MADRS response and remission rates and the proportion of patients with a CGI-I of 1 ("very much improved")

Figure 1. Patient Disposition During the Study Evaluating Quetiapine Extended Release (XR) as an Adjunct to Antidepressant Therapy



or 2 ("much improved") at week 6 were analyzed by the Cochran-Mantel-Haenszel test using a logistic regression model. Other efficacy variables were analyzed using the same ANCOVA model as the primary efficacy variable. The number needed to treat (NNT) for responders was also calculated: NNT = 100/(% responders with quetiapine XR–% responders with placebo).

Efficacy analyses were based on the mITT population; a last-observation-carried-forward (LOCF) approach was used for missing data. Statistical analyses were 2-sided, with a significance level of 5%.

For safety measurements, descriptive statistics only were provided (because of difficulties inherent in statistically analyzing such data) and were based on observed cases data.

RESULTS

Patient Population

At 84 of the 87 study centers that screened subjects (mean [SD] number of patients per center = 5.9 [4.7]), a total of 493 patients were randomly assigned to treatment. Of these, 424 patients (86.0%) completed the study (Figure 1). Completion rates were 87.4% in the quetiapine XR 150 mg/day group, 81.6% in the quetiapine XR 300 mg/day group, and 89.0% in the placebo group.

The mITT population comprised 487 patients: 166, 161, and 160 patients in the quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, and placebo groups, respectively. There were 430 patients in the per-protocol population (146, 139, and 145 patients, respectively). The safety population comprised 491 patients (167, 163, and 161 patients, respectively).

The groups were well matched in terms of demographic and clinical characteristics at randomization and in terms of the antidepressants used as combination therapy (Table 1). At screening, a small proportion of patients in the safety population had previously been treated with an atypical antipsychotic (olanzapine, 4.1%; risperidone, 3.5%; quetiapine, 2.2%; aripiprazole, 1.4%; clozapine, 0.4%; ziprasidone, 0.4%). The mean dose and mean duration of the antidepressants used prior to randomization were venlafaxine 171.3 mg/day and 154.9 days for venlafaxine (20.1%), 37.8 mg/day and 173.7 days for citalopram (17.9%), 106.6 mg/day and 158.5 days for sertraline (17.0%), 17.7 mg/day and 143.2 days for escitalopram (16.8%), 39.1 mg/day and 161.4 days for fluoxetine (8.8%), 35.4 mg/day and 160.6 days for paroxetine

Table 1. Demographic and Clinical Characteristics at Randomization of Patients Who Were Assigned to Either Quetiapine Extended Release (XR) or Placebo (modified intent-to-treat population)

Characteristic	Placebo (n = 160)	Quetiapine XR 150 mg/d (n = 166)	Quetiapine XR 300 mg/d (n = 161)
Gender, n (%)			
Male	56 (35.0)	51 (30.7)	51 (31.7)
Female	104 (65.0)	115 (69.3)	110 (68.3)
Age, y			
Mean (SD)	44.8 (10.4)	46.0 (10.1)	45.5 (11.1)
Range	20–64	21–65	18–65
Ethnicity, n (%)			
White	157 (98.1)	165 (99.4)	156 (96.9)
Black	2 (1.3)	0 (0.0)	2 (1.2)
Asian	1 (0.6)	0 (0.0)	1 (0.6)
Other	0 (0.0)	1 (0.6)	2 (1.2)
DSM-IV diagnosis of MDD, n (%)			
Single episode (296.2x)	31 (19.4)	32 (19.3)	29 (18.0)
Recurrent (296.3x)	129 (80.6)	134 (80.7)	132 (82.0)
No. of depressive episodes in past year, mean (SD)	0.9 (1.9)	1.0 (1.5)	1.2 (4.6)
MADRS total score, mean (SD)	28.2 (5.6)	28.6 (5.4)	28.4 (5.5)
HAM-D total score, mean (SD)	24.5 (3.4)	24.6 (3.0)	24.8 (3.2)
HAM-A total score, mean (SD)	20.2 (5.9)	21.0 (6.4)	21.1 (6.0)
CGI-S score, mean (SD)	4.6 (0.8)	4.6 (0.7)	4.7 (0.7)
Q-LES-Q percent maximum total score, mean (SD)	41.0 (13.3)	39.3 (12.2)	40.6 (12.6)
Antidepressant used as combination therapy, n (%)[a]			
SSRI			
Citalopram	31 (19.4)	32 (19.3)	24 (14.9)
Escitalopram	25 (15.6)	28 (16.9)	29 (18.0)
Fluoxetine	15 (9.4)	13 (7.8)	15 (9.3)
Paroxetine	19 (11.9)	12 (7.2)	10 (6.2)
Sertraline	26 (16.3)	32 (19.3)	25 (15.5)
SNRI			
Duloxetine	10 (6.3)	9 (5.4)	16 (9.9)
Venlafaxine	31 (19.4)	32 (19.3)	35 (21.7)
Other antidepressant			
Amitriptyline	2 (1.3)	6 (3.6)	3 (1.9)
Bupropion	1 (0.6)	2 (1.2)	4 (2.5)
Sleep medication usage, %	23.1	31.1	25.6

