ORIGINAL RESEARCH

Key Words: Clinical trial, Phase III; anxiety disorders; sustained-release preparations; antipsychotics; treatment efficacy

Extended Release Quetiapine Fumarate (Quetiapine XR) as Adjunct Therapy in Patients with Generalized Anxiety Disorder and a History of Inadequate Treatment Response: A Randomized, Double-Blind Study

By Arifulla Khan, Sarah Atkinson, Irina Mezhebovsky, Fahua She, Todd Leathers, Sanjeev Pathak

ABSTRACT ~ Objective: *To evaluate the efficacy and tolerability of adjunct extended release quetiapine fumarate (quetiapine XR) in patients with generalized anxiety disorder (GAD) and inadequate response to selective serotonin reuptake inhibitors/serotonin norepinephrine reuptake inhibitors (SSRI/SNRIs).* ***Methods:*** *11-week (1-week single-blind placebo run-in; 8-week randomized treatment; 2-week post-treatment period), double-blind, placebo-controlled study. Patients were randomized to quetiapine XR or placebo adjunct to SSRI/SNRI. 50 mg initial dose; 150 mg/day, Day 3; 300 mg/day, Weeks 3 and 4 if indicated (Clinical Global Impressions-Severity of Illness [CGI-S] ≥ 4; 150 mg/day tolerated). Primary endpoint: change from randomization to Week 8 in HAM-A total score. Secondary variables: Hamilton Rating Scale for Anxiety (HAM-A) psychic/somatic clusters, response and remission; and CGI-S.* ***Results:*** *409 patients were randomized to quetiapine XR (n = 209) or placebo (n = 200); 41% and 55% of patients, respectively, had dose increases (300 mg/day). Week 8 mean change in HAM-A total score was not statistically significant for quetiapine XR (−10.74; p = 0.079) versus placebo (−9.61). Secondary variables were generally consistent with the primary analysis, except a significant reduction in HAM-A total score at Week 1 (−6.45, quetiapine XR versus −4.47, placebo; p < 0.001); significant improvements in HAM-A psychic cluster (p < 0.05) and CGI-S total*

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($p < 0.05$) scores at Week 8. Adverse events (>10% either group) were dry mouth, somnolence, sedation, headache, and dizziness. ***Conclusions:*** *In patients with GAD and inadequate response to SSRI/SNRI, adjunct quetiapine XR did not show a statistically significant effect for the primary endpoint at Week 8, although some secondary endpoints were statistically significant versus placebo. Quetiapine XR was generally well tolerated.*
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INTRODUCTION

Generalized anxiety disorder (GAD) is a chronic condition with low recovery rates and a high likelihood of recurrence. For example, the 12-year Harvard-Brown Anxiety Research Project predicted probabilities for recovery and recurrence of GAD of 0.58 and 0.45, respectively.[1] Patients with GAD experience impaired functioning, decreased work productivity, and increased healthcare utilization.[2,3]

Published guidelines recommend selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) as first-line treatment of GAD.[4–7] In clinical studies, remission rates of 33–39% have been reported with paroxetine[8] and 43% with venlafaxine XR.[9] The World Federation of Societies of Biological Psychiatry also includes pregabalin as a first-line option.[5] However, for many patients with GAD, initial pharmacotherapy does not lead to remission[2] and the concept of 'refractory' or 'treatment-resistant' GAD has emerged. As yet a uniform definition of treatment-resistant GAD is lacking, although failure to achieve remission following treatment with an adequate antidepressant dose for an appropriate length of time has been used to define treatment resistance in clinical trials.[10,11] Benzodiazepines may be used for short-term (2–4 weeks) therapy,[4,7] second-line treatment,[6] or treatment-resistant cases.[5] Other strategies for treatment-resistant GAD include tricyclic antidepressants, or adjunct therapy with an atypical antipsychotic.[5]

The efficacy and tolerability of once-daily extended release quetiapine fumarate (quetiapine XR) have been evaluated in GAD; three acute monotherapy studies in adults[12–14] and one in the elderly[15] demonstrated that quetiapine XR was effective at significantly reducing anxiety symptoms compared with placebo. Also, in a long-term (up to 52-week) monotherapy maintenance study in patients stabilized on quetiapine XR, improvement in anxiety symptoms was maintained and the risk of recurrence of anxiety was significantly reduced with quetiapine XR compared with placebo.[16] In all five studies the overall tolerability and safety results among quetiapine XR-treated patients were consistent with the known profile of quetiapine.[17,18] Currently, quetiapine XR is not approved for the treatment of GAD in the USA or Europe.

This study evaluated the efficacy and tolerability of quetiapine XR as adjunct to SSRI/SNRI therapy in patients with GAD with a history of partial or no (inadequate) response to SSRI/SNRI treatment either as monotherapy or in combination with a benzodiazepine.

METHODS

Study Design

This was an 11-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled study (D1441L00016; Palladium; NCT00534599). Eligible patients entered a 1-week single-blind placebo run-in period, followed by an 8-week randomized active treatment phase and a 2-week post-treatment period (Figure 1).

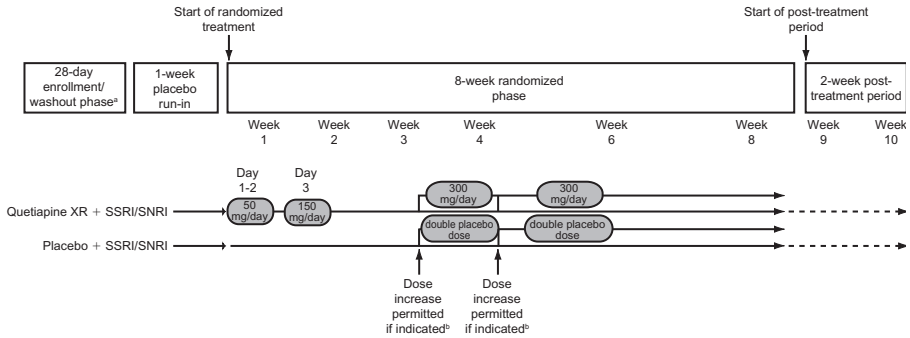
The study was approved by the institutional review board or independent ethics committee for each site and performed in accordance with the Declaration of Helsinki, the International Conference on Harmonization, Good Clinical Practice guidelines, and applicable regulatory requirements. After complete description of the study to the patients, written informed consent was obtained.

Patients

Male or female outpatients (aged 18–65 years) with a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)[19]

FIGURE 1

STUDY DESIGN



[a]Enrollment was a maximum of 28 days prior to placebo run-in period.
[b]Dose increase in patients who continued to have a CGI-S score ⩾4 and who were able to tolerate the 150 mg/day dose.
CGI-S, Clinical Global Impressions-Severity of Illness; SNRI, selective norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

diagnosis of GAD as assessed by the Mini International Neuropsychiatric Interview[20] were eligible for inclusion in the study. Patients were required to have a Hamilton Rating Scale for Anxiety (HAM-A)[21] total score ⩾20 with Item 1 (anxious mood) and Item 2 (tension) scores ⩾2 at enrollment, placebo run-in and randomization, and a Clinical Global Impressions-Severity of Illness (CGI-S)[22] score ⩾4 at enrollment and randomization. During the current anxious episode, patients were required to have a history of partial or no (inadequate) response to duloxetine, escitalopram, paroxetine, or venlafaxine XR. Partial or no (inadequate) response was defined as continuing symptoms following ⩾8 weeks of therapy prior to enrollment at adequate doses (minimum effective dose according to US label and including ⩾1 dose increase as permitted by US label).

