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Efficacy and tolerability of extended release quetiapine fumarate (quetiapine XR) monotherapy in patients with generalised anxiety disorder: an analysis of pooled data from three 8-week placebo-controlled studies

Dan J. Stein[1]*, Borwin Bandelow[2], Charles Merideth[3], Bengt Olausson[4], Johan Szamosi[4] and Hans Eriksson[4]

[1]*Department of Psychiatry, University of Cape Town, Cape Town, South Africa*
[2]*Department of Psychiatry and Psychotherapy, University of Goettingen, Goettingen, Germany*
[3]*Affiliated Research Institute Inc., San Diego, California, USA*
[4]*AstraZeneca R&D, Sodertalje, Sweden*

Objective Prospectively planned pooled analysis evaluating efficacy and tolerability of acute quetiapine XR monotherapy in generalised anxiety disorder.
Methods Data from three 10-week, randomised, double-blind, placebo-controlled studies of similar design were analysed.
Results At Week 8, Hamilton Anxiety Rating Scale (HAM-A) total score significantly improved with quetiapine XR: least squares means change −13.31, $p < 0.001$ (50 mg/day, $n = 452$), −14.39, $p < 0.001$ (150 mg/day, $n = 673$) and −12.50, $p < 0.05$ (300 mg/day, $n = 444$) versus −11.30 placebo; significant ($p < 0.001$, $n = 665$) improvements versus placebo were observed with each dose at Week 1. Significant improvements versus placebo at Week 8 are as follows: HAM-A psychic symptom subscale, Montgomery-Åsberg Depression Rating Scale total, Pittsburgh Sleep Quality Index global scores for all quetiapine XR doses; HAM-A response and remission rates, HAM-A somatic symptom subscale score, Clinical Global Impression-Severity of Illness total score, % patients with Clinical Global Impression-Improvement score ≤2 with quetiapine XR 50 and 150 mg/day; and Quality of Life Enjoyment and Satisfaction Questionnaire short form % maximum total score with quetiapine XR 150 mg/day. In the quetiapine XR 50, 150 and 300 mg/day and placebo groups, 13.2%, 16.5%, 24.0% and 5.4% of patients discontinued because of an adverse event, and 1.9%, 1.4%, 3.7% and 1.8% of patients experienced clinically significant changes in glucose. The most common adverse events with quetiapine XR included dry mouth, somnolence, sedation and constipation.
Conclusion Quetiapine XR monotherapy reduced the symptoms of generalised anxiety disorder, with improvement from Week 1. Adverse events were consistent with the known tolerability profile of quetiapine.

KEY WORDS—quetiapine XR; generalised anxiety disorder; clinical trial, phase III; pooled analysis; antipsychotic

INTRODUCTION

Generalised anxiety disorder (GAD) is a frequently occurring chronic condition, with an estimated lifetime prevalence of approximately 5.7% in the USA (Kessler *et al*., 2005) and ranging from 0.1%–6.4% in Europe (Lieb *et al*., 2005). Patients with GAD often present with physical symptoms (Wittchen *et al*., 2002) and experience decreased quality of life and impaired social functioning compared with individuals without GAD, with the level of impairment being equivalent to that of major depressive disorder (MDD) (Kessler *et al*., 1999; Henning *et al*., 2007). Furthermore, GAD is associated with an increased economic burden for reasons including more frequent use of healthcare providers (Bereza *et al*., 2009).

Current treatment guidelines recommend the use of a selective serotonin reuptake inhibitor (SSRI) or a serotonin norepinephrine reuptake inhibitor (SNRI) as first-line pharmacotherapy for GAD (Baldwin *et al*., 2005; Canadian Psychiatric Association, 2006; Bandelow *et al*., 2008; National Institute for Health and Clinical Excellence, 2011). Other treatment options include benzodiazepines, which may be used for short-term symptom relief; however, their long-term use is not recommended for reasons including development of tolerance, side effects and a withdrawal reaction on discontinuation (Allgulander *et al*., 2003; Baldwin and Polkinghorn, 2005). In addition, the calcium channel

*Correspondence to: D. Stein, Professor, Department of Psychiatry, University of Cape Town, Cape Town, South Africa. E-mail: dan.stein@uct.ac.za
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modulator pregabalin has shown efficacy in the treatment of GAD (Montgomery *et al*., 2006; Feltner *et al*., 2008) and has received approval for its use in GAD in Europe (Katzman, 2009). Antihistamines have also been investigated as possible treatment options for GAD; however, the evidence for their efficacy is mixed (Gambi *et al*., 2005; Guaiana *et al*., 2010; Schutters *et al*., 2010).