[a]One patient took both amitriptyline and venlafaxine and was excluded from the per protocol population.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale; 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-Asberg Depression Rating Scale; MDD = major depressive disorder; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

(8.4%), 67.7 mg/day and 166.7 days for duloxetine (7.2%), 118.2 mg/day and 150.6 days for amitriptyline (2.3%), and 278.6 mg/day 145.4 days for bupropion (1.4%).

At week 1, concomitant sleep medication was used by 31.7%, 26.4%, and 21.7% of patients receiving quetiapine XR 150 mg/day, 300 mg/day, and placebo, respectively; these proportions remained consistent throughout the randomized phase.

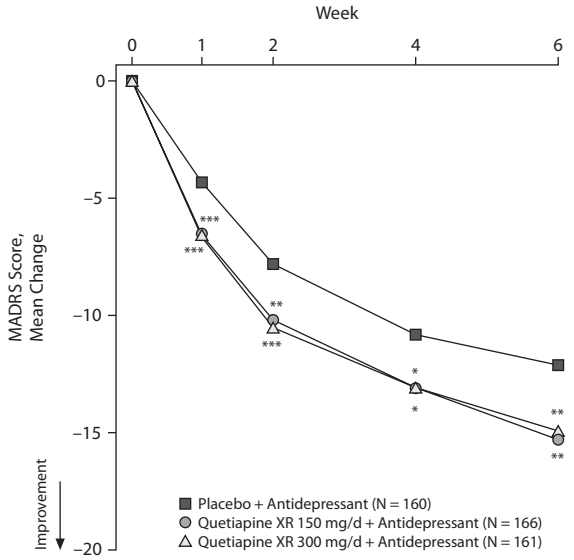
Efficacy

The primary endpoint of mean change in MADRS total score from randomization to week 6 was significantly reduced compared with placebo (–12.21) in the quetiapine XR 150 mg/day (–15.26, $p < .01$ [adjusted $p < .01$]) and 300 mg/day groups (–14.94, $p < .01$ [adjusted $p < .01$]). At week 1 (day 8), mean MADRS total scores were significantly reduced compared with placebo (–4.16) by quetiapine XR 150 mg/day (–6.52, $p < .001$) and quetiapine XR 300 mg/day (–6.38, $p < .001$) (Figure 2).

The per-protocol population analysis of the primary efficacy variable confirmed the primary analysis results using the mITT population: mean change in MADRS total score from randomization to week 6 was –15.35 ($p < .01$ vs. placebo) for quetiapine XR 150 mg/day, –15.15 ($p < .01$ vs. placebo) for quetiapine XR 300 mg/day, and –12.49 for placebo.