Exclusion criteria included: any DSM-IV Axis I disorder other than GAD within 6 months prior to enrollment; presence or history of schizophrenia or other psychotic disorders using DSM-IV criteria; any DSM-IV Axis II disorder likely to interfere with the patient's participation in the study; depressive symptoms (Montgomery-Åsberg Depression Rating Scale [MADRS] total score >16 at enrollment or randomization); current serious suicidal or homicidal risk, MADRS Item 10 score ⩾4, or a suicide attempt during the 6 months prior to enrollment; substance or alcohol abuse within 6 months prior to enrollment; evidence of clinically relevant disease; clinically significant deviation from reference range in clinical laboratory results. Patients could not have received an antipsychotic, antidepressant (except those listed above), or benzodiazepine (unless ongoing at a stable dose for ⩾4 weeks prior to enrollment) within 7 days of randomization; mood stabilizers or monoamine oxidase inhibitors within 14 days prior to randomization; or fluoxetine within 28 days. Patients were permitted to continue receiving psychotherapy if it had been ongoing for ⩾3 months prior to randomization.

Treatment

Following placebo run-in, patients were randomized (1:1 ratio using a computer-based system to generate the randomization list) to quetiapine XR + SSRI/SNRI or placebo + SSRI/SNRI for 8 weeks. Placebo tablets were identical in size, color, smell, and taste to quetiapine XR 50 mg or 300 mg tablets and packaging was identical. Quetiapine XR or placebo was administered orally, once-daily in the evening.

Quetiapine XR was initiated at 50 mg/day, with the dose increased to 150 mg/day on Day 3. At Weeks 3 or 4 a mandatory dose increase to

300 mg/day was made in patients with a CGI-S score ⩾4 who tolerated the 150 mg/day dose. No dose increases were permitted after Week 4. Patients unable to tolerate the higher dose returned to 150 mg/day at anytime at the investigator's discretion. Patients continued to receive the same SSRI or SNRI at the same dose as at enrollment throughout the study.

Adherence

Treatment adherence was assessed at each visit based on returned tablet count; defined as a ⩾70% to ⩽120% consumption of doses. Patients repeatedly or severely nonadherent were discontinued at the investigator's discretion.

Concomitant Treatment

Chloral hydrate (1 g), zaleplon (20 mg), zolpidem tartrate (10 mg), or zopiclone (7.5 mg) were permitted twice weekly for insomnia up to Day 14 (except before study assessments). Other psychoactive medication was not permitted. Anticholinergics for extrapyramidal symptoms (EPS) were permitted, but were not permitted for prophylactic use.

Efficacy Evaluations

The primary efficacy endpoint was change from randomization to Week 8 in HAM-A total score.

Secondary endpoints included: change in HAM-A total score from randomization to Week 1; change from randomization in HAM-A psychic and somatic cluster scores at Weeks 1 and 8; HAM-A response (⩾50% decrease in HAM-A total score from randomization) rate at Weeks 1 and 8; HAM-A remission (HAM-A total score ⩽7) rate at Week 8; change from randomization in CGI-S total score at Weeks 1 and Week 8; and the proportion of patients with a CGI-Improvement (CGI-I) score of 1 ('very much improved') or 2 ('much improved') at Week 8.

HAM-A and CGI-S scores were assessed at enrollment, randomization (Day 1), and Weeks 1–4, 6, and 8. HAM-A scores were also determined at the start of placebo run-in. CGI-I scores were determined at Weeks 1–4, 6, and 8. Standardized training was provided to ensure inter-rater reliability for the HAM-A, CGI-S, and CGI-I scales. To reduce scoring variability, the same rater conducted all assessments for a given patient for a specific scale whenever possible.

Health-Related Quality of Life

The 16-item Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)[23] was administered at randomization and Weeks 2, 4, and 8. Each item was scored on a scale of 1 (very poor) to 5 (very good) for overall satisfaction. The total score was the sum of the scores for Items 1–14. The percentage of the maximum possible score (Q-LES-Q%) was calculated by subtracting 14 from the total score, dividing by 56, then multiplying by 100.[23] The change from randomization at Week 8 in Q-LES-Q% maximum total score (Items 1–14), Item 15 (satisfaction with medication), and Item 16 (overall life satisfaction) were recorded.

Safety and Tolerability Evaluations

The incidence and severity of adverse events (AEs), and AEs leading to withdrawals were recorded throughout the study. Serious AEs (SAEs) were recorded until 30 days after the last dose of study medication. All AEs and SAEs were followed until resolution or the investigator decided no further follow-up was necessary.

All AEs of suicidality (suicide attempts, ideation, completed suicide, and suicidal behavior) were monitored during the study. The number of patients with either a MADRS Item 10 score ⩾4 or an AE associated with suicidality was assessed. An analysis of suicidality using a classification system similar to that established by Columbia University[24] was also conducted; incidences of suicidal behavior/ideation (Columbia codes 1, 2, 3, 4) and possible suicidal behavior/ideation (Columbia codes 5, 6, 9) were evaluated.

A physical examination and electrocardiogram (ECG) were conducted at enrollment and Week 8. Laboratory measurements were performed at enrollment and Weeks 4 and 8. Vital signs and body weight were recorded at enrollment and all subsequent visits. Simpson-Angus Scale (SAS)[25] and Barnes Akathisia Rating Scale (BARS)[26] total scores were assessed at randomization and Weeks 2, 4, 6, and 8. MADRS scores (evaluating depressive symptoms) were assessed at enrollment, randomization, Weeks 4 and 8.

During the post-treatment period, a modified 18-item Treatment Discontinuation Signs and Symptoms (TDSS) scale was used. This scale was a hybrid of the 43-item discontinuation emergent signs and symptoms scale[27] and the 17-item discontinuation scale[28] and included additional AEs of 'vomiting', 'nausea', and 'trouble-sleeping, insomnia'. Patients completing the randomized phase rated discontinuation symptoms using the TDSS scale via a telephone-based interactive voice

response system at Week 8 (TDSS baseline) and post-treatment Days 1, 3, 5, 7, and 14.

Statistical Analysis

To provide 90% power, the target sample size was 191 evaluable patients per group based on a treatment difference of 2.5 points between quetiapine XR and placebo, and a standard deviation (SD) of 7.5 for the mean change from randomization in HAM-A total score at Week 8.

