Notice of Correction: The phrase "if the current episode was associated with psychotic features" was deleted from the exclusionary criteria in the second paragraph of the subsection "Patient Population" in the Method (p 527).

Extended Release Quetiapine Fumarate Monotherapy in Major Depressive Disorder: A Placebo- and Duloxetine-Controlled Study

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Objective: To evaluate the efficacy and tolerability of once-daily extended release quetiapine fumarate (quetiapine XR) as monotherapy treatment for major depressive disorder (MDD).

Method: This 8-week (6-week active-treatment, randomized phase; 2-week posttreatment drug-discontinuation/tapering phase), multicenter, double-blind, randomized, parallel-group, placebo- and active-controlled, phase 3 study was conducted between April 2006 and May 2007. In total, 612 patients with *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV)–defined MDD were randomly assigned to quetiapine XR 150 mg/day or 300 mg/day, duloxetine 60 mg/day (active control), or placebo. The primary endpoint was the change from baseline to week 6 in Montgomery-Asberg Depression Rating Scale (MADRS) total score.

Results: At week 6, both doses of quetiapine XR ($p < .001$) and duloxetine ($p < .01$) significantly reduced mean MADRS total score versus placebo. A significant reduction was seen at week 1 with quetiapine XR 150 mg/day and 300 mg/day versus placebo ($p < .01$), but not with duloxetine. Response rates (≥ 50% reduction in MADRS total score) at week 6 were significantly higher for both doses of quetiapine XR ($p < .01$) and duloxetine ($p < .05$) versus placebo. Remission rates (MADRS score ≤ 8) were significantly higher for quetiapine XR 300 mg/day and duloxetine versus placebo ($p < .05$), but not for quetiapine XR 150 mg/day. Hamilton Rating Scale for Depression, Hamilton Rating Scale for Anxiety, and Clinical Global Impressions-Severity of Illness total scores and the proportion of patients with Clinical Global Impressions-Improvement scores of 1 or 2 ("much/very much improved") were significantly improved with both doses of quetiapine XR and duloxetine versus placebo. The most common adverse events reported were dry mouth, sedation, and somnolence for quetiapine XR and nausea, headache, dizziness, and dry mouth for duloxetine.

Conclusion: Quetiapine XR monotherapy (150 mg/day and 300 mg/day) is effective, with safety and tolerability consistent with the known profile of quetiapine XR, in the treatment of patients with MDD, with onset of symptom improvement demonstrated at week 1.

Trial Registration: clinicaltrials.gov Identifier: NCT00321490

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Study investigators and financial disclosure are listed at the end of the article.

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Major depressive disorder (MDD) is currently the second most common cause of disability worldwide, and it is anticipated that MDD will become the leading cause of disability by 2020 in the developed world.[1] This illness also poses a significant economic burden; for example, in 2000 the total economic cost of MDD for the United States alone was an estimated $83.1 billion.[2]

Commonly used drug therapies for the treatment of patients with MDD include selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), as well as older treatments: tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and heterocyclic antidepressants (trazodone, nefazodone, and bupropion). However, none of these agents produce full remission of symptoms in a large proportion of patients, and the onset of symptom relief may not occur for several weeks.[3,4] In addition, the tolerability profiles of current treatments mean there is a need for alternative therapies for MDD.[5–8]

Quetiapine is U.S. Food and Drug Administration (FDA) approved for the treatment of acute and chronic schizophrenia and for bipolar mania and bipolar

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depression. It has been shown to have effects on depressive symptoms in schizophrenia[9] and bipolar depression[10,11] and to be effective as adjunct treatment to antidepressants in MDD with comorbid anxiety and in treatment-resistant depression.[12–17]

Most commonly used antidepressants presumably act on monoamine reuptake transporters, inhibiting serotonin and/or norepinephrine reuptake. There is growing evidence that acting on these alone may not be optimal for efficacy in MDD and that dopamine neurotransmission may also play an important role.[18–20] Quetiapine and norquetiapine, an active metabolite of quetiapine, have a combination of effects on several central neuroreceptors, including moderate antagonist affinity for dopamine D_2 and serotonin 5-HT_{2A} receptors and mild to moderate affinity for 5-HT_{1A} receptors. Norquetiapine is also a potent inhibitor of the norepinephrine transporter,[21] a property that is not shared by similar atypical antipsychotics at clinically relevant doses and that may at least partly explain its antidepressant effects.

The hypothesis tested in this study was that once-daily extended release quetiapine fumarate (quetiapine XR) monotherapy was more effective than placebo in patients with MDD over an 8-week period.

METHOD

Study Design and Treatment

This 8-week, multicenter, double-blind, parallel-group, randomized, phase 3 study (study code: D1448C00002 [Diamond]) of quetiapine XR (150 mg/day and 300 mg/day) and duloxetine (60 mg/day) versus placebo in the treatment of patients with MDD was conducted at 38 centers in the United States between April 2006 and May 2007.[22] Duloxetine was included to determine assay sensitivity and not as a direct comparator. After a 7- to 28-day enrollment and washout period of any prior psychotropic medications, patients were randomly assigned to a 6-week active treatment phase followed by a 2-week drug discontinuation/tapering period. Patients who were randomly assigned to receive quetiapine XR 300 mg/day or duloxetine 60 mg/day had their dose titrated downward during the drug discontinuation/tapering period.

The duration of this study is in line with guidelines from the European Agency for the Evaluation of Medicinal Products (EMEA)[23] and the FDA,[24] which recommend that short-term antidepressant studies have a duration of 4 to 8 weeks in order to establish therapeutic activity but minimize any impact of the study on the participants. This study also included a 2-week follow-up period to assess discontinuation symptoms, as recommended by the EMEA.[23]

The study was approved by institutional review boards for each site and performed in accordance with the current amendment of the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice guidelines. Written informed consent was obtained from all patients before participation.

Patient Population

Male or female outpatients, aged 18 to 65 years inclusive, with a *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV) diagnosis of MDD (single episode or recurrent), were eligible for inclusion in the study.[25] The diagnosis was confirmed by the Mini-International Neuropsychiatric Interview.[26] Patients were required to have a 17-item Hamilton Rating Scale for Depression (HAM-D)[27] total score ≥ 22 and HAM-D item 1 (depressed mood) score ≥ 2 at enrollment and randomization.

Patients were excluded from the study if they were diagnosed with a DSM-IV Axis I disorder other than MDD within 6 months prior to enrollment, if they had any DSM-IV Axis II disorder that would significantly impact on the patient's current psychiatric status, if the duration of their current MDD episode exceeded 12 months or was less than 4 weeks, or if they had had an inadequate response to at least 6 weeks of treatment with 2 or more classes of antidepressants during the current episode. Psychotherapy was allowed only if it had been ongoing for at least 3 months prior to randomization. Additional exclusion criteria included a clinically significant medical illness (including diabetes mellitus) or any clinically significant findings on physical examination, laboratory tests, or electrocardiogram (ECG). Patients who posed a current serious suicidal or homicidal risk were also excluded. Patients were not permitted to take antipsychotic, mood stabilizer, or antidepressant drugs within 7 days before randomization. Fluoxetine was prohibited within 28 days before randomization, and use of MAOIs, anxiolytics, and hypnotics was prohibited within 14 days before randomization.

Random assignment was achieved in a non–center-specific manner and was generated using a computer-based randomization system. Patients were randomly assigned in a 1:1:1:1 manner to one of 4 groups: quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, duloxetine 60 mg/day, or placebo.