The proportion of patients who experienced a MADRS response (≥ 50% reduction in MADRS score) at week 6 was 55.4%, 57.8%, and 46.3% for quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, and placebo groups, respectively. The difference between quetiapine XR 300 mg/day and placebo was statistically significant ($p < .05$); for quetiapine XR 150 mg/day versus placebo, it was not ($p = .107$). Response rates at week 1 were 11.6%, 9.4%, and 7.6%, respectively. The NNT to achieve a MADRS response at week 6 was 10.9 and 8.7 in the quetiapine XR 150 mg/day and 300 mg/day groups, respectively. Remission (MADRS total score ≤ 8) rates at week 6 were

Figure 2. Change in Montgomery-Asberg Depression Rating Scale (MADRS) Total Score From Randomization Over Time (last observation carried forward; modified intent-to-treat population)



*p < .05.
**p < .01.
***p < .001.
Abbreviation: XR = extended release.

36.1%, 31.1%, and 23.8% in the quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, and placebo groups, respectively. The difference between quetiapine XR 150 mg/day and placebo was statistically significant ($p < .05$); for quetiapine XR 300 mg/day versus placebo, it was not ($p = .126$). When post hoc remission criteria (MADRS total score ≤ 10 and ≤ 12) were used, the rates of remission at week 6 in the quetiapine XR 150 mg/day and 300 mg/day groups were 41.6% and 40.4% ($p < .05$ and $p = .073$ versus placebo [31.3%]) and 50.6% and 50.9% ($p < .05$ each vs. placebo [38.8%]), respectively.

The differences between both quetiapine XR groups and placebo were statistically significant for change at week 6 in HAM-D total score, HAM-A total score, HAM-A psychic anxiety subscale score, and CGI-S score (Table 2). The difference in the proportion of patients with a CGI-I score of 1 ("very much improved") or 2 ("much improved") at week 6 was statistically significant for quetiapine XR 150 mg/day.

Although not statistically significant, mean changes at week 6 in Q-LES-Q percentage maximum scores were greater in both quetiapine XR 150 mg/day and 300 mg/day groups (14.70 and 12.81, respectively) compared with placebo (12.58). Mean change in overall quality of life (Q-LES-Q, item 16) scores were 0.9, 0.8, and 0.6, respectively. Mean change in satisfaction with medication (Q-LES-Q, item 15) scores were 0.7, 0.5, and 0.4, respectively. Mean change in PSQI total score at week 6 was significantly greater for both quetiapine XR 150 mg/day and 300 mg/day groups (–5.41 and –5.44) compared with placebo (–3.17; $p < .001$ for both).

Safety and Tolerability

Adverse events. The overall incidence of adverse events was 65%, 75%, and 54% in the quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, and placebo groups, respectively. Most adverse events were mild to moderate in severity. Serious adverse events occurred in 1.2%, 1.8%, and 1.9% of patients, and the percentage of patients who discontinued due to adverse events was 6.6%, 11.7%, and 3.7% in the quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, and placebo groups, respectively. The most common reasons for discontinuation due to an adverse event were somnolence (4 patients [2.4%]) and sedation (3 patients [1.8%]) in the quetiapine XR 150 mg/day group; somnolence (4 patients [2.5%]), sedation (4 patients [2.5%]), and fatigue (4 patients [2.5%]) in the quetiapine XR 300 mg/day group; and depression (2 patients [1.2%]) in the placebo group. The majority of adverse events leading to discontinuation commenced within the first 8 days of randomization. The most common adverse events (occurring at an incidence of > 5% in any group) are shown in Table 3.

Adverse events potentially related to somnolence. Adverse events potentially related to somnolence that were reported during the study were somnolence, sedation, and lethargy. The incidences of these adverse events during the randomized phase were 16.8%, 23.3%, and 3.1% for somnolence; 9.6%, 12.9%, and 4.3% for sedation; and 3.0%, 1.2%, and 1.2% for lethargy in the quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, and placebo groups, respectively.