Efficacy analyses used the modified intention-to-treat (MITT) population (randomized patients who received study drug, and had randomization and ⩾1 post-randomization HAM-A total score). The per protocol (PP) population was a subset of the MITT population who had no significant protocol violations or deviations potentially affecting efficacy. The safety population included all patients who received ⩾1 dose of study medication. The TDSS population included patients who completed 8 weeks of treatment, had a Week 8 and ⩾1 other TDSS score.

The last observation carried forward (LOCF) approach was used for imputation of missing data. Statistical tests were two-sided with an alpha level of significance of 0.05 ($\alpha = 0.05$), unless otherwise specified. Secondary analyses reported nominal 5% levels of significance. No confirmatory analyses were made for secondary variables other than Q-LES-Q% maximum total score.

For the primary efficacy endpoint an analysis of covariance (ANCOVA) model was used, with HAM-A total score at randomization as a covariate, treatment as a fixed effect, and center as a random effect. To control overall Type 1 error rate at 0.05,[29] a sequential stepwise procedure was used, starting with the primary efficacy variable followed by the Q-LES-Q% maximum score, both nominal and adjusted p-values were presented. A similar ANCOVA model was used for other continuous variables. Logistic regression (with score at randomization as covariate and treatment included as a fixed effect) was used to compare quetiapine XR with placebo for categorical variables including HAM-A response, HAM-A remission, and CGI-I.

To assess the robustness of the primary analysis, a mixed-model repeated measures (MMRM) analysis was performed on the change from randomization over time in HAM-A total score (observed cases [OC]); treatment, visit, and treatment-by-visit interactions were included as fixed effects, center was included as a random effect, and baseline HAM-A total score was adjusted as a covariate. A robustness analysis for the primary efficacy variable using an ANCOVA model on the PP analysis population was also performed.

A subgroup analysis of change from randomization in HAM-A total score according to final prescribed quetiapine XR dose (150 mg/day or 300 mg/day) and an ANCOVA including final prescribed dose group were performed. Similarly, an ANCOVA of the primary efficacy variable by: gender, age group (18–39, 40–65), baseline body mass index (BMI), and baseline severity subgroup of 'severe' (HAM-A total score at baseline ⩾29) versus 'non-severe' (HAM-A total score at baseline <29) was conducted.

Number needed to treat (NNT) was calculated using the formula[30]:

> 1/([proportion of quetiapine XR-treated patients with positive response] − [proportion of placebo-treated patients with positive response])

Descriptive statistics were provided for tolerability variables and TDSS total scores. In addition, for the assessment of suicidal ideation/behavior (Columbia Classification codes 1, 2, 3, 4), a log binomial regression analysis was performed to estimate the relative risk ratio and 95% confidence interval (CI) (treatment was included as a fixed effect) for quetiapine XR versus placebo.

RESULTS

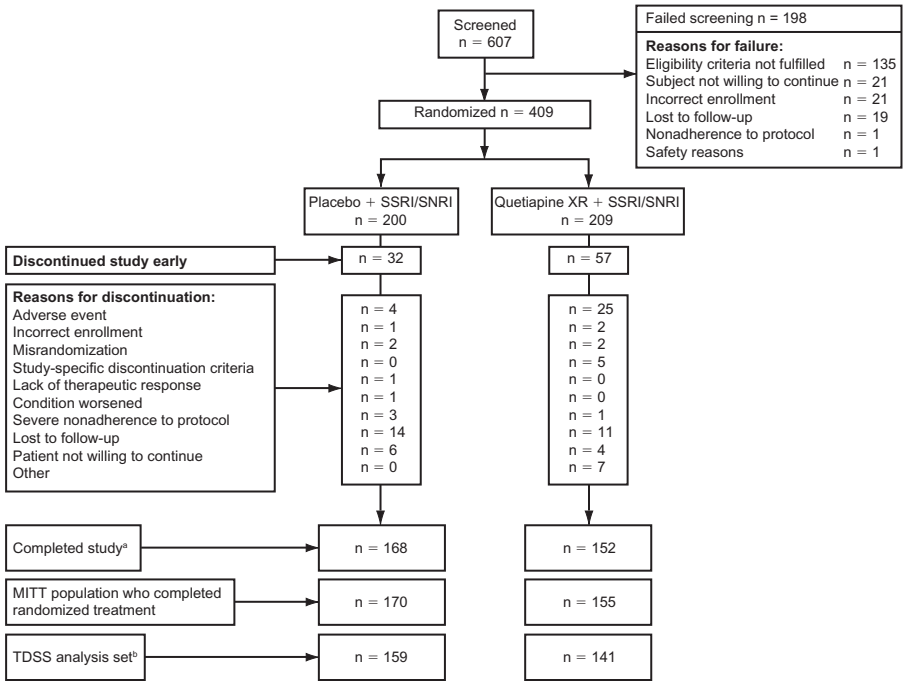
Patient Population

The first patient was enrolled on August 31, 2007, and the last patient completed on September 2, 2008. Of the 607 patients recruited from 54 centers in the USA, 409 were randomized to quetiapine XR + SSRI/SNRI (n = 209) or placebo + SSRI/SNRI (n = 200); no randomized patients were excluded from the safety population (Figure 2). The MITT population comprised 402 patients (7 patients were excluded due to missing/invalid randomization or post-randomization HAM-A scores): quetiapine XR + SSRI/SNRI (n = 204) or placebo + SSRI/SNRI (n = 198). The PP population comprised 181 and 177 patients and the TDSS population comprised 141 and 159 patients in the quetiapine XR + SSRI/SNRI and placebo + SSRI/SNRI groups, respectively. A total of 320/409 (78.2%) patients completed the study: 152/209 quetiapine XR-treated and 168/200 placebo-treated patients. In the quetiapine XR + SSRI/SNRI group the most common reason for withdrawal was an AE (n = 25); in the placebo + SSRI/SNRI group the most common reason for withdrawal was 'lost to follow-up' (n = 14) (Figure 2).

Treatment groups were generally well matched with respect to demographic and clinical characteristics at randomization and the SSRI or

FIGURE 2

PATIENT DISPOSITION



[a]Completed the randomized treatment period and the 2-week post-treatment period.
[b]Subset of MITT population that includes only patients who completed 8 weeks of treatment and entered the Post-treatment period.

MITT, modified intention-to-treat; SNRI, selective norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TDSS, treatment discontinuation signs and symptoms.

SNRI used (Table 1). The mean dose at randomization and duration of treatment prior to randomization of the combination therapies is shown in Table 1.

Study Treatment

The mean (SD) dose of adjunct agent (quetiapine XR or placebo) was 174.3 (49.0) mg/day and 190.3 (49.6) mg/day for quetiapine XR-treated and placebo-treated patients, respectively. In total, 86/209 (41.1%) quetiapine XR-treated and 110/200 (55.0%) placebo-treated patients received a maximum dose of 300 mg/day; 4 quetiapine XR-treated and 3 placebo-treated patients received a maximum dose of 50 mg/day.

In the MITT population, 95.1% and 95.5% of patients in the quetiapine XR + SSRI/SNRI and placebo + SSRI/SNRI groups, respectively, were treatment adherent.