Study Medication and Dosing Schedule

Quetiapine XR (150 mg/day or 300 mg/day), duloxetine (60 mg/day), or placebo was administered orally, in a single dose, once daily in the evening. All patients randomly assigned to receive quetiapine XR started at 50 mg/day, and their dose was increased to 150 mg/day at day 3 and, for the 300 mg/day group, to 300 mg/day at day 5. Patients randomly assigned to receive duloxetine started at 60 mg/day on day 1. The daily dose of duloxetine was based on the prescribing information and the

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EMEA guidelines, which recommend that the minimum effective dose is used.[23,28] All treatment groups continued to receive their respective doses for the remainder of the 6-week treatment period.

During the drug-discontinuation/tapering phase (weeks 6–8), patients randomly assigned to quetiapine XR 150 mg/day were discontinued from active medication and took placebo (as did those assigned to placebo) to maintain blinding until week 8. Patients receiving quetiapine XR 300 mg/day or duloxetine 60 mg/day had their dose halved for 1 week prior to discontinuing study medication for the final week of the posttreatment period. All packaging of treatments was identical, with placebo and active tablets also identical in appearance, smell, taste, and number.

Prior and Concomitant Medication

Prior to entry into the study, the use of psychoactive drugs was prohibited as follows: antipsychotics, mood stabilizers, and antidepressants were prohibited 7 days prior to randomization, MAOIs and anxiolytics were prohibited 14 days prior to randomization, and use of fluoxetine was prohibited 28 days prior to randomization. Nonpsychotropic medication, including over-the-counter medications and contraceptives taken before entry into the study, could be continued. Lorazepam (2 mg/day), zolpidem tartrate (10 mg/day), zaleplon (20 mg/day), zopiclone (7.5 mg/day), or chloral hydrate (1 g/day) were permitted, at the discretion of the investigator, for insomnia. Anticholinergics could be used to treat extrapyramidal symptoms (EPS). The use of all other psychotropic drugs was prohibited during the active treatment period of the study. During the second week of the drug-discontinuation/tapering period, physicians were strongly discouraged from prescribing other medications unless clinically indicated.

Efficacy Evaluations

The primary efficacy variable was the mean change in the Montgomery-Asberg Depression Rating Scale (MADRS)[29] total score from baseline to week 6. Clinical assessments were conducted at baseline and at weeks 1, 2, 4, and 6. The HAM-D was used to assess patient eligibility for the study. The MADRS was used to assess efficacy, as using a different assessment measure reduces the potential for rater-associated inflation of the initial scale.[23]

Additional efficacy evaluations included the change in MADRS total score from baseline at each assessment starting at week 1 (day 8) and MADRS response (defined as ≥ 50% reduction in MADRS total score from baseline) and remission (defined conservatively as MADRS total score ≤ 8) at week 6. Post hoc analyses of MADRS remission rates were carried out using remission definitions of MADRS total score ≤ 10 and MADRS total score ≤ 12 at week 6.

The change from baseline to week 6 in HAM-D score and changes from baseline to weeks 1, 2, 4, and 6 in Hamilton Rating Scale for Anxiety (HAM-A) score,[30] Clinical Global Impressions-Severity of Illness scale (CGI-S)[31] score, and the proportion of patients with a Clinical Global Impressions-Improvement scale (CGI-I)[31] score of 1 ("very much improved") or 2 ("much improved") were also assessed. Quality of sleep was assessed at baseline and weeks 4 and 6 with the Pittsburgh Sleep Quality Index (PSQI),[32] which measures several dimensions of sleep, including quality, latency, duration, efficiency, use of medication, and daytime dysfunction.

To ensure consistency throughout the study, investigators and study personnel received central and standardized training approved by the sponsor. All personnel administering the MADRS, HAM-D, HAM-A, and CGI scales received computer-based training. The HAM-A was conducted using the Structured Interview Guide for the HAM-A (SIGH-A).[33] For the primary efficacy measure (MADRS) and the inclusion criteria (HAM-D), raters were approved and certified by the sponsor. To reduce scoring variability, it was recommended that the same rater conduct all assessments for a given patient for a specific scale. Only qualified physician raters administered the CGI.

Safety and Tolerability Evaluations

Safety and tolerability were evaluated by assessing the incidence and severity of adverse events (AEs), as well as withdrawals due to AEs throughout the study. Treatment discontinuation signs and symptoms (TDSS) during the 2-week drug-discontinuation/tapering phase were measured using an 18-item TDSS scale, which was developed by AstraZeneca as a hybrid of the 17-item discontinuation scale developed by Michelson et al.[34] and the 43-item Discontinuation Emergent Signs and Symptoms scale.[35] All patients assigned to randomized treatment who had completed the treatment period were asked to rate discontinuation symptoms assessed by the TDSS scale. Baseline TDSS scores were collected at the study center during the final randomized treatment period visit (day 43). Patients completed TDSS assessments by telephone on posttreatment days 1, 3, and 5 and at the study center on posttreatment days 7 and 14. Patients were asked whether the symptom was "present" or "absent." If a symptom was present at a visit on posttreatment days 1, 3, 5, 7, and 14, and it was also present on day 43, the patient was asked whether the symptom was better, unchanged, or worse as compared with baseline.

EPS were assessed with the Simpson-Angus Rating Scale (SAS),[36] and drug-induced akathisia was assessed using the Barnes Akathisia Rating Scale (BARS)[37] at randomization and at weeks 4 and 6. The self-administered Changes in Sexual Functioning Questionnaire (CSFQ)[38] was used to measure medication-related changes in sexual

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functioning from baseline to week 6. The 14 items in the CSFQ measure 5 different dimensions of sexual functioning: pleasure, desire/frequency, desire/interest, arousal/excitement, and orgasm/completion. Men and women completed separate versions of the questionnaire.

Measurements of vital signs and weight, including clinically significant increases in weight (defined by the FDA as ≥ 7% change in weight), were obtained at each study visit. Twelve-lead ECG measurements were made at enrollment and week 6, and clinical chemistry (including fasting serum glucose) and hematology assessments were performed at screening and at weeks 4 and 6.

Statistical Analysis

The predefined criteria for inclusion in the intent-to-treat (ITT) population were that patients must have taken at least 1 dose of medication and must have had at least 1 postrandomization assessment of the primary variable. For inclusion in the modified intent-to-treat (MITT) population, randomized patients must have taken at least 1 dose of medication and must have had a baseline and at least 1 postrandomization assessment of the primary variable.

For the primary analysis of changes in MADRS total score from randomization to week 6, an analysis of covariance (ANCOVA) model (with treatment and study as fixed events, center as random effect, and baseline MADRS score as covariate) was used. Odds ratio, estimated by logistic regression, was used to analyze MADRS response and remission and CGI-I. All additional endpoints were analyzed using the same ANCOVA model. For each ANCOVA, least squares means change from baseline was calculated, together with corresponding standard error as well as 95% confidence interval (CI) and p value, testing the hypothesis that the change from baseline is equal to zero. For efficacy variables, a last-observation-carried-forward (LOCF) approach was used for imputation of missing data. All statistical analyses were 2-sided with a significance level of 5%. A stepwise sequential testing procedure was used to ensure that the overall significance level of .05 was preserved. Descriptive statistics including 95% CIs around ANCOVA model–based point estimates were provided for the comparison of duloxetine with placebo to address assay sensitivity. The change in MADRS total score from randomization to week 6 was tested for each dose versus placebo. To handle multiplicity within each step, the Simes-Hommel procedure was used.[39] Correction of multiplicity was applied for MADRS total score, and no correction of multiplicity was applied for any other variables or for the placebo and quetiapine XR comparisons with duloxetine.