Despite the treatment options available, GAD remains a persistent condition, with the probability of recovery in a prospective, naturalistic study over a 12-year period being 0.58 and the probability of recurrence following recovery being 0.45 (Bruce *et al*., 2005). Such data emphasise the need for additional therapies. In addition to suboptimal efficacy, there are tolerability concerns associated with current treatments; these include rebound anxiety, memory impairment, abuse and discontinuation syndrome with benzodiazepines (Chouinard, 2004), and nausea, sleep disturbances and sexual dysfunction with SSRIs (Gorman, 2003).

The utility of extended release quetiapine fumarate (quetiapine XR, AstraZeneca) as a potential treatment option for patients with GAD has recently been investigated as part of a global clinical development programme. To date, four acute studies (three in adult populations (Bandelow *et al*., 2010; Khan *et al*., 2011; Merideth *et al*.,) and one in an elderly population (Magi *et al*., 2009)) and one long-term maintenance study (Katzman *et al*., 2011) have been carried out. Data from these studies have shown that quetiapine XR (50–300 mg/day) improves a broad range of anxiety symptoms in patients with GAD and is generally well tolerated in this patient population. At the time of writing, quetiapine XR has only been approved for the treatment of patients with GAD in Australia, the Philippines and Venezuela.

The quetiapine XR dose range chosen for the acute monotherapy studies was selected on the basis of data from studies in bipolar depression, in which quetiapine XR 300 and 600 mg/day significantly reduced anxiety symptoms following 8 weeks of treatment (Calabrese *et al*., 2005). In the acute monotherapy studies investigating quetiapine XR for the treatment of GAD, a dose of 300 mg/day was chosen for the high-dose treatment arm, and doses of 50 and 150 mg/day were included to investigate any potential dose–response relationship and to help define the minimum effective dose.

Here, we present results from a prospectively planned pooled analysis of efficacy and tolerability data from three 10-week studies of quetiapine XR monotherapy in patients with GAD, each with an 8-week acute treatment period and a 2-week follow-up period (Bandelow *et al*., 2010; Khan *et al*., 2011; Merideth *et al*.,). This analysis was conducted to obtain a more precise estimate of the treatment effect of quetiapine XR on primary and secondary efficacy and safety outcomes compared with placebo, to characterise the dose effect and to investigate efficacy and safety across subgroups of patients.

METHODS

The design and methodology of all three studies have been detailed previously (Bandelow *et al*., 2010; Khan *et al*., 2011; Merideth *et al*.,). Descriptions of study designs reported here are intended as a brief summary. Study designs were similar, and the pooled analysis was prospectively planned to provide a larger sample size. Although the original studies were adequately sized for the evaluation of treatment effect on anxiety symptoms, the larger sample size enables a more robust analysis with even greater sensitivity to detect statistically significant and clinically meaningful changes in study outcomes for quetiapine XR compared with placebo and to provide an adequate population for subgroup analyses.

Study design

All three studies were 10-week, multicentre, randomised, parallel-group, double-blind, placebo-controlled phase III studies (DC144800009 [Study 9, NCT00329264]; DC144800010 [Study 10, NCT00329446]; DC144800011 [Study 11, NCT00322595]), each consisting of an 8-week acute treatment period followed by a 2-week follow-up period.

The study protocols were approved by the relevant local ethics committees and conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation/Good Clinical Practice guidelines. All patients provided written informed consent.

Patients

Eligible patients were male or female, aged 18–65 years and with a documented clinical diagnosis of GAD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria (American Psychiatric Association, 2000), as assessed by the Mini-International Neuropsychiatric Interview (Sheehan *et al*., 1998). Patients were required to have a Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959) total score $\geq$20, with Items 1 (anxious mood) and 2 (tension) scores $\geq$2; a Clinical Global Impression-Severity of Illness

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(CGI-S) (Guy, 1976) score ≥4 and a Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) score ≤16 at enrolment and randomisation.

Exclusion criteria included the following: any DSM-IV-TR Axis I disorder other than GAD within 6 months prior to enrolment or any DSM-IV-TR Axis II disorder likely to interfere with the patient's ability to participate in the study; a current serious suicidal or homicidal risk or a suicide attempt within the 6 months prior to enrolment or a MADRS Item 10 (suicidality) score ≥4; substance or alcohol abuse within 6 months prior to enrolment; a history of a clinically significant or unstable medical condition; clinically significant laboratory test results at enrolment; and the inability to discontinue all psychoactive medications, including benzodiazepines, antidepressants, antipsychotics and mood stabilisers, for the required washout period appropriate for each class of drug. Patients were permitted to receive psychotherapy during the study period if it had been ongoing for a minimum of 3 months prior to randomisation.