TABLE 1

PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS AT RANDOMIZATION (MITT POPULATION)

	QUETIAPINE XR + ANTIDEPRESSANT (N = 204)	PLACEBO + ANTIDEPRESSANT (N = 198)
Gender, n (%)		
Male	58 (28.4)	48 (24.2)
Female	146 (71.6)	150 (75.8)
Age, years		
Mean (SD)	44.6 (12.1)	44.2 (10.9)
Ethnicity, n (%)		
White	181 (88.7)	177 (89.4)
Black	18 (8.8)	18 (9.1)
Asian	3 (1.5)	2 (1.0)
Other	2 (1.0)	1 (0.5)
Weight, kg		
Mean (SD)	81.8 (20.7)	80.7 (22.6)
Body mass index, kg/m^2		
Mean (SD)	29.5 (6.5)	29.5 (8.1)
Time since first diagnosis of GAD, years		
Mean (SD)	8.2 (9.2)	8.3 (9.4)
Time since onset of anxiety symptoms, years		
Mean (SD)	15.8 (13.0)	15.0 (12.7)
Time since first treated for anxiety, years		
Mean (SD)	7.8 (8.4)	8.5 (9.4)
Rating scale scores, mean (SD)		
HAM-A total	24.5 (3.9)	24.6 (3.7)
HAM-A psychic cluster	13.7 (2.4)	14.0 (2.4)
HAM-A somatic cluster	10.8 (2.9)	10.7 (2.6)
CGI-S total	4.3 (0.6)	4.3 (0.5)
Q-LES-Q% maximum total	53.2 (15.8)	53.6 (14.6)
Q-LES-Q item 15	3.2 (0.8)	3.2 (0.9)
Q-LES-Q item 16 score	3.1 (0.9)	3.1 (0.8)
MADRS total[a]	11.7 (2.8)	11.6 (2.9)
Combination therapy used, n (%)[a]		
SSRI		
Escitalopram	99 (48.5)	89 (44.9)
Mean dose (mg/day)[b]	19.3	20.8
Treatment duration (days)[c]	148.5	173.8
Paroxetine	53 (26.0)	55 (27.8)
Mean dose (mg/day)[b]	38.0	36.8
Treatment duration (days)[c]	131.7	97.7

(*continued*)

TABLE 1 (*CONTINUED*)

	QUETIAPINE XR + ANTIDEPRESSANT (N = 204)	PLACEBO + ANTIDEPRESSANT (N = 198)
SNRI		
Duloxetine	17 (8.3)	16 (8.1)
Mean dose[b]	76.7	73.4
Treatment duration[c]	162.4	126.1
Venlafaxine	36 (17.6)	38 (19.2)
Mean dose[b]	151.3	155.9
Treatment duration[c]	138.4	286.6

[a]All patients in the MITT population received an SSRI/SNRI; one patient received escitalopram and venlafaxine prior to and at randomization.
[b]Mean daily dose at randomization.
[c]Duration of treatment prior to randomization.

CGI-S, Clinical Global Impression-Severity of Illness; GAD, generalized anxiety disorder; HAM-A, Hamilton Rating Scale for Anxiety; MADRS, Montgomery-Åsberg Depression Rating Scale; MITT, modified intention-to-treat; Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire; SD, standard deviation; SNRI, selective norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Concomitant Medication

At Week 1, concomitant sleep medication was used by 10.0% and 12.5% of patients in the quetiapine XR and placebo + SSRI/SNRI groups, respectively; this level of use remained consistent throughout the randomized period. Benzodiazepines were used by 10.4% of quetiapine XR-treated patients and 12.0% of placebo-treated patients at the end of the randomized period.

During the randomized period, anticholinergic medication usage was low in both groups: 0.5–1.2%, quetiapine XR + SSRI/SNRI and 1.5–1.7%, placebo + SSRI/SNRI.

Efficacy

Primary Efficacy Endpoint

At Week 8, quetiapine XR + SSRI/SNRI (–10.74; p = 0.079; adjusted p = 0.079) did not demonstrate a statistically significant reduction from randomization in least squares means (LSM) HAM-A total score compared with placebo + SSRI/SNRI (–9.61) (Figure 3a).

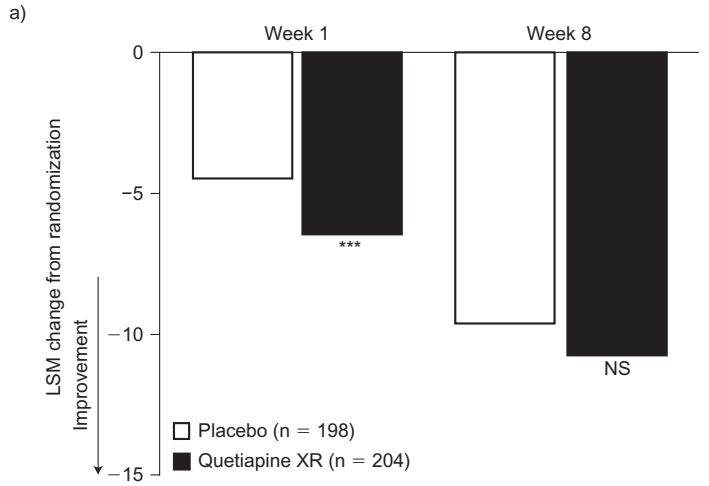
The PP population analysis of the primary efficacy variable confirmed the results of the primary analysis in the MITT population. MMRM analysis (OC, MITT population) results were also similar to the primary efficacy analysis results.

Secondary Endpoints

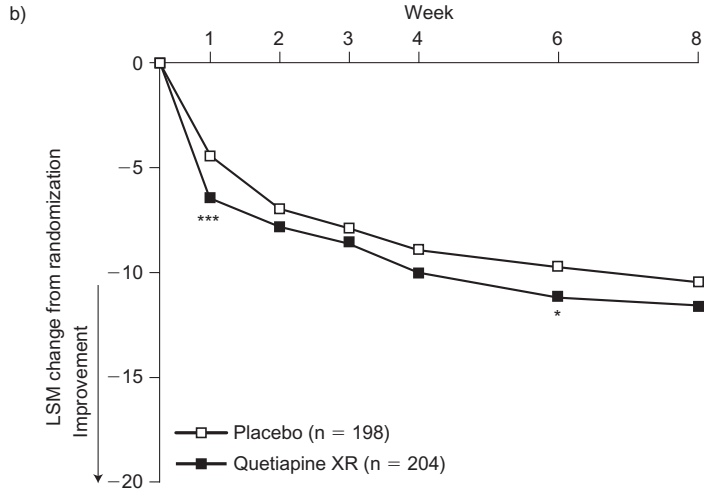
At Week 1, quetiapine XR + SSRI/SNRI significantly reduced mean HAM-A total scores compared with placebo + SSRI/SNRI: LSM changes from randomization were −6.45 versus −4.47 (95% CI −2.88,