Effect size (improvement with quetiapine XR over placebo divided by pooled standard deviation [SD]) was determined by means of a mixed-model repeated-measures analysis of the MITT population. Exploratory analysis was limited to the effect size of the primary outcome measure for the groups taking quetiapine XR 150 mg/day and 300 mg/day only.

Descriptive statistics including 95% CIs around baseline adjusted point estimates at the time of assessment and p values were provided for the comparison of duloxetine to placebo to address assay sensitivity further. The study was not powered for a comparison of quetiapine XR versus duloxetine; however, a prespecified secondary outcome was to compare both doses of quetiapine XR and duloxetine at week 1 on improvement versus placebo.

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Descriptive statistics were used to assess all measures of tolerability. Significance testing was not applied to AEs or laboratory values due to multiplicity concerns.

The sample size calculation in this study was done to ensure an 80% power in demonstrating superior efficacy of each of the 2 quetiapine XR doses over placebo with regard to the primary outcome variable. The appropriate sample size was attained by assuming an anticipated difference of 3.5 units from placebo and an SD of 9 for the change in MADRS total score from randomization to week 6. Based on a 2-sided test at a 5% significance level, it was planned to randomize a sample size of 140 per treatment group and 560 in total to ensure a power of 90% in each individual comparison and an overall power of at least 80%.

RESULTS

Patients and Disposition

In total, 912 patients were screened and 612 patients with MDD were randomly assigned to quetiapine XR 150 mg/day (N = 152), quetiapine XR 300 mg/day (N = 152), duloxetine 60 mg/day (N = 151), or placebo (N = 157). The mean number of patients randomly assigned by each center was 16 (range, 1–60). Figure 1 illustrates the disposition of patients during the study. Of the 612 randomly assigned patients, 610 received treatment and were included in the safety analysis set. A total of 587 patients (quetiapine XR 150 mg/day [N = 147], quetiapine XR 300 mg/day [N = 147], duloxetine [N = 141], and placebo [N = 152]) were analyzed for efficacy in the MITT analysis after 25 patients were excluded because they did not meet the predefined MITT criteria (23 patients did not have a baseline and at least 1 postrandomization assessment of the primary variable; 2 patients did not receive at least 1 dose of study medication).

The 4 groups were generally well matched in terms of demographic and clinical characteristics (Table 1), with the exception of gender in the quetiapine XR 300 mg/day group, which had a lower percentage of women than the other treatment groups. Mean age was 41.3 years. The majority of patients had a DSM-IV diagnosis of recurrent

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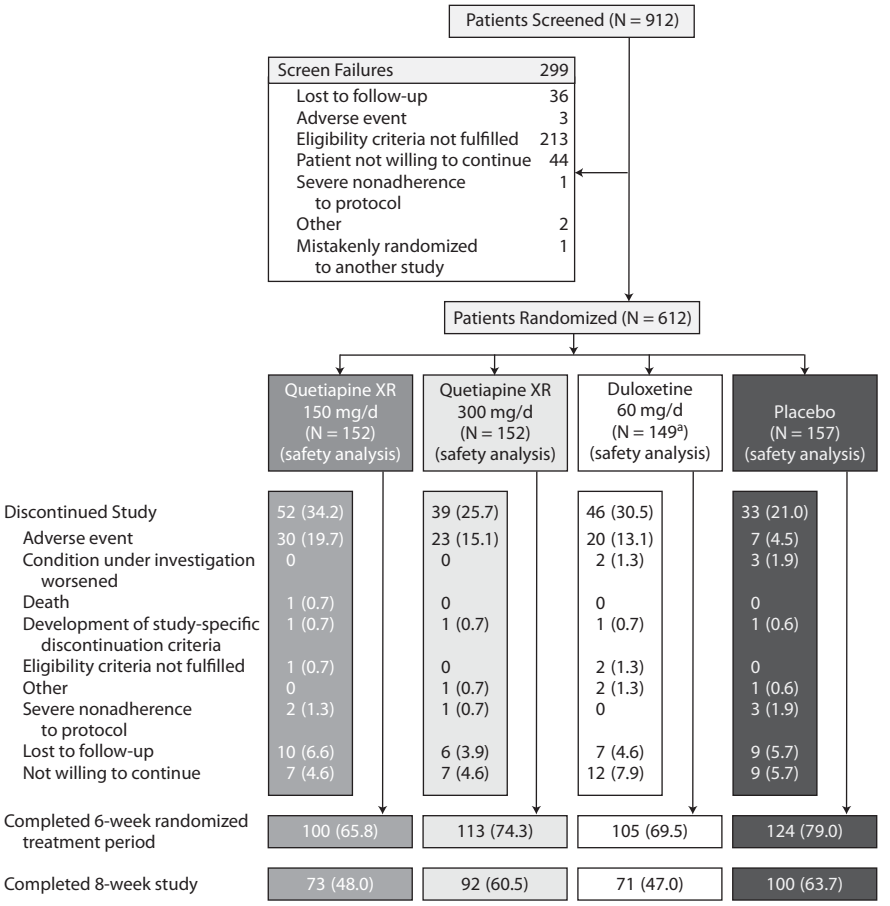
Figure 1. Disposition of Patients With Major Depressive Disorder at Each Stage of the Study



[a]Two patients were not treated. They were included in the "discontinued from study treatment" set but were not included in the safety analysis.
Abbreviation: XR = extended release.

MDD (87.6%), and 21.8% of patients had HAM-D scores ≥ 28 at randomization. The quetiapine XR 300 mg/day group contained the largest proportion of patients with a HAM-D total score ≥ 28 (25.9%).

The proportion of patients who completed the 6-week treatment period was lower in the quetiapine XR 150 mg/day group (65.8%) and duloxetine group (69.5%) than in the quetiapine XR 300 mg/day group (74.3%) and placebo group (79.0%). The most common reasons for withdrawal were related to AEs in the quetiapine XR (150 and 300 mg/day) and duloxetine groups (19.7%, 15.1%, 13.1%, respectively) and lost to follow-up and not willing to continue in the placebo group (5.7% each). Discontinuations due to worsening of MDD occurred in 1.9% of placebo patients and 1.3% of duloxetine patients. None of the quetiapine XR patients at either dose discontinued for this reason.

Before study entry, 7.9% and 2.5% of patients were taking an SSRI or SNRI, respectively. The use of benzodiazepines was generally low across all treatment groups during the randomized treatment phase: quetiapine XR 150 mg/day 0.8%, quetiapine XR 300 mg/day 1.5%, duloxetine 0%, and placebo 2.3%.

The mean (SD) daily doses during the randomized treatment period were 124.7 (21.0) mg, 244.8 (55.4) mg, and 56.3 (4.1) mg in the quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, and duloxetine groups, respectively. The mean daily doses were lower in all treatment groups due to the initial dose titration period and some patients being included who were judged to be occasionally nonadherent to their medication. Patients with overall adherence < 70% in the randomized treatment period were excluded from the per-protocol analysis population.