EPS-related adverse events. The incidences of adverse events potentially related to EPS were similar in the quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, and placebo groups (4.2%, 4.9%, and 5.0%, respectively). Mean BAS scores at baseline were 0.1, 0.2, and 0.2 in the quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, and placebo groups, respectively. The BAS scores had improved or were unchanged at week 6 from baseline in 97.5%, 95.6%, and 98.7% of patients, respectively. Mean Simpson-Angus Scale scores at baseline were 0.6, 0.7, and 0.8, respectively. Simpson-Angus Scale scores had improved or were unchanged at week 6 in 88.8%, 85.4%, and 88.7% of patients, respectively. No patient required anticholinergic medication during the 6-week randomized treatment period.

Weight, clinical laboratory assessments, and electrocardiogram. Table 3 presents weight data and clinical laboratory assessment results, including prolactin, lipids, and glucose regulation parameters, and the proportion of patients with potentially clinically relevant shifts in these parameters. At treatment end, mean glucose levels had

Table 2. Results for Secondary Efficacy Parameters Assessing Symptom Severity and Improvement (modified intent-to-treat population)

Measure	Placebo (n = 160)	Quetiapine XR 150 mg/d (n = 166)	Quetiapine XR 300 mg/d (n = 161)
HAM-D total score			
Change at wk 6, LSM	–11.13	–13.81	–13.56
Difference (95% CI) vs placebo	NA	–2.68 (–4.21 to –1.15)	–2.43 (–3.96 to –0.90)
p Value		< .001	< .01
HAM-D item 1 score			
Baseline, mean (SD)	2.9 (0.6)	2.8 (0.6)	2.9 (0.5)
Change at wk 6, LSM	–1.35	–1.56	–1.57
Difference (95% CI) vs placebo	NA	–0.21 (–0.43 to 0.02)	–0.21 (–0.43 to 0.01)
p Value		.068	.058
HAM-D anxiety items score			
Baseline, mean (SD)	4.1 (1.1)	4.1 (1.0)	4.1 (1.1)
Change at wk 6, mean (SD)	–1.7 (1.7)	–2.1 (1.7)	–2.0 (1.6)
HAM-D sleep disturbance items score			
Baseline, mean (SD)	4.2 (1.5)	4.5 (1.4)	4.3 (1.5)
Change at wk 6, mean (SD)	–1.9 (2.1)	–3.3 (1.9)	–3.0 (2.0)
HAM-A total score			
Change at wk 6, LSM	–7.92	–10.27	–9.70
Difference (95% CI) vs placebo	NA	–2.35 (–3.76 to –0.94)	–1.78 (–3.20 to –0.36)
p Value		< .01	< .05
HAM-A psychic anxiety subscale score[a]			
Baseline, mean (SD)	12.5 (3.2)	12.9 (3.3)	13.1 (3.2)
Change at wk 6, LSM	–5.11	–6.82	–6.47
Difference (95% CI) vs placebo	NA	–1.70 (–2.59 to –0.81)	–1.35 (–2.25 to –0.45)
p Value		< .001	< .01
HAM-A somatic anxiety subscale score[b]			
Baseline, mean (SD)	7.7 (3.6)	8.1 (4.0)	8.0 (3.7)
Change at wk 6, LSM	–2.83	–3.43	–3.19
Difference (95% CI) vs placebo	NA	–0.60 (–1.27 to 0.06)	–0.37 (–1.04 to 0.30)
p Value		.076	.279
CGI-S score			
Baseline, mean (SD)	4.6 (0.8)	4.6 (0.7)	4.7 (0.7)
Change at wk 6, LSM	–1.25	–1.72	–1.64
Difference (95% CI) vs placebo	NA	–0.47 (–0.75 to –0.19)	–0.39 (–0.67 to –0.10)
p Value		< .01	< .01
CGI-I			
Score of 1 or 2 at wk 6, n (%)	84 (52.5)	107 (64.5)	101 (62.7)
Difference vs placebo, OR (95% CI)	NA	1.64 (1.05 to 2.56)	1.54 (0.98 to 2.41)
p Value		< .05	.058