FIGURE 3

LSM CHANGE IN HAM-A TOTAL SCORE FROM RANDOMIZATION A) AT WEEK 1 AND WEEK 8 (LOCF, MITT POPULATION) AND B) OVER TIME (OC, MITT POPULATION, MMRM ANALYSIS)



***p < 0.001 vs placebo
NS, p = 0.079



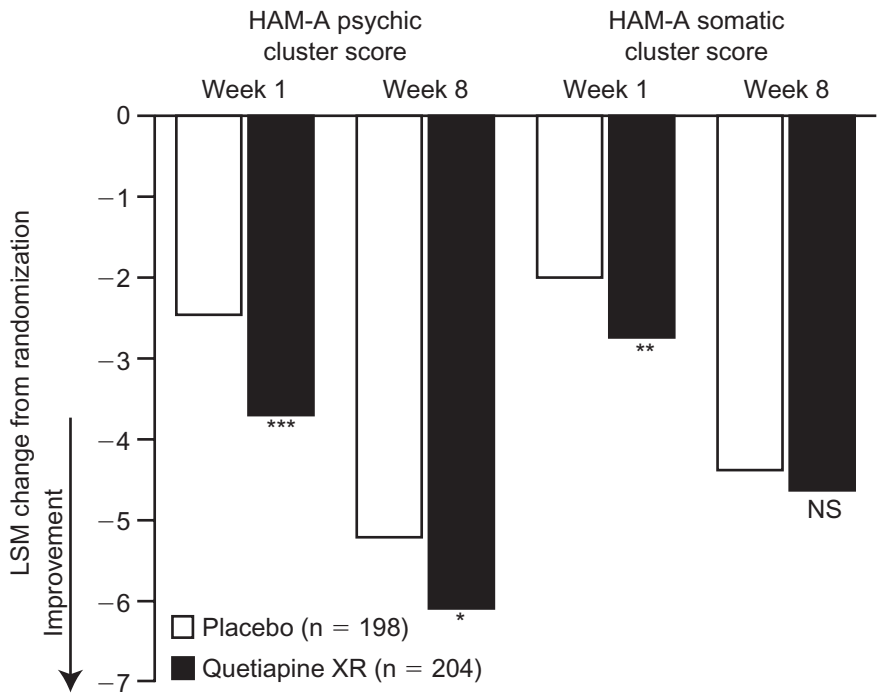
*p < 0.05; ***p < 0.001 vs placebo

HAM-A, Hamilton Rating Scale for Anxiety; LOCF, last observation carried forward; LSM, least squares means; MITT, modified intention-to-treat; MMRM, mixed-model repeated measures; OC observed cases

−1.09; $p < 0.001$; Figure 3a). Figure 3b shows the MMRM analysis of mean change in HAM-A total score from randomization at each timepoint. A significant reduction in HAM-A total score was seen with quetiapine XR + SSRI/SNRI at Week 1 (−6.43; $p < 0.001$) and Week 6 (−11.13; $p < 0.05$) compared with placebo + SSRI/SNRI (−4.45, −9.69, respectively), but not at the other timepoints. The effect of explanatory variables including final prescribed dose, baseline severity subgroup 'severe' versus 'non-severe' (HAM-A ⩾29 versus HAM-A <29), gender, age, and baseline BMI subgroups were investigated with respect to the primary outcome variable (Table 2). With the adjustment of each of these effects, at Week 8, quetiapine XR + SSRI/SNRI did not demonstrate a statistically significant difference from placebo in HAM-A total score change from randomization.

FIGURE 4

LSM CHANGE FROM RANDOMIZATION IN HAM-A PSYCHIC AND SOMATIC CLUSTER SCORES (LOCF, MITT POPULATION)



*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ vs placebo
NS, $p = 0.421$

HAM-A, Hamilton Rating Scale for Anxiety; LOCF, last observation carried forward; LSM, least squares means; MITT, modified intention-to-treat.

TABLE 2

RESULTS FOR CHANGE FROM RANDOMIZATION FOR SECONDARY EFFICACY ENDPOINTS (MITT POPULATION, LOCF)

	QUETIAPINE XR + ANTIDEPRESSANT (N = 204)	PLACEBO + ANTIDEPRESSANT (N = 198)
HAM-A total		
Week 1 LSM change	−6.45	−4.47
LSM difference (95% CI) versus placebo	−1.99 (−2.88, −1.09)	
p-value	<0.001	
Week 8 LSM change	−10.74	−9.61
LSM difference (95% CI) versus placebo	−1.13 (2.39, 0.13)	
p-value	0.079	
HAM-A adjusted by final prescribed dose		
Week 8 LSM change	−10.06	−9.56
LSM difference (95% CI) versus placebo	−0.50 (−1.73, 0.73)	
p-value	0.425	
HAM-A adjusted by baseline disease severity		
Week 8 LSM change	−11.36	−10.23
LSM difference (95% CI) versus placebo	−1.13 (−2.39, 0.13)	
p-value	0.278	
HAM-A adjusted by gender		
Week 8 LSM change	−11.06	−9.99
LSM difference (95% CI) versus placebo	−1.07 (−2.33, 0.18)	
p-value	0.059	
HAM-A adjusted by age		
Week 8 LSM change	−10.89	−9.75
LSM difference (95% CI) versus placebo	−1.14 (−2.40, 0.12)	
p-value	0.157	
HAM-A adjusted by baseline BMI		
Week 8 LSM change	−11.63	−10.47
LSM difference (95% CI) versus placebo	−1.16 (−2.43, 0.11)	
p-value	0.521	
HAM-A psychic cluster		
Week 8 LSM change	−6.09	−5.21
LSM difference (95% CI) versus placebo	−0.88 (−1.66, –0.09)	
p-value	<0.05	
HAM-A somatic cluster		
Week 8 LSM change	−4.63	−4.38
LSM difference (95% CI) versus placebo	−0.25 (−0.87, 0.37)	
p-value	0.421	

(*continued*)

TABLE 2 (*CONTINUED*)

	QUETIAPINE XR + ANTIDEPRESSANT (N = 204)	PLACEBO + ANTIDEPRESSANT (N = 198)
HAM-A response, n (%)		
Week 1	33 (16.9)	22 (11.5)
Odds ratio (95% CI) versus placebo	1.55 (0.87, 2.78)	
p-value	0.138	
Week 8	84 (41.2)	72 (36.4)
Odds ratio (95% CI) versus placebo	1.22 (0.81, 1.82)	
p-value	0.342	
HAM-A remission (HAM-A total score ≤8), n (%)		
Week 8	48 (23.5)	34 (17.2)
Odds ratio (95% CI) versus placebo	1.47 (0.89, 2.42)	
p-value	0.134	
CGI-S total score		
Week 1 LSM change	−0.56	−0.35
LSM difference (95% CI) versus placebo	−0.21 (−0.33, −0.09)	
p-value	<0.001	
Week 8 LSM change	−1.36	−1.13
LSM difference (95% CI) versus placebo	−0.23 (−0.42, −0.03)	
p-value	<0.05	
CGI-I score		
Patients 'very much' or 'much' improved at Week 8, %	55.9	49.0
Odds ratio (95% CI) versus placebo	1.33 (0.90, 1.97)	
p-value	0.158	
Q-LES-Q % maximum total score		
Week 8 LSM change	7.33	6.43
LSM difference (95% CI) versus placebo	0.90 (−1.79, 3.59)	
p-value	0.512	
Q-LES-Q item 15 score[a]		
Week 8 LSM change	0.3	0.4
Q-LES-Q item 16 score[a]		
Week 8 LSM change	0.3	0.2

The HAM-A psychic cluster comprised the following items: anxious mood, tension, fears, insomnia, intellectual difficulties, depressed mood, and behavior at interview. The HAM-A somatic cluster comprised the following items: somatic muscular, somatic sensory, cardiovascular system, respiratory system, gastrointestinal system, genitourinary system, and autonomic system.