Efficacy

At week 6, MADRS total score was significantly reduced from baseline compared with placebo (–11.18) in the quetiapine XR 150 mg/day (–14.81; $p < .001$ [adjusted $p < .001$]), quetiapine XR 300 mg/day (–15.29, $p < .001$ [adjusted $p < .001$]), and duloxetine (–14.64,

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Table 1. Patient Demographics and Clinical Characteristics at Baseline (MITT population)

Characteristic	Placebo (N = 152)	Quetiapine XR 150 mg/d (N = 147)	Quetiapine XR 300 mg/d (N = 147)	Duloxetine (N = 141)
Gender, N (%)				
Male	54 (35.5)	54 (36.7)	72 (49.0)	53 (37.6)
Female	98 (64.5)	93 (63.3)	75 (51.0)	88 (62.4)
Age, y				
Mean (SD)	42.3 (11.5)	40.9 (12.3)	41.6 (12.0)	40.2 (12.5)
Range	19–63	18–64	19–65	19–65
Ethnicity, N (%)				
White	105 (69.1)	111 (75.5)	110 (74.8)	107 (75.9)
Black	39 (25.7)	30 (20.4)	31 (21.1)	25 (17.7)
Asian	2 (1.3)	1 (0.7)	1 (0.7)	1 (0.7)
Other	6 (3.9)	5 (3.4)	5 (3.4)	8 (5.7)
DSM-IV diagnosis of MDD, N (%)				
Single episode (296.2)	22 (14.5)	17 (11.6)	18 (12.2)	16 (11.3)
Recurrent (296.3)	130 (85.5)	130 (88.4)	129 (87.8)	125 (88.7)
No. of depressive episodes in past year, mean (SD)	1.0 (1.7)	1.0 (1.6)	0.8 (1.6)	0.9 (1.4)
No. of depressive episodes over lifetime, mean (SD)	9.2 (26.7)	8.6 (13.1)	6.0 (8.5)	7.1 (8.8)
Score, mean (SD)				
MADRS total	30.3 (5.0)	29.8 (5.3)	30.1 (5.2)	30.4 (4.5)
HAM-D total	25.2 (2.7)	25.2 (2.9)	25.4 (3.2)	25.2 (2.6)
HAM-D item 1	3.0 (0.4)	3.1 (0.5)	3.0 (0.5)	3.0 (0.4)
HAM-A total	18.3 (5.6)	18.4 (5.7)	18.4 (5.2)	19.3 (5.2)
HAM-A psychic anxiety	11.9 (2.9)	12.0 (3.0)	12.1 (2.8)	12.7 (2.6)
HAM-A somatic anxiety	6.4 (3.6)	6.5 (3.4)	6.3 (3.2)	6.6 (3.4)
CGI-S total	4.4 (0.6)	4.4 (0.6)	4.4 (0.5)	4.4 (0.6)
PSQI	11.9 (3.9)	11.4 (3.6)	11.3 (3.5)	12.1 (4.0)
HAM-D total score ≥ 28, N (%)	28 (18.4)	33 (22.4)	38 (25.9)	29 (20.6)

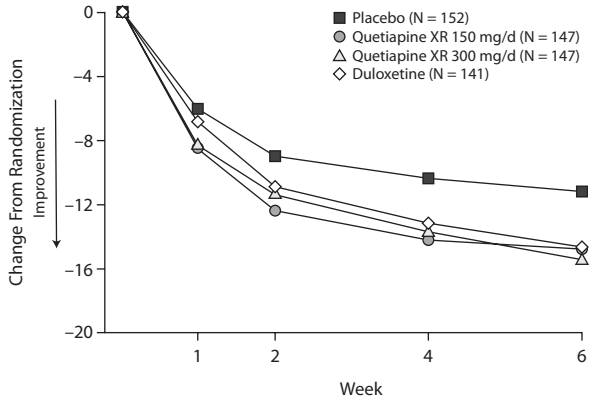
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, MITT = modified intent-to-treat, PSQI = Pittsburgh Sleep Quality Index, XR = extended release.

p < .01) groups. This significant reduction in MADRS scores was seen as early as week 1 (day 8) for quetiapine XR 150 mg/day (–8.36; p < .01) and 300 mg/day (–8.19; p < .01) compared with placebo (–6.01), but not for duloxetine (–6.81; p = .301) (Figure 2). At week 6, the effect sizes were 0.38 for quetiapine XR 150 mg/day and 0.42 for quetiapine XR 300 mg/day.

Individual items of the MADRS generally showed a significant improvement for both quetiapine XR doses and duloxetine versus placebo at week 6, including apparent sadness (item 1), reported sadness (item 2), and inability to feel (item 8), while at week 1 quetiapine XR 150 mg/day significantly improved item 2 (reported sadness), item 4 (reduced sleep), and item 10 (suicidal thoughts); quetiapine XR 300 mg/day only significantly improved item 4 (reduced sleep); and duloxetine showed significant improvements in item 2 (reported sadness) and a significant decline in item 5 (reduced appetite) (Figure 3). All of the treatment groups showed a similar improvement from randomization in MADRS item 10 (suicidal thoughts) score at week 6.

At week 6, response rates were significantly higher with quetiapine XR 150 mg/day (54.4%; p < .01), quetiapine XR 300 mg/day (55.1%; p < .01), and duloxetine

Figure 2. Change in MADRS Total Score From Baseline Over Time (LOCF; MITT population)



p Value vs Placebo:				
Quetiapine XR 150 mg/d	< .01	< .001	< .001	< .001
Quetiapine XR 300 mg/d	< .01	< .01	< .001	< .001
Duloxetine	.301	< .05	< .01	< .01

Abbreviations: LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, MITT = modified intent-to-treat, XR = extended release.

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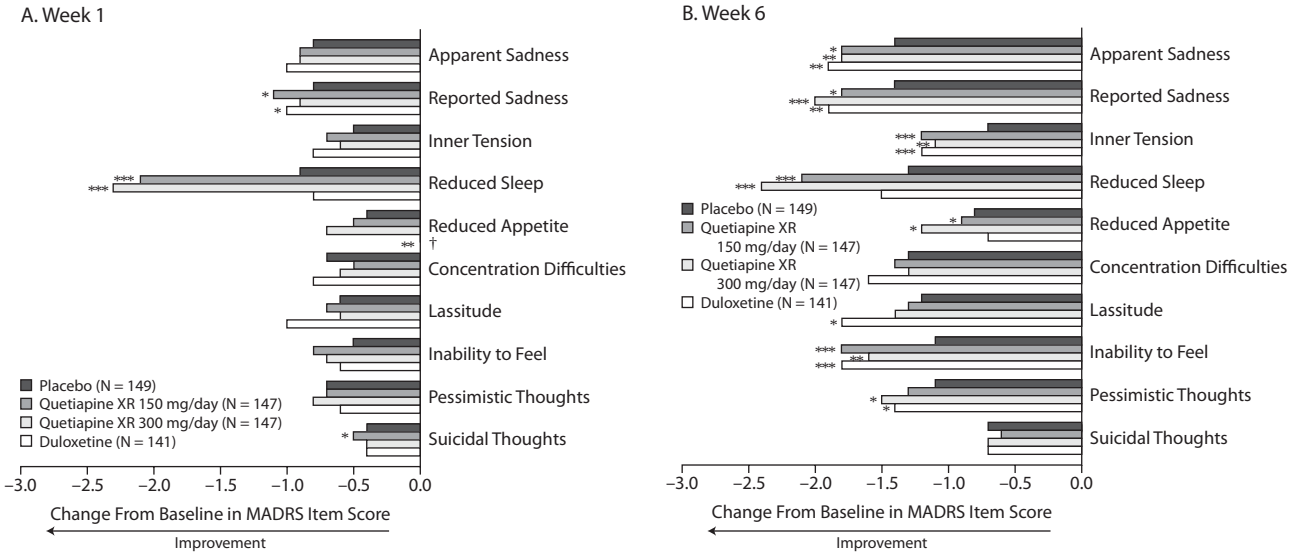
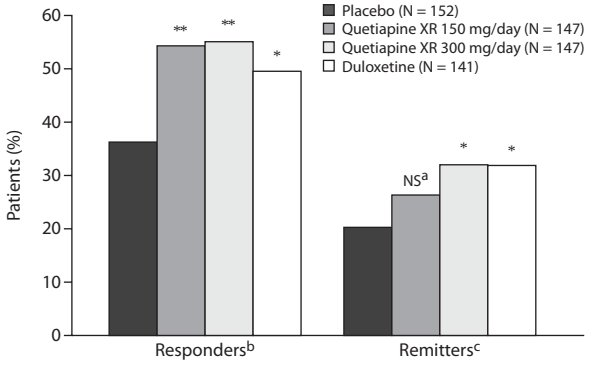
Figure 3. Change in MADRS Individual Item Scores From Baseline to (A) Week 1 and (B) Week 6 (LOCF; MITT population)



*p < .05, **p < .01, ***p < .001 vs. placebo.
†Change from baseline for duloxetine = 0; p value quoted is for duloxetine vs. placebo.
Abbreviations: LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, MITT = modified intent-to-treat, XR = extended release.