Study treatment

Patients were randomised to receive quetiapine XR (50, 150 or 300 mg/day) or placebo (Study 9); quetiapine XR (150 or 300 mg/day), placebo or escitalopram 10 mg/day (Study 10) and quetiapine XR (50 or 150 mg/day), placebo or paroxetine 20 mg/day (Study 11). Escitalopram and paroxetine were included as active controls in Studies 10 and 11, respectively, to determine assay sensitivity. All study medications were administered orally, once daily, in the evening. The schedule for administration, up-titration and discontinuation of study treatments is shown in Figure 1.

Efficacy evaluations

The primary efficacy variable was mean change in HAM-A total score (calculated from the 14 items of the HAM-A scale) from randomisation at Week 8. Secondary efficacy variables included change in the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) (Endicott *et al.*, 1993) short-form (SF) % maximum total score (calculated as a percentage of the maximum possible score for Items 1–14) from randomisation at Week 8; mean change from randomisation in HAM-A total score at Week 1, HAM-A response (≥50% reduction from randomisation in HAM-A total score) rate at Weeks 1 and 8 and HAM-A remission (HAM-A total score ≤7) rate; change from randomisation in HAM-A psychic and somatic symptom subscales, CGI-S and MADRS total scores and proportion of patients with CGI-Improvement (CGI-I) score of 1 or 2 ('very much/much improved') at Week 8. Sleep quality was assessed by the change from randomisation in the Pittsburgh Sleep Quality Index (PSQI) global score (Buysse *et al.*, 1989) at Week 8.

Clinical assessments of HAM-A, CGI-S and MADRS were conducted at enrolment (Visit 1), Days

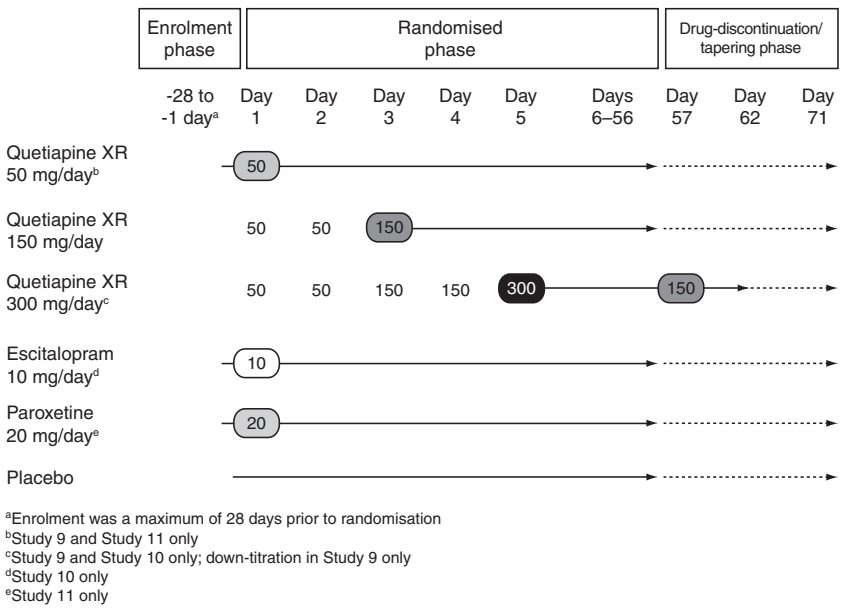

Figure 1. Schedule for study treatments

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1 (Visit 2; randomisation) and 4 (Visit 3; Studies 10 and 11) and Weeks 1–4, 6 and 8 (Study 9, Visits 3–8; Studies 10 and 11, Visits 4–9). Q-LES-Q-SF % maximum total scores and PSQI global scores were recorded at randomisation, Weeks 4 and 8.

Safety and tolerability

The incidence and severity of adverse events (AEs), and AE-related withdrawals were recorded throughout. Judgements with regard to the severity of AEs were based on the investigator's decision. All AEs were followed until resolution or until the investigator decided that no further follow-up was necessary. Serious AEs were recorded until 30 days after the last dose of study drug. Safety was assessed through physical examination and 12-lead electrocardiogram recordings at enrolment and Week 8. Laboratory measurements, including fasting lipid and fasting glucose serum levels, were performed at enrolment and Weeks 4 and 8, and recording of vital signs and body weight were made at enrolment and all subsequent visits. The Changes in Sexual Function Questionnaire (CSFQ) (Keller *et al*., 2006) was completed at randomisation and Weeks 2, 4 and 8, with males and females completing different versions of the questionnaire. Mean changes in CSFQ total scores for all quetiapine XR dose groups (i.e. 50–300 mg/day) in all three studies were pooled and compared with placebo. Simpson-Angus Scale (Simpson and Angus, 1970b) total and Barnes Akathisia Rating Scale (Simpson and Angus, 1970a) global scores were determined at randomisation and Weeks 2, 4, 6 and 8.