[a]These variables were not assessed statistically.

BMI, body mass index; CGI-S, Clinical Global Impression-Severity of Illness; CI, confidence interval; HAM-A, Hamilton Rating Scale for Anxiety; LSM, least squares means; MITT, modified intention-to-treat ; Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire.

Quetiapine XR + SSRI/SNRI significantly reduced HAM-A psychic cluster scores at Week 1 (−3.70; $p < 0.001$) and Week 8 (−6.09; $p < 0.05$) compared with placebo + SSRI/SNRI (2.46 at Week 1 and 5.21 at Week 8) (Figure 4). Significant reductions were also seen in the HAM-A somatic cluster scores at Week 1 for quetiapine XR + SSRI/SNRI (−2.74; $p < 0.01$) compared with placebo + SSRI/SNRI (2.00), but not at Week 8 (−4.63 versus −4.38; $p = 0.421$) (Figure 4).

In addition, quetiapine XR + SSRI/SNRI significantly reduced CGI-S total scores from randomization at Week 1 (−0.56; $p < 0.001$) and Week 8 (−1.36; $p < 0.05$) compared with placebo + SSRI/SNRI (−0.35 and −1.13, respectively).

For other secondary endpoints relating to the HAM-A and CGI-I scales there were no statistically significant differences between treatment groups in change from randomization to Week 8 (Table 2).

The NNT value calculated using the end of treatment response data for quetiapine XR was 20.8.

Health-Related Quality of Life

There was no statistically significant difference between treatment groups in change from randomization to Week 8 in Q-LES-Q % maximum total score (Table 2). In addition, the magnitude of improvement (randomization to Week 8) in Q-LES-Q Item 15 and item 16 scores was similar in the two groups (Table 2).

Safety and Tolerability

Adverse Events

The overall incidence of AEs was 73.7% and 60.0% in the quetiapine XR + SSRI/SNRI and placebo + SSRI/SNRI groups, respectively. The most common AEs (>5% in either group) are reported in Table 3. The percentages of patients with an AE considered to be treatment-related were 62.2% and 36.0% in the quetiapine XR + SSRI/SNRI and placebo + SSRI/SNRI groups, respectively. No deaths or SAEs occurred during the study.

No AEs potentially related to suicidality were reported and no incidences of suicidal behavior/ideation (Columbia Classification codes 1, 2, 3, 4) were reported in either treatment group. The incidence of possible suicidal behavior/ideation (Columbia Classification codes 5, 6, 9) was 1.4% and 1.5% with quetiapine XR + SSRI/SNRI and placebo + SSRI/SNRI, respectively. The relative risk (95% CI) for suicidal behavior/ideation and possible suicidal behavior/ideation for

TABLE 3

MOST COMMON ADVERSE EVENTS (OCCURRING AT AN INCIDENCE >5% IN EITHER GROUP) DURING THE STUDY (SAFETY POPULATION)

	QUETIAPINE XR + ANTIDEPRESSANT (N = 209)	PLACEBO + ANTIDEPRESSANT (N = 200)
Adverse event, n (%)[a]		
Dry mouth	49 (23.4)	16 (8.0)
Somnolence	47 (22.5)	24 (12.0)
Sedation	26 (12.4)	5 (2.5)
Headache	24 (11.5)	21 (10.5)
Dizziness	22 (10.5)	9 (4.5)
Fatigue	20 (9.6)	8 (4.0)
Insomnia	15 (7.2)	3 (1.5)
Constipation	13 (6.2)	8 (4.0)
Nausea	12 (5.7)	12 (6.0)
Nasopharyngitis	7 (3.3)	17 (8.5)

[a]MedDRA preferred term.

quetiapine XR + SSRI/SNRI versus placebo + SSRI/SNRI treatment was 0.96 (95% CI: 0.195, 4.686).

AEs potentially related to somnolence (MedDRA preferred terms: lethargy, sedation, sluggishness, and somnolence) were reported by 35.9% and 14.5% of patients in the quetiapine XR + SSRI/SNRI and placebo + SSRI/SNRI groups, respectively. The majority of AEs associated with somnolence were mild to moderate in intensity and the median time to onset of these AEs was 3 days with quetiapine XR + SSRI/SNRI and 10 days with placebo + SSRI/SNRI.

The incidences of AEs potentially related to EPS (MedDRA preferred terms: akathisia, psychomotor hyperactivity, restlessness, and tremor) were 3.8% and 2.0% in the quetiapine XR + SSRI/SNRI and placebo + SSRI/SNRI groups, respectively. All of the EPS-related AEs were mild to moderate in severity. At treatment end, the majority of patients in both groups experienced either 'no change' or 'improvement' in SAS (88.8%, quetiapine XR + SSRI/SNRI; 93.3%, placebo + SSRI/SNRI) and BARS (95.1%, quetiapine XR + SSRI/SNRI; 96.4%, placebo + SSRI/SNRI) total scores from randomization.

AEs potentially related to sexual dysfunction (MedDRA preferred terms: libido decreased and ejaculation delayed) were reported by 2.9% of patients in the quetiapine XR + SSRI/SNRI group and no patients in the placebo + SSRI/SNRI group.

The percentage of patients who discontinued the study (from start of study treatment to last dose) due to an AE was 11.0% (n = 23) for quetiapine XR + SSRI/SNRI and 2.0% (n = 4) for placebo + SSRI/SNRI. One patient randomized to the quetiapine XR group discontinued treatment due to an AE in the placebo run-in period and one patient discontinued after the treatment period. The most common AEs leading to discontinuation were sedation (n = 11 quetiapine XR + SSRI/SNRI; n = 0 placebo + SSRI/SNRI) and somnolence (n = 6 quetiapine XR + SSRI/SNRI; n = 0 placebo + SSRI/SNRI).

The mean change from randomization in MADRS total score was −2.8 and −1.8 at Week 4 and −3.4 and −2.5 at Week 8 with quetiapine XR + SSRI/SNRI and placebo + SSRI/SNRI, respectively.

No clinically relevant differences between groups were seen in mean change from randomization to Week 8 for vital signs, ECG, or hematology data. There was no indication of increased QTc interval in either group.