Figure 4. Proportion of MADRS Responders and Remitters at Week 6 (LOCF; MITT population)



[a]NS, p = .267.
[b]Response defined as ≥ 50% reduction in MADRS total score from baseline.
[c]Remission defined as MADRS total score ≤ 8.
*p < .05, **p < .01 vs. placebo.
Abbreviations: LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, MITT = modified intent-to-treat, XR = extended release.

(49.6%; p < .05) compared with placebo (36.2%) (Figure 4). Although there was a greater response in the active-treatment groups at week 1 (day 8) (quetiapine XR 150 mg/day, 19.0%; quetiapine XR 300 mg/day, 17.3%; duloxetine, 14.2%), these results were not statistically different from the rate in the placebo group (13.4%).

Remission rates at week 6 (Figure 4) were significantly higher than those for placebo (20.4%) for quetiapine XR 300 mg/day (32.0%; p < .05) and duloxetine (31.9%; p < .05), but the difference between quetiapine XR 150 mg/day (26.5%) and placebo was not statistically significant (p = .267). Post hoc analysis of remission rates using usual definitions of remission (MADRS total score ≤ 10 and MADRS total score ≤ 12) showed remission rates of 38.1% (p = .075), 39.5% (p < .05), 39.0% (p < .05), and 27.6% for MADRS ≤ 10 and 42.2% (p = .079), 47.6% (p < .01), 45.4% (p < .05), and 31.6% when MADRS ≤ 12 for the quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, duloxetine, and placebo groups, respectively.

HAM-D total and HAM-D scale item 1 (depressed mood) scores were significantly improved from baseline to week 6 in all active-treatment groups compared with placebo. HAM-D item 3 (suicide) scores were also statistically improved with quetiapine XR 150 mg/day and 300 mg/day, but not with duloxetine compared with placebo (Table 2).

At week 6, HAM-A total and HAM-A psychic anxiety subscale scores were significantly reduced in all active treatment groups compared with placebo, although this significant effect was not seen for HAM-A somatic anxiety subscale scores for any treatment (Table 2).

Quetiapine XR– and duloxetine-treated patients experienced a statistically significant improvement on the CGI-S scale versus placebo at week 6 (Table 2).

Numerical differences between the placebo and quetiapine XR and duloxetine groups were apparent as early as week 1 for the proportion of patients with CGI-I scores of

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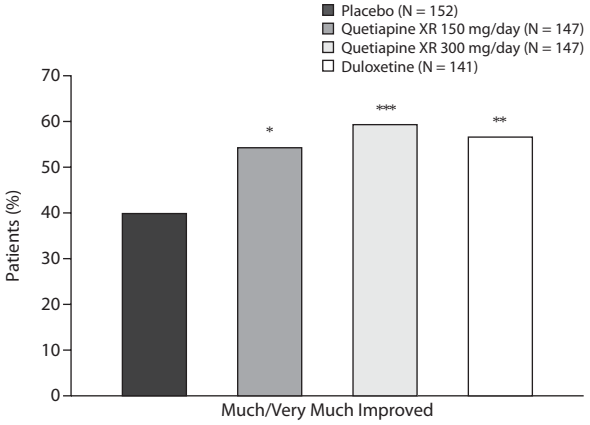
Table 2. Change From Baseline to Week 6 in Secondary Endpoints (MITT, LOCF)

Endpoint	Placebo (N = 152)	Quetiapine XR 150 mg/d (N = 147)		Quetiapine XR 300 mg/d (N = 147)		Duloxetine (N = 141)	
		Change	p Value	Change	p Value	Change	p Value
HAM-D total score	–10.26	–13.12	< .01	–14.02	< .001	–12.37	< .05
HAM-D item 1 (depressed item) score	–1.07	–1.49	< .01	–1.56	< .001	–1.53	< .001
HAM-D item 3 (suicide) score	–0.50	–0.64	< .05	–0.66	< .05	–0.60	.124
HAM-A total score	–5.55	–7.76	< .01	–7.38	< .01	–7.83	< .01
HAM-A psychic subscale score	–3.56	–5.27	< .001	–5.50	< .001	–5.40	< .001
HAM-A somatic subscale score	–1.96	–2.45	.142	–1.88	.804	–2.42	.174
CGI-S score	–1.06	–1.43	< .01	–1.60	< .001	–1.53	< .001
PSQI	–2.95	–4.59	< .001	–4.93	< .001	–3.24	.481

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward, MITT = modified intent-to-treat, PSQI = Pittsburgh Sleep Quality Index, XR = extended release.

Figure 5. Proportions of Patients Who Had a CGI-I Score of 1 or 2 at Week 6 (LOCF; MITT population)



*p < .05, **p < .01, ***p < .001 vs. placebo.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, LOCF = last observation carried forward, MITT = modified intent-to-treat, XR = extended release.

1 or 2 ("much/very much improved") (19.1% [p = .432], 22.3% [p = .147], and 19.4% [p = .411] in the quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, and duloxetine groups, respectively, vs. 15.4% in the placebo group). This effect became significant at week 4 with CGI-I "much/very much improved" proportions of 52.1% (p < .05), 50.3% (p < .05), and 52.5% (p < .05) in the quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, and duloxetine groups, respectively, versus placebo (38.2%). At week 6, a significantly greater proportion of patients had a CGI-I score of 1 or 2 ("much/very much improved") in all active treatment groups compared with placebo (Figure 5).

The quality of sleep improved significantly among those patients treated with both doses of quetiapine XR compared with placebo. Duloxetine showed no significant change from placebo in the PSQI analysis (Table 2).

Tolerability

Six-week active treatment randomized phase. Common AEs (whether or not considered treatment related) occurring in > 5% of patients during the randomized active treatment phase are shown in Table 3. The most common AEs reported for quetiapine XR were dry mouth, sedation, and somnolence, while the most common AEs reported with duloxetine were nausea, dry mouth, and headache. Thirty (19.7%) patients, 23 (15.1%) patients, 20 (13.1%) patients, and 7 (4.5%) patients discontinued the study due to AEs during the randomized phase in the quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, duloxetine, and placebo groups, respectively. The most common AEs leading to discontinuation were sedation and somnolence in the quetiapine XR group, nausea and sedation in the duloxetine group, and anxiety and depression in the placebo group.

The incidence of AEs associated with EPS (MedDRA preferred terms: akathisia, dyskinesia, drooling, restlessness, tremor, and psychomotor hyperactivity) in the quetiapine XR treatment groups was low (4.6% and 5.3% for 150 mg/day and 300 mg/day, respectively) and mild to moderate in intensity with no dose-related pattern, compared with placebo (3.2%). The overall incidence of AEs related to EPS was highest in the duloxetine group (8.1%). At the end of treatment, changes in mean SAS total scores were similar for all groups: 0.1, –0.1, and –0.2 for the quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, and duloxetine groups, respectively, compared with placebo (0.0). A decrease in mean BARS scores that was of similar intensity was seen for all treatment groups: –0.2, –0.1, and –0.1 for the quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, and duloxetine groups, respectively, compared with placebo (0.0).