[a]Hamilton Rating Scale for Anxiety psychic anxiety subscale consists of items 1 through 6 and 14 (anxious mood, tension, fears, insomnia, intellectual, depressed mood, and behavior at interview).
[b]Hamilton Rating Scale for Anxiety somatic anxiety subscale consists of items 7 through 13 (somatic complaints muscular and sensory, cardiovascular symptoms, respiratory symptoms, gastrointestinal symptoms, genitourinary symptoms, and autonomic symptoms).
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, LSM = least squares means, NA = not applicable, XR = extended release.

increased from baseline in the placebo (1.9 mg/dL) and quetiapine XR 300 mg/day (1.5 mg/dL) groups; levels had decreased in the quetiapine XR 150 mg/day group (–0.6 mg/dL). Mean increases (mg/dL) from baseline were seen with quetiapine XR 150 mg/day and 300 mg/day versus placebo for triglycerides (14.9 and 13.9 vs. –5.2), total cholesterol (6.8 and 4.3 vs. –0.9), and low-density lipoprotein (LDL) cholesterol (4.9 and 2.7 vs. –0.8). Mean high-density lipoprotein cholesterol levels decreased in both quetiapine XR groups (150 mg/day group, –0.9 mg/dL; 300 mg/day group, –0.9 mg/dL). At week 6, there were no clinically relevant mean changes from baseline in vital signs and electrocardiogram data. There was no indication of increased QTc interval in any treatment group.

Sexual dysfunction. Mean (SD) CSFQ scores at baseline were 36.3 (10.3), 35.5 (9.1), and 36.7 (9.6) for quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, and placebo, respectively. At week 6, slight improvements in mean CSFQ scores were seen: 38.2 (11.4), 36.6 (10.1), and 38.1 (10.0), respectively.

Only 2 adverse events potentially related to sexual dysfunction were reported: "libido decrease" of severe intensity and "loss of libido" of moderate intensity in male patients receiving quetiapine XR 300 mg/day. Both adverse events were considered possibly related to study medication by the investigator; neither adverse event resulted in discontinuation.

DISCUSSION

This is the first large-scale placebo-controlled, randomized study to evaluate the efficacy and safety of

Table 3. Results of the Safety Assessments: Most Common Adverse Events (occurring at an incidence of >5% in any group), Changes in Clinical Laboratory Parameters and Body Weight From Baseline to Treatment End, and Proportions of Patients With Clinically Relevant Shifts in Levels at Treatment End (Safety Population)