Table 4 presents mean changes and proportion of patients with a clinically relevant shift (including the definition of a clinically relevant shift for each parameter) in glucose and lipid laboratory parameters in the fasting status confirmed safety population. More patients in the placebo group experienced a clinically relevant shift (elevation) from randomization to

TABLE 4

CHANGES IN GLUCOSE AND LIPID DATA AND BODY WEIGHT AND THE PROPORTIONS OF PATIENTS WITH CLINICALLY RELEVANT SHIFTS FROM NORMAL IN THESE PARAMETERS FROM RANDOMIZATION TO TREATMENT END (SAFETY POPULATION)

PARAMETER[a]	QUETIAPINE XR + ANTIDEPRESSANT (N = 209)	PLACEBO + ANTIDEPRESSANT (N = 200)
Glucose (mg/dL)[b]		
Randomization	90.65 (10.0)	93.18 (15.40)
Change	0.38 (16.75) (n = 146)	1.7 (16.54) (n = 135)
Patients with clinically relevant shift in fasting glucose (⩾126 mg/dL), n (%)	3 (1.7) (n = 173)	5 (3.0) (n = 164)
Total cholesterol (mg/dL)[b]		
Randomization	206.67 (43.22)	203.05 (46.83)
Change	−1.65 (27.46) (n = 144)	−6.83 (27.48) (n = 124)
Patients with clinically relevant shift in fasting total cholesterol (⩾240 mg/dL), n (%)	11 (8.6) (n = 128)	4 (3.5) (n = 114)

(*continued*)

TABLE 4 (*CONTINUED*)

PARAMETER[a]	QUETIAPINE XR + ANTIDEPRESSANT (N = 209)	PLACEBO + ANTIDEPRESSANT (N = 200)
HDL-cholesterol (mg/dL)[b]		
Randomization	52.64 (13.86)	55.07 (14.88)
Change	−1.61 (9.87) (n = 144)	0.45 (8.12) (n = 124)
Patients with clinically relevant shift in fasting HDL-cholesterol (≤40 mg/dL), n (%)	15 (11.6) (n = 114)	12 (10.1) (n = 107)
LDL-cholesterol (mg/dL)[b]		
Randomization	124.76 (38.03)	122.23 (39.05)
Change	−2.27 (24.81) (n = 144)	−6.76 (22.79) (n = 124)
Patients with clinically relevant shift in fasting LDL-cholesterol (≥160 mg/dL), n (%)	7 (5.1) (n = 136)	2 (1.7) (n = 117)
Triglycerides (mg/dL)[b]		
Randomization	147.53 (84.47)	128.83 (73.80)
Change	13.60 (71.58) (n = 144)	−2.03 (68.18) (n = 124)
Patients with clinically relevant shift in fasting triglycerides (≥200 mg/dL), n (%)	20 (16.8) (n = 119)	12 (10.3) (n = 117)
Prolactin (ng/mL)		
Randomization	8.65 (6.18)	8.29 (6.67)
Change	1.19 (9.91) (n = 187)	1.58 (11.59) (n = 179)
Weight, kg		
Randomization	81.9 (20.6)	80.6 (22.6)
Change	1.0 (2.3) (n = 207)	0.3 (2.3) (n = 199)
Patients with clinically relevant shift in weight (≥7% increase), n (%)	4.3%	1.0%

The numbers of patients are for those who were assessed.

[a]Values shown as mean (SD) unless otherwise indicated.
[b]Fasting status was determined based upon a documented patient report that last meal was ≥8 hours before blood sample taken for randomization and post-randomization laboratory measurements. However, not all samples could be confirmed as fasted despite there being an 8-hour interval since last meal, as patients could have had calorific intake.

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

treatment end in plasma glucose levels (3.0%) compared with the quetiapine XR group (1.7%). Conversely, more patients in the quetiapine XR + SSRI/SNRI group (16.8%) experienced a clinically relevant shift (elevation) from randomization to treatment end in triglyceride levels than in the placebo + SSRI/SNRI group (10.3%; Table 4).

Mean change in body weight at treatment end was +1.0 kg in the quetiapine XR + SSRI/SNRI group and +0.3 kg in the placebo + SSRI/SNRI group; 4.3% and 1.0% of patients, respectively, experienced a ⩾7% increase in body weight (Table 4).

Post-Treatment Period

The most common (>2%) AEs reported during the 2-week post-treatment period, were insomnia (4.8%) and nausea (2.4%) in the quetiapine XR + SSRI/SNRI group; these AEs were reported during the post-treatment period by 0% and 1.0% of patients in the placebo + SSRI/SNRI groups, respectively.

Mean (SD) TDSS total scores at Day 7 and 14 of the post-treatment period were 6.0 (4.2) and 5.8 (4.4) in the quetiapine XR + SSRI/SNRI group and 5.5 (4.0) and 5.6 (4.2) in the placebo + SSRI/SNRI group, respectively.

DISCUSSION

This study evaluated the efficacy and tolerability of quetiapine XR adjunct to SSRI/SNRI therapy in patients with GAD who demonstrated partial or no (inadequate) response to SSRI/SNRI treatment (alone or in combination with a benzodiazepine). The primary efficacy variable did not show statistical separation for quetiapine XR compared with placebo. This contrasts with the findings of previous studies conducted with quetiapine XR monotherapy in patients with GAD (not specified as being treatment-resistant GAD) that found quetiapine XR to be effective in reducing anxiety symptoms when compared with placebo.[12–16]

Failure of active treatment to separate from placebo is not unusual; around half (51.8%) of the clinical studies evaluating antidepressant and anxiolytic drugs do not show statistical superiority to placebo.[31] High placebo response is often a major contributory factor, although other possibilities include: inclusion/exclusion criteria; high attrition rates; outcome measure sensitivity; unreliable rating scales; misdiagnosis; severity of illness; and study design.[32,33]

The single-blind placebo run-in period included in the current study was designed to reduce the effects of any potential placebo response.

However, the magnitude of change in HAM-A total score seen here for the placebo group (−9.61) was unexpectedly high when compared with those seen in other placebo-controlled adjunct studies. For example, in a 5-week study in patients with GAD who continued to experience symptoms despite previous therapy, the mean changes in HAM-A total scores were −9.8 and −6.2 with adjunct risperidone and placebo plus antidepressant, respectively.[34]

The changes in HAM-A total score in the current study with adjunct quetiapine XR are lower than those reported in previous short-term studies (10-week studies with an 8-week active treatment period) of quetiapine XR monotherapy (from −13.5 to −16.0 in the 150 mg/day groups).[12–14] Patients in the current study had already received treatment (SSRI/SNRI) for their anxiety, therefore, it might be expected that on study entry some improvement in symptoms would have already occurred. However, baseline HAM-A scores in the present study (24.5, quetiapine XR; 24.6, placebo) were similar to those in two previous studies of quetiapine XR monotherapy in GAD: Studies D1448C00009 (24.5, quetiapine XR 150 mg/day; 24.9, placebo)[12] and D1448C00010 (25.0, quetiapine XR 150 mg/day; 25.3, placebo),[14] whereas baseline HAM-A scores reported in Study D1448C00011 (26.6, quetiapine XR 150 mg/day; 27.3, placebo)[13] were higher than those seen here. In addition, patients in the current study had on average been experiencing anxiety symptoms for a longer duration (15–16 years) than in Study D1448C00009 (13–15 years), Study D1448C00010 (13–15 years), and Study D1448C00011 (11–12 years). It has been suggested that duration of neuropsychological disease may be associated with treatment resistance; if this is the case then the patients enrolled in this study may be representative of a more treatment-resistant patient population.