AEs potentially related to sexual dysfunction (MedDRA preferred terms: anorgasmia, orgasm abnormal, erectile dysfunction, libido decreased, retrograde ejaculation, sexual dysfunction) were more common with duloxetine (8.7%) than with quetiapine XR 150 mg/day,

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quetiapine XR 300 mg/day, or placebo (1.3% in each group). CSFQ total score change from baseline to end of treatment showed that sexual functioning improved slightly in all 4 treatment groups, with no apparent difference between the groups (mean [SD] change: quetiapine XR 150 mg/day 0.7 [6.3], quetiapine XR 300 mg/day 1.6 [6.5], duloxetine 1.8 [6.8], and placebo 1.4 [7.3]). In addition, there were no clear differences between men and women with regard to sexual functioning.

No clinically relevant differences between groups were seen in the mean change from baseline to end of treatment for vital signs, ECGs, or hematology. There was no indication of increased QTc interval in any treatment group.

Changes in glucose and lipid laboratory parameters in the fasting-confirmed safety population are shown in Table 4. Fasting was confirmed by a documented report from the patient that last meal was ≥ 8 hours before blood sample taken for baseline and postbaseline laboratory measurements. Increases in mean glucose were observed in the quetiapine XR 150 mg/day (3.4 mg/dL), quetiapine XR 300 mg/day (4.6 mg/dL), and duloxetine (1.6 mg/dL) groups compared with placebo (1.3 mg/dL). The proportion of patients who experienced a clinically important shift (from normal to high, ≥ 126 mg/dL) of fasting glucose at the end of treatment was 2.9%, 6.3%, 1.1%, and 0.9% in the quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, duloxetine, and placebo groups, respectively. Mean decreases in low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol were observed in all groups, especially the quetiapine XR 150 mg/day group. Mean decreases in total cholesterol were observed in the quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, and placebo groups. Mean increases in triglycerides were observed in the quetiapine XR 150 mg/day and 300 mg/day groups

Table 3. Most Common Adverse Events (> 5%) in Any Treatment Group During the 6-Week Active Treatment/Randomized Phase Ordered by Incidence in the Quetiapine XR 300 mg/day Group (safety population)

Adverse Event,[a] N (%)	Placebo (N = 157)	Quetiapine XR 150 mg/d (N = 152)	Quetiapine XR 300 mg/d (N = 152)	Duloxetine (N = 149)
Dry mouth	14 (8.9)	51 (33.6)	58 (38.2)	28 (18.8)
Sedation	8 (5.1)	59 (38.8)	56 (36.8)	24 (16.1)
Somnolence	11 (7.0)	37 (24.3)	41 (27.0)	19 (12.8)
Dizziness	17 (10.8)	22 (14.5)	29 (19.1)	25 (16.8)
Headache	16 (10.2)	16 (10.5)	14 (9.2)	27 (18.1)
Constipation	10 (6.4)	9 (5.9)	13 (8.6)	17 (11.4)
Irritability	7 (4.5)	2 (1.3)	9 (5.9)	0
Dyspepsia	5 (3.2)	6 (3.9)	8 (5.3)	8 (5.4)
Fatigue	0	4 (2.6)	8 (5.3)	10 (6.7)
Nausea	15 (9.6)	16 (10.5)	8 (5.3)	54 (36.2)
Vision blurred	3 (1.9)	8 (5.3)	8 (5.3)	4 (2.7)
Increased appetite	3 (1.9)	9 (5.9)	6 (3.9)	3 (2.0)
Diarrhea	10 (6.4)	7 (4.6)	4 (2.6)	16 (10.7)
Upper respiratory tract infection	11 (7.0)	3 (2.0)	4 (2.6)	6 (4.0)
Abnormal dreams	1 (0.6)	10 (6.6)	3 (2.0)	4 (2.7)
Pollakiuria	2 (1.3)	5 (3.3)	3 (2.0)	8 (5.4)
Insomnia	11 (7.0)	2 (1.3)	2 (1.3)	22 (14.8)
Decreased appetite	1 (0.6)	5 (3.3)	0	8 (5.4)
Hyperhidrosis	1 (0.6)	0	0	11 (7.4)

[a]MedDRA preferred term.
Abbreviation: XR = extended release.

Table 4. Clinical Laboratory Parameters and Body Weight at Baseline and Changes in Parameters to Treatment End (safety population)[a]

Parameter	Placebo (N = 157)	Quetiapine XR 150 mg/d (N = 152)	Quetiapine XR 300 mg/d (N = 152)	Duloxetine (N = 149)
Glucose, mg/dL[b]				
Baseline	89.8 (9.9)	90.1 (12.2)	89.2 (10.4)	89.9 (9.8)
Change	1.3 (8.9)	3.4 (12.9)	4.6 (14.1)	1.6 (14.0)
Patients with clinically important elevated glucose values[b] (≥ 126 mg/dL) at the end of treatment, N (%)	1 (0.9)	3 (2.9)	6 (6.3)	1 (1.1)
Insulin, µIU/mL				
Baseline	11.9 (7.9)	14.2 (24.5)	12.1 (12.8)	10.5 (8.3)
Change	3.1 (17.0)	0.8 (29.0)	4.1 (9.4)	3.4 (11.7)
Total cholesterol, mg/dL[b]				
Baseline	192.7 (40.2)	194.8 (41.7)	194.0 (42.8)	194.7 (41.7)
Change	–3.3 (19.9)	–7.1 (26.3)	–1.4 (28.1)	0.4 (26.5)
LDL cholesterol, mg/dL[b]				
Baseline	113.6 (36.2)	112.9 (35.7)	115.9 (36.1)	115.5 (34.9)
Change	–2.1 (20.9)	–6.4 (25.8)	–2.4 (24.2)	–0.3 (22.1)
HDL cholesterol, mg/dL[b]				
Baseline	53.1 (14.3)	55.1 (16.2)	52.4 (15.5)	53.6 (14.3)
Change	–1.2 (7.7)	–3.1 (8.2)	–2.1 (7.7)	–0.6 (7.5)
Triglycerides, mg/dL[b]				
Baseline	130.2 (65.7)	140.0 (100.6)	129.7 (75.6)	127.9 (77.1)
Change	3.9 (59.8)	10.0 (78.5)	17.6 (65.6)	10.2 (93.9)
Prolactin, ng/mL				
Baseline	6.9 (3.5)	7.0 (3.9)	7.5 (4.9)	7.4 (5.6)
Change	0.3 (3.2)	1.1 (3.7)	1.1 (6.1)	1.0 (6.2)
Weight, kg				
Baseline	84.5 (23.3)	85.8 (22.9)	86.2 (22.8)	85.2 (19.7)
Change	0.1 (1.9)	1.0 (1.9)	1.3 (2.0)	–0.5 (2.6)
Patients with ≥ 7% increase in body weight, N (%)	0	3 (2.1)	5 (3.4)	1 (0.7)

[a]Values shown as mean (SD) unless otherwise indicated.
[b]Fasting documented by patient report of ≥ 8 h since last meal before blood sample taken for baseline and postbaseline laboratory measurements.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein, XR = extended release.