Variable	Placebo + Antidepressant (n = 161)	Quetiapine XR 150 mg/d + Antidepressant (n = 167)	Quetiapine XR 300 mg/d + Antidepressant (n = 163)
Adverse event, n (%)			
Dry mouth	11 (6.8)	34 (20.4)	58 (35.6)
Somnolence	5 (3.1)	28 (16.8)	38 (23.3)
Fatigue	5 (3.1)	22 (13.2)	24 (14.7)
Sedation	7 (4.3)	16 (9.6)	21 (12.9)
Constipation	6 (3.7)	7 (4.2)	17 (10.4)
Dizziness	12 (7.5)	19 (11.4)	15 (9.2)
Headache	16 (9.9)	15 (9.0)	13 (8.0)
Nausea	10 (6.2)	9 (5.4)	9 (5.5)
Nasopharyngitis	10 (6.2)	5 (3.0)	5 (3.1)
Clinical laboratory parameters			
Glucose, mg/dL[a]			
Baseline, mean (SD)	93.8 (13.7)	95.2 (14.9)	98.2 (18.7)
Change, mean (SD)	1.9 (19.6)	–0.6 (13.2)	1.5 (15.8)
Proportion of patients with potentially clinically relevant shifts to elevated values (≥ 126)[b]	2.6	2.4	6.6
Total cholesterol, mg/dL[a]			
Baseline, mean (SD)	215.0 (49.1)	214.9 (43.3)	218.1 (47.8)
Change, mean (SD)	–0.9 (30.2)	6.8 (29.8)	4.3 (31.9)
Proportion of patients with potentially clinically relevant shifts to elevated values (≥ 240)[b]	8.4	21.1	15.3
LDL cholesterol, mg/dL[a]			
Baseline, mean (SD)	130.2 (43.3)	127.9 (36.8)	130.9 (42.4)
Change, mean (SD)	–0.8 (26.2)	4.9 (25.5)	2.7 (30.7)
Proportion of patients with potentially clinically relevant shifts to elevated values (≥ 160)[b]	11.1	16.2	12.0
HDL cholesterol, mg/dL[a]			
Baseline, mean (SD)	57.8 (17.0)	60.7 (17.1)	60.0 (16.9)
Change, mean (SD)	0.1 (7.3)	–0.9 (9.7)	–0.9 (8.9)
Proportion of patients with potentially clinically relevant shifts to lowered values (≤ 40)[c]	4.1	1.9	5.9
Triglycerides, mg/dL[a]			
Baseline, mean (SD)	140.1 (99.8)	134.8 (105.5)	136.4 (76.8)
Change, mean (SD)	–5.2 (64.0)	14.9 (72.3)	13.9 (81.3)
Proportion of patients with potentially clinically relevant shifts to elevated values (≥ 200)[b]	3.2	11.4	13.0
Prolactin, ng/mL			
Baseline, mean (SD)	10.0 (15.4)	9.6 (8.6)	9.9 (10.2)
Change, mean (SD)	0.3 (15.4)	–0.5 (8.8)	0.4 (13.1)
Proportion of patients with clinically relevant shifts to elevated values (males, ≥ 20; females, > 30)[b]	2.0	1.3	2.7
Body weight			
Weight, kg			
Baseline, mean (SD)	78.5 (20.8)	75.5 (16.7)	78.9 (17.9)
Change, mean (SD)	0.0 (2.5)	0.9 (2.2)	1.0 (2.3)
≥ 7% increase in body weight, n (%)	2 (1.3)	7 (4.2)	7 (4.4)

[a]Fasting status confirmed. Fasting status documented by patient report of ≥ 8 hours since last meal before lab draw for both baseline and postbaseline laboratory measurements.
[b]Excluding patients who had a high level at baseline.
[c]Excluding patients who had a low level at baseline.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein, XR = extended release.

quetiapine XR in the adjunctive treatment of MDD. The results indicate that adjunctive quetiapine XR (150 and 300 mg/day) was efficacious in the treatment of patients with MDD who have shown an inadequate response to their current antidepressant treatment. The effect of adjunctive quetiapine XR in reducing symptoms of depression was greater than that seen with placebo, and this difference was observed as early as week 1.

In this study, both the 150 and 300 mg/day doses of quetiapine XR exhibited significant improvements compared with placebo in MADRS total score over time. The antidepressant effect was confirmed through a range of secondary efficacy assessment scales. The HAM-D total and item scores indicated that adjunctive quetiapine XR led to improvements across the range of symptoms of depression. Further, symptom improvement was seen in this group of patients who were receiving a range of antidepressants.

Patients with comorbid anxiety disorders were excluded from the study; however, mean HAM-A total

scores at entry were approximately 21, indicating that patients had moderate levels of anxiety. Adjunctive quetiapine XR had significantly reduced HAM-A scores from baseline at week 6 compared with placebo, indicating its efficacy against anxiety symptoms.