During the 2-week post-treatment phase, treatment discontinuation signs and symptoms (TDSS) were assessed by using a modified TDSS scale (Michelson *et al*., 2000). Patients completing the randomised treatment period of the studies were asked to assess their discontinuation symptoms at Week 8 (baseline) and Days 1, 3, 5, 7 and 14 post-treatment, and TDSS total scores were calculated.

Statistical analysis

The sample size for each study was based on an anticipated difference of 2.75 points between active treatment and placebo in HAM-A total score at Week 8 and an assumed standard deviation of 7.5. All statistical analyses described herein relate to pooled data.

The modified intent-to-treat population (randomised patients who received study drug and had randomisation and $\geq$1 post-randomisation HAM-A total score assessments) was used for analysis of the primary and secondary efficacy variables. For all efficacy variables, the last observation carried forward approach was used for imputation of missing data. No adjustment for multiplicity was performed for any analysis of pooled data.

Table 1. Demographics and baseline characteristics (pooled modified intent-to-treat population)

	Placebo (n = 654)	Quetiapine XR 50 mg/day (n = 438)	Quetiapine XR 150 mg/day (n = 654)	Quetiapine XR 300 mg/day (n = 425)
Gender, *n* (%)				
Male	236 (36.1)	164 (37.4)	225 (34.4)	146 (34.4)
Female	418 (63.9)	274 (62.6)	429 (65.6)	279 (65.6)
Age, years				
Mean (SD)	39.0 (12.4)	39.9 (11.7)	40.4 (12.0)	40.0 (12.3)
Ethnicity, *n* (%)				
White	558 (85.3)	378 (86.3)	567 (86.7)	343 (80.7)
Black	70 (10.7)	45 (10.3)	64 (9.8)	52 (12.2)
Asian	2 (0.3)	1 (0.2)	2 (0.3)	8 (1.9)
Other	24 (3.7)	14 (3.2)	21 (3.2)	22 (5.2)
Weight, kg				
Mean (SD)	79.2 (20.5)	76.5 (18.9)	77.4 (19.3)	79.7 (20.1)
Body mass index, kg/m^2				
Mean (SD)	27.8 (6.8)	26.7 (6.0)	27.3 (6.2)	28.1 (6.5)
Time since first diagnosis of GAD, years				
Mean (SD)	4.8 (6.8)	4.5 (6.1)	4.5 (6.0)	5.6 (7.4)
Rating scale scores, mean (SD)				
HAM-A total	25.8 (4.3)	25.8 (4.2)	25.4 (4.1)	24.8 (3.7)
CGI-S	4.5 (0.7)	4.6 (0.7)	4.5 (0.6)	4.4 (0.6)
MADRS total	12.4 (3.1)	12.1 (2.9)	12.2 (3.0)	12.5 (3.2)
Q-LES-Q-SF % maximum total	51.1 (15.4)	50.1 (14.0)	51.1 (14.8)	53.6 (14.5)

SD, standard deviation; GAD, generalised anxiety disorder; HAM-A, Hamilton Anxiety Rating Scale; CGI-S, Clinical Global Impression-Severity of Illness; MADRS, Montgomery-Åsberg Depression Rating Scale; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire short form.

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For the analysis of the primary efficacy variable (mean change in HAM-A total score) and Q-LES-Q-SF % maximum total score, an analysis of covariance model was used, which included study as an additional fixed effect; hence, a random effect of centre was nested within the fixed effect for study. To assess the robustness of the primary analysis results, a mixed-model repeated measures analysis was performed on change from randomization HAM-A total score with fixed effects of treatment, visit and treatment by visit interaction and randomization HAM-A total score as a covariate. Analysis of the primary efficacy variable by subgroup (including age, gender, ethnicity and baseline disease severity [HAM-A total score at baseline ≥ 29 / <29]) was carried out to test the hypothesis that quetiapine XR is efficacious in these subgroups. In addition, to test the hypothesis that treatment effect does not decrease with higher doses, an exploratory analysis of the change from randomisation in HAM-A total scores and Q-LES-Q-SF % maximum total scores according to dose was conducted by using the Jonckheere–Terpstra test.