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Table 5. Most Common Adverse Events (> 3%) in Any Treatment Group During the 2-Week Discontinuation/Tapering Phase (safety population)

Adverse Event, N (%)	Placebo (N = 157)	Quetiapine XR 150 mg/d (N = 152)	Quetiapine XR 300 mg/d (N = 152)	Duloxetine (N = 149)
Nausea	1 (0.6)	9 (5.9)	8 (5.3)	2 (1.3)
Headache	6 (3.8)	7 (4.6)	6 (3.9)	9 (6.0)
Insomnia	3 (1.9)	9 (5.9)	4 (2.6)	2 (1.3)
Diarrhea	4 (2.5)	5 (3.3)	4 (2.6)	4 (2.7)
Dizziness	1 (0.6)	2 (1.3)	2 (1.3)	8 (5.4)
Vomiting	3 (1.9)	5 (3.3)	2 (1.3)	1 (0.7)

Abbreviation: XR = extended release.

(10.0 and 17.6 mg/dL) compared with the duloxetine (10.2 mg/dL) and placebo (3.9 mg/dL) groups. Changes in mean insulin levels were 0.8, 4.1, 3.4, and 3.1 μIU/mL in the quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, duloxetine, and placebo groups, respectively.

Small increases in mean weight were observed in the quetiapine XR 150 mg/day and 300 mg/day groups (1.0 kg and 1.3 kg, respectively) compared with duloxetine (–0.5 kg) and placebo (0.1 kg) (Table 4). The percentages of patients with weight increases of ≥ 7% were higher in patients receiving quetiapine XR 150 mg/day (2.1%) and 300 mg/day (3.4%) compared with placebo (0%) and duloxetine (0.7%).

Two-week discontinuation phase. Of those patients who completed the 6-week randomized treatment phase, 73.0% of quetiapine XR 150 mg/day patients, 81.4% of quetiapine XR 300 mg/day patients, 67.6% of duloxetine patients, and 80.6% of placebo patients completed the 2-week drug-discontinuation TDSS phase.

During the 2-week discontinuation/tapering phase, the most common reasons for discontinuation, after subject not completing the 2-week assessment, were subject lost to follow-up and subject not willing to continue study, in all treatment groups. Two patients in the quetiapine XR 150 mg/day group and 4 patients in the duloxetine group discontinued due to an AE. One patient in the quetiapine XR 150 mg/day group discontinued due to gastroenteritis, and 1 patient in the duloxetine group discontinued due to aggression and alcohol poisoning.

During this phase, the range of TDSS total mean scores was 2.6 to 4.3 for patients in the down-titrated quetiapine XR 150 mg/day group, 1.7 to 3.8 for quetiapine XR 300 mg/day, 2.4 to 4.3 for duloxetine, and 1.6 to 2.9 for placebo. The most common AEs during the discontinuation period were headache and dizziness for duloxetine, nausea and insomnia for quetiapine XR 150 mg/day, and nausea and headache for quetiapine XR 300 mg/day (Table 5).

DISCUSSION

This is the first large-scale, double-blind, randomized, parallel-group, placebo-controlled study to evaluate the efficacy of atypical antipsychotic monotherapy in patients with MDD. Other studies have looked at the use of atypical antipsychotics as augmentation or adjunct therapy.

At endpoint, quetiapine XR monotherapy showed a statistically significant improvement on depressive symptoms as measured by the MADRS. As well as significant improvement in the MADRS total score versus placebo, 7 out of the 10 individual MADRS items also showed a positive response. Improvement in items 1 (apparent sadness), 2 (reported sadness), 3 (inner tension), 4 (reduced sleep), 5 (reduced appetite), and 8 (inability to feel) was seen in both the quetiapine XR 150 mg/day and 300 mg/day groups compared with placebo. Significant improvement was also seen in the quetiapine XR 300 mg/day group in item 9 (pessimistic thoughts) compared with placebo. These results suggest that the improvement in MADRS scores was not attributable only to decreases in the reduced sleep item (5). This indicates an antidepressant effect on core symptoms of depression rather than merely a secondary effect by improving only nonspecific symptoms, such as insomnia. Differences from placebo of around 2 points on the HAM-D were reported for a range of antidepressants in the FDA pivotal studies.[40] In this study, differences from placebo were 2.86 and 3.76 points on the HAM-D total score and 3.63 and 4.11 points on the MADRS total score for the quetiapine XR 150 mg/day and 300 mg/day groups, respectively. Therefore, the magnitude of effect of quetiapine XR on depressive symptoms is consistent with those observed for a range of FDA-approved antidepressants.[40]

Quetiapine XR was effective in improving the symptoms of depression over the 6-week period, and both quetiapine XR groups showed a statistically significant improvement in total MADRS scores compared with placebo at week 1, whereas duloxetine did not. Significant separation from placebo was not seen with duloxetine until 2 weeks, which is consistent with its phase 3 study results.[41] This early symptom improvement with quetiapine XR has also been seen in earlier quetiapine studies in patients with bipolar depression.[10,11,42,43] While the largest improvement at week 1 with quetiapine XR was seen in the reduced sleep item, significant improvement was also seen in reported sadness and suicidal thoughts, which suggests improvement beyond reduced sleep. The benefits of earlier symptom improvement include a potential reduction in the risk of suicide and lowered costs due to a reduction in hospitalization and return to productivity.[44] The changes at week 1 for quetiapine XR in this study were statistically significant and are a sign of early symptom improvement that may be clinically relevant for some patients.

Significant improvements were observed in response (quetiapine XR 150 and 300 mg/day) and remission (quetiapine XR 300 mg/day) at week 6. For this study,

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MADRS remission was defined as a MADRS total score ≤ 8 at week 6. This is conservative compared with most studies, which use a MADRS total score ≤ 10[45] or ≤ 12.[46] Post hoc analysis of MADRS remission rates using the more usual definitions of remission (MADRS total score ≤ 10 and ≤ 12) showed significant improvement in the quetiapine XR 300 mg/day group versus placebo, but not for quetiapine XR 150 mg/day. Quetiapine XR 150 mg/day only showed a trend ($p = .075$ and $p = .079$) using the more usual criteria (MADRS total score ≤ 10 and ≤ 12, respectively), which suggests that for some patients 300 mg/day of quetiapine XR is the more effective dose. The response and remission rates seen for placebo in this study are consistent with those seen in other positive clinical trials of MDD.[47]

There was no evidence to indicate a relationship between quetiapine XR treatment and increased suicidality. In fact, suicidality as measured by MADRS item 10 numerically decreased in the quetiapine XR 150 and 300 mg/day groups, in a magnitude similar to placebo. At week 1, quetiapine XR 150 mg/day significantly improved the MADRS item 10 score, and quetiapine XR 300 mg/day numerically decreased the MADRS item 10 score in a magnitude similar to placebo. Furthermore, significantly greater improvements were seen in the HAM-D item 3 (suicide) scores in the quetiapine XR 150 and 300 mg/day groups compared with placebo. This is consistent with previous findings in bipolar depression studies; however, a full evaluation of this outcome across all MDD studies with quetiapine XR is required.[48] While preliminary, these results are important in light of the black box warnings about suicidality for antidepressants, which were also included for quetiapine on its U.S. approval for bipolar depression, as well as the FDA's new requirement for suicidality monitoring in all clinical trials.[49]

This patient population had relatively elevated psychic anxiety and low somatic anxiety scores at baseline, consistent with a diagnosis of MDD without comorbid anxiety disorder. Quetiapine XR monotherapy was effective in improving these psychic anxiety symptoms compared with placebo as measured by HAM-A total scores. Anxiety symptoms are often distressing for patients and often lead to polypharmacy as well.[50] The changes in HAM-A scores seen in this study warrant further investigation of quetiapine XR for the treatment of anxiety disorders, and publication of recently completed large-scale studies in generalized anxiety disorder is awaited.