Sleep disturbance (most commonly insomnia) is a core symptom of depression,[13] and adjunctive quetiapine XR had a positive effect on sleep as demonstrated by the HAM-D sleep disturbance items and PSQI scores. The effectiveness of quetiapine XR across the spectrum of symptoms of depression and anxiety shown here demonstrates that the effect of this agent goes beyond its beneficial effects on sleep. There was a higher incidence of sleep medication usage in patients receiving quetiapine XR compared with those receiving placebo; further investigation of this observed trend would be required to elucidate whether this was due to random variation or drug-drug interactions.

Overall, adjunctive quetiapine XR was well tolerated, with few serious adverse events reported. The most common adverse events with quetiapine XR were dry mouth, somnolence, fatigue, sedation, constipation, and dizziness, and the tolerability findings were consistent with the known safety profile of quetiapine in other indications.[25] Adjunctive quetiapine XR was associated with greater weight gain and a higher proportion of patients with a ≥ 7% increase in body weight (approximately 4% vs. 1%) than placebo. Numerical increases in total cholesterol, LDL cholesterol, and triglycerides were observed with adjunctive quetiapine XR compared with placebo; elevations of these parameters are consistent with the pharmacologic profile of quetiapine.[25] Physicians should consider the potential for such effects before initiating any treatment option in patients with MDD. Further data are needed to understand the long-term effects of the adjunctive use of quetiapine.

The main strengths of this study include the large patient population, its robust design, the variety of antidepressants allowed, and the number of assessment scales evaluating efficacy. In addition, measures to reduce inter-rater variability were employed. The inclusion of patients receiving a wide range of antidepressants is an important study strength because it emulates the "real-life" situation in which patients may be prescribed any of the available antidepressant drugs. However, conclusions regarding specific quetiapine XR antidepressant combinations cannot be made. Study limitations include the short duration, lack of an active comparator, and the fact that other doses were not evaluated. Further investigation of other doses, specific combinations, and longer treatment durations would provide valuable information.

The remission rates reported here for quetiapine XR as adjunct to antidepressants (36.1% and 31.1%) are similar to those reported with citalopram monotherapy (36.8%) in step 1 and switching/adjunct therapy/cognitive therapy in step 2 (30.6%) of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study.[26] Remission rates reported in step 3 or step 4 of the STAR*D study were 13.7% and 13.0%, respectively.[26] In contrast to the remission rates reported here with adjunctive quetiapine, remission rates were 15.9% with lithium and 24.7% with triiodothyronine adjunct therapy in the STAR*D study[27] and 26% with adjunctive aripiprazole in patients with treatment-resistant MDD.[6] The response rates for adjunctive quetiapine XR in the present study are similar to that reported in a recent meta-analysis of lithium augmentation studies in a similar patient population (41%).[4] Recently, a short-term study of risperidone adjunct to antidepressants in patients with treatment-resistant MDD reported response and remission rates of 46.2% and 24.5%, respectively.[28]

A potential explanation for the antidepressant effect of quetiapine would be its interaction with 3 principal neurotransmitter systems involved in psychosis and mood disorders (dopamine, serotonin, and norepinephrine). Both quetiapine and its major active human metabolite norquetiapine have moderate to high affinity for dopamine D_2 and serotonin 5-HT_{2A} receptors. Norquetiapine is a potent inhibitor of the norepinephrine transporter and is a 5-HT_{1A} partial agonist.[12]

In summary, this large, placebo-controlled, double-blind study demonstrated that quetiapine XR at doses of 150 mg/day and 300 mg/day was efficacious as an adjunctive therapy to antidepressants in patients with MDD who have shown an inadequate response to their current antidepressant treatment. Adjunctive quetiapine XR was effective across the range of depressive symptoms, going beyond sleep improvement, with its antidepressant effect seen as early as week 1. Findings were consistent with the known safety and tolerability profile of quetiapine.

Drug names: aripiprazole (Abilify), bupropion (Aplenzin, Wellbutrin, and others), citalopram (Celexa and others), clozapine (FazaClo, Clozaril, and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal and others), sertraline (Zoloft and others), venlafaxine (Effexor and others), ziprasidone (Geodon).

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