Continuous secondary variables were analysed by using the same analysis of covariance model as for the primary efficacy variable. A logistic regression analysis was used to test the superiority of each dose of quetiapine XR versus placebo. For HAM-A response and HAM-A remission, score at baseline was used as a covariate along with treatment and study. For proportion of patients with CGI-I score of 1 or 2, CGI-S randomisation score was used as a covariate along with treatment and study.

The number needed to treat for responders at Week 8 was calculated for each quetiapine XR dose (1/[proportion of quetiapine XR-treated patients experiencing a response − proportion of placebo-treated patients experiencing a response]). Effect size (improvement with quetiapine XR vs. placebo divided by pooled standard deviation) was determined by means of a mixed-model repeated measures analysis of the modified intention-to-treat population.

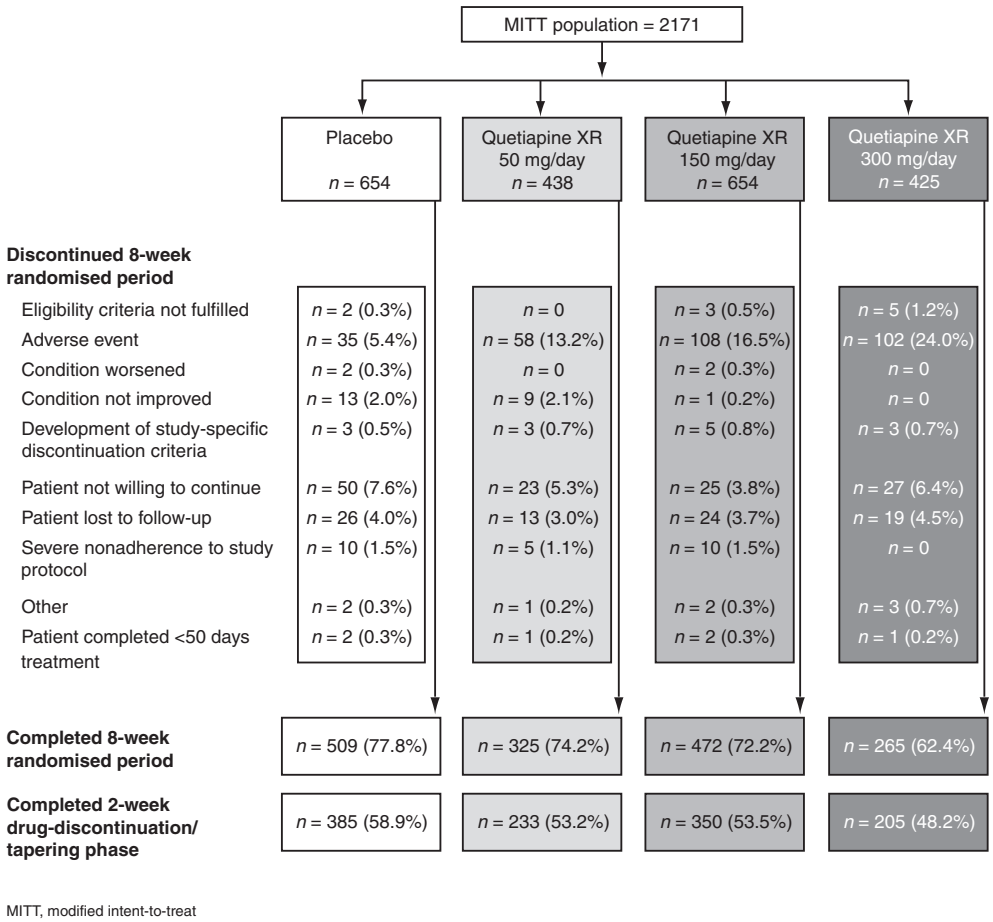

Figure 2. Patient disposition (pooled modified intent-to-treat population)

DOI: 10.1002/hup

The drug discontinuation/tapering phase population included those patients who completed 8 weeks of double-blind treatment and had baseline (Week 8) and ≥1 post-baseline TDSS score assessment. The pooled safety population included patients who received ≥1 dose of study drug. Analysis of tolerability variables, CSFQ total scores and TDSS total scores was performed by using descriptive statistics. For CSFQ total score, non-inferiority between quetiapine XR and placebo was established if the lower limit of the two-sided 95% confidence interval for the estimated difference between quetiapine and placebo did not exceed a pre-defined non-inferiority limit of -0.75.

RESULTS

Patient population

The patient populations for each of the three studies have been described previously (Bandelow *et al*., 2010; Khan *et al*., 2011; Merideth *et al*.,); only data for quetiapine XR and placebo were pooled. A total of 2248 patients were randomised to receive either quetiapine XR 50 ($n = 455$), 150 ($n = 678$) or 300 ($n = 448$) mg/day or placebo ($