Insomnia is a core symptom of depression (according to the DSM-IV) and is one of the most common presenting symptoms.[51] The SSRIs and SNRIs appear to have a disruptive effect on sleep and sleep architecture,[52] and the failure of duloxetine to show any benefit on sleep in this study is a representative finding. In contrast, quetiapine XR at both doses tested had a significant beneficial effect on sleep, as shown by the significant changes in MADRS item 4 (reduced sleep), which were seen as early as week 1 and also in the PSQI total score at week 6.

Quetiapine XR monotherapy (150 and 300 mg/day) was generally well tolerated in this study with a safety profile consistent with that seen previously in other studies with quetiapine and its known pharmacologic profile.[10,11] The most common AEs were dry mouth, sedation, somnolence, dizziness, and headache in the quetiapine XR treatment group and nausea, dry mouth, headache, dizziness, and sedation in the duloxetine treatment group. The majority of AEs experienced were mild to moderate in intensity.

The most common AEs that led to discontinuation were sedation and somnolence in the quetiapine XR groups, nausea and sedation in the duloxetine group, and anxiety and depression in the placebo group. There appeared to be a dose-related increase in the incidence of somnolence, dizziness, and fatigue with quetiapine XR; however, fewer patients discontinued in the quetiapine XR 300 mg/day group during the randomized phase due to AEs (15.1%) compared with the quetiapine XR 150 mg/day group (19.7%).

Discontinuation effects can be seen with most currently approved antidepressants; however, low rates were observed in this study. The most common AEs during the TDSS period were nausea, headache, and insomnia in the quetiapine XR groups and headache and dizziness in the duloxetine group.

Overall, the number of patients who discontinued due to condition worsening was low in all treatment groups, particularly the placebo group (1.9%). It is possible that some of the patients who were recorded as lost to follow-up and not willing to continue (5.7% each for placebo) may have discontinued due to lack of efficacy.

The incidence of spontaneously reported EPS-related AEs in the quetiapine XR groups was low and generally mild to moderate. These results were confirmed by the assessment of parkinsonian and akathisia symptoms using SAS and BARS scores, which indicated that quetiapine XR treatment was similar to placebo, with the majority of patients in each treatment group experiencing no change or an improvement in score at the end of treatment. EPS-like symptoms are known to occur with SSRI and SNRI treatments,[53] and this was seen in the present study, in which duloxetine was associated with higher levels of these symptoms than either quetiapine XR or placebo. While the long-term tolerability profile of quetiapine XR has not been established, quetiapine IR is characterized by a lower propensity to cause EPS than other antipsychotics.[54–56] This predicts that quetiapine may have less potential than standard antipsychotic agents to induce tardive dyskinesia.[57]

Loss of libido and disorders of arousal and orgasm are common and affect up to 75% of patients with MDD.[58] It is therefore important that treatment does not exacerbate

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these symptoms. Sexual dysfunction is a well-known side effect of SSRIs and SNRIs that compromises treatment and adherence.[59,60] In the present study, duloxetine AEs related to sexual dysfunction were 6-fold higher than with quetiapine XR or placebo, which did not differ from each other in this regard.

In the present study, all treatment groups showed small increases in mean glucose, with the greatest increases in the quetiapine XR groups, and the numbers of patients who experienced clinically important elevated glucose values at the end of treatment were 3, 6, 1, and 1 in the quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, duloxetine, and placebo groups, respectively. In this trial, the increase in glucose levels may be dose related and independent of an increase in insulin, because there were not large increases in the quetiapine XR groups relative to placebo. Small decreases in total cholesterol (< 5%) were observed with both doses of quetiapine XR and in the placebo group; a slight increase was observed in the duloxetine group. LDL and HDL cholesterol were also decreased with quetiapine XR at both doses and with duloxetine. Increases in triglycerides were observed in all 3 active treatment groups. Both quetiapine XR groups showed a small increase in mean weight (1.0 kg and 1.3 kg in the quetiapine XR 150 mg/day and 300 mg/day groups, respectively) and a higher percentage of patients experiencing weight gain ≥ 7% during the study, in comparison with duloxetine and placebo. There also appeared to be a possible dose relationship for weight gain. Although numerical increases in glucose levels, triglycerides, and weight were seen in this trial for quetiapine XR, additional assessments of quetiapine XR are needed to further understand these effects in a larger patient population and over longer term treatment. Psychiatric patients (especially patients with bipolar disorder and schizophrenia) tend to be overweight and at metabolic risk.[61–63] There is also an increased incidence of smoking in patients with psychotic and mood disorders.[64] Weight increases have also been observed with SSRIs and with other antidepressants.[65] While some patients may experience greater efficacy with higher doses, quetiapine XR should be individualized for each patient to achieve the optimal balance of efficacy with safety and tolerability.

While the long-term tolerability profile of quetiapine XR has not yet been established in MDD, increases in weight have been observed in treatment with quetiapine IR.[43,66] Although a causal relationship with diabetes has not been established, patients who are at risk for developing diabetes are advised to have appropriate clinical monitoring. Similarly, patients with existing diabetes should be monitored for exacerbation. The study was designed to evaluate quetiapine XR in the acute treatment of MDD and therefore lasted for 8 weeks, including 6 weeks of active treatment. Publication of results from a completed maintenance study is awaited.

A limitation of the study was that the dosing was not flexible for any of the active treatments, which is not reflective of clinical practice. It is possible that some patients may have been assigned a dose of quetiapine XR that was either too high or too low. Doses other than 150 or 300 mg/day may need to be studied in order to fully characterize the optimal dose range. Another limitation of the study included the use of a fixed dose with no titration for duloxetine; however, this is consistent with the prescribing information and EMEA requirement to use a minimum effective dose.[23,28] The dosing used for duloxetine in this study may have led to a higher incidence of AEs and discontinuation for some patients; however, using 30 mg/day for the first week could be seen to bias the study in favor of quetiapine XR, especially in view of the findings of 1-week efficacy for quetiapine XR and not for duloxetine. Moreover, duloxetine was included as a measure of assay sensitivity.

Atypical antipsychotics have demonstrated antidepressant efficacy in the treatment of bipolar depression and as add-on therapy to antidepressants in MDD. This study adds to the evidence for the effect of quetiapine XR on depressive symptoms.

Quetiapine has demonstrated efficacy for psychotic and mood disorders including bipolar mania, bipolar depression, and unipolar MDD. Some other medications in this class have also demonstrated efficacy and have certain FDA approvals for schizophrenia, bipolar disorder, and treatment-resistant depression. At this time, however, none have shown efficacy as monotherapy for MDD.

In conclusion, this large, multicenter, double-blind, randomized, parallel-group, placebo- and active-controlled, phase 3 study provides the first data showing quetiapine XR monotherapy is effective and generally well tolerated as a short-term treatment for patients with MDD. These results, along with the positive findings from a recent clinical trial of quetiapine XR as adjunct treatment to antidepressant therapy in patients with inadequate antidepressant response[67] and those from a study of quetiapine XR monotherapy for long-term, maintenance (up to 52-week) treatment of MDD,[68] provide evidence of a broad spectrum of effect for quetiapine XR in the treatment of patients with MDD.

Drug names: bupropion (Aplenzin, Wellbutrin, and others), duloxetine (Cymbalta), fluoxetine (Prozac and others), lorazepam (Ativan and others), quetiapine (Seroquel), zaleplon (Sonata and others), zolpidem tartrate (Zolpimist, Ambien, and others), zopiclone (Lunesta).

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