The patients in the current study had an inadequate response to prior treatment and so, compared with treatment-naïve or -responsive patients, may have a reduced capacity for symptom improvement and any benefits experienced by these patients may not be captured by HAM-A score change.

Since the baseline characteristics of the two treatment groups were well matched, it is not unexpected that the findings of the analysis of the primary efficacy variable by baseline severity ('severe' versus 'non-severe'), gender, age, and baseline BMI were similar to those of the primary analysis. The MMRM analysis of change in HAM-A total score also failed to reach statistical significance for quetiapine XR compared with placebo at Week 8; however, a significant difference from placebo was found at Weeks 1 and 6. The analysis using change from

randomization in HAM-A total score according to final prescribed quetiapine XR dose (150 mg/day or 300 mg/day) at Week 8 also found no statistical significant difference between quetiapine XR and placebo.

The discontinuation rate in the present study (22%) was comparable with that seen in other studies: approximate discontinuation rates of 35%, 29%, and 23% were reported in quetiapine XR studies D1448C00009, D1448C00010, and D1448C00011, respectively,[12–14] and approximately 23% of patients discontinued in a study of adjunctive risperidone.[34] High attrition does not explain the lack of statistical separation from placebo for the primary efficacy variable. Likewise, failure to statistically separate cannot be explained by treatment adherence as this was similar in the two groups. It is important to note that in the current study, benzodiazepine usage was slightly lower in the quetiapine XR group (10.4%) than in the placebo group (12.0%). Benzodiazepines have been shown to improve psychic and somatic symptoms of anxiety[35] and so concomitant benzodiazepine use may have been an important factor in the symptom improvement seen for some patients receiving placebo in the current study. Concomitant benzodiazepine use was specifically excluded in the aforementioned quetiapine XR monotherapy studies.[12–14]

At Week 8, significant reductions in CGI-S total score were seen with quetiapine XR compared with placebo. Significant differences between quetiapine XR and placebo at timepoints other than Week 8 were seen for several secondary outcome variables. For example, at Week 1 significant differences between quetiapine XR and placebo were seen for HAM-A total, HAM-A psychic and somatic cluster scores, and CGI-S total score. Significant separation from placebo with quetiapine XR at Week 1 but not Week 8 cannot be easily explained. One possible explanation is that placebo-treated patients may have taken benzodiazepines due to a lack of symptom improvement. However, benzodiazepine usage remained relatively constant over the 8-week randomized period. Moreover, the adjunct quetiapine XR group approached a significant level of separation from placebo at Week 8 although statistical significance was not reached.

The NNT value reported here (20.8) for quetiapine XR may be explained by the comparatively low response rate for quetiapine XR (41.2%) versus placebo (36.4%) compared with response rates reported for quetiapine XR monotherapy (55–71%) in other GAD clinical trials.[12–14]

At Week 8, significant reductions in the HAM-A psychic cluster score were seen with quetiapine XR compared with placebo. The anxiolytic effect of quetiapine XR may be translated through the psychic cluster items (anxious mood, tension, fears, insomnia, intellectual

difficulties, depressed mood, and behavior at interview). Quetiapine XR has demonstrated a beneficial effect on sleep in patients with GAD[12–14] and major depressive disorder (MDD)[36–39] and has improved cognitive function in patients with schizophrenia.[40]

Quetiapine XR (at doses of 50, 150, and 300 mg/day) has previously demonstrated efficacy in the treatment of depressive symptoms in patients with MDD as a monotherapy[37,38,41,42] and adjunct treatment.[36,39] Also, in the current study, quetiapine XR reduced symptoms of depression assessed by the MADRS. The broad spectrum of efficacy demonstrated by quetiapine XR against symptoms of anxiety and depression may be explained by its mechanism of action. Quetiapine and norquetiapine (the major active metabolite of quetiapine) have moderate-to-high affinity for serotonin $5HT_{2A}$ and dopamine D_2 receptors; norquetiapine is also a potent inhibitor of the norepinephrine transporter (NET).[43,44] NET inhibition has not been demonstrated by other atypical antipsychotics at clinically relevant doses; however, it is a property shared by a number of traditional antidepressants, such as SNRIs,[45] and is believed to contribute to the therapeutic effect of quetiapine.[44]

In this study, the overall tolerability and safety results in quetiapine XR-treated patients were consistent with the known profile of quetiapine.[12–14,16,37,38,41,42,46–48] Patients received concomitant SSRI/SNRI therapy and were permitted to receive benzodiazepines; therefore, safety/tolerability data reported here may be due to the effects of several agents. The clinical laboratory data reported here for quetiapine XR + SSRI/SNRI are consistent with those from acute studies of quetiapine XR monotherapy in adult patients with GAD.[12–14]

This was the first randomized, placebo-controlled study to evaluate the efficacy of quetiapine XR adjunct to antidepressants for the treatment of GAD in patients with an inadequate response to SSRI/SNRI treatment in a large patient population. Study limitations include the lack of an active comparator and the use of inclusion criteria relating to disease status (HAM-A and CGI-S scores) that were similar to those in acute studies of quetiapine XR monotherapy, despite the fact that this study assessed quetiapine XR as adjunct therapy. More restrictive exclusion criteria could have been utilized to better determine the potential effect of adjunct quetiapine XR, for example, exclusion of patients who had anxiety for >10 years, and concomitant benzodiazepine use. In addition, the HAM-A may have been an insensitive measure in this patient population where little improvement in symptoms could be expected in the context of prior treatment failure.

In conclusion, in this study statistical separation from placebo with adjunct quetiapine XR was not achieved in patients with GAD and an

inadequate response to previous therapy for the primary efficacy variable. Statistical separation was achieved for some secondary variables, including change in HAM-A psychic cluster scores and CGI-S total scores at Weeks 1 and 8. Quetiapine XR was generally well tolerated and its safety profile was consistent with the known profile of quetiapine. Further studies to evaluate the efficacy of adjunct quetiapine XR in patients with GAD and an inadequate response to previous treatment should take into consideration the methodological difficulties that may be encountered. ✤

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DISCLOSURES

Arifulla Khan has been the principal investigator in over 330 trials sponsored by more than 55 pharmaceutical companies and 30 CROs and has done no compensated consulting or speaking on their behalf, nor does he own stock in any of these companies. Dr Khan enrolled 12 patients into Study D1441L00016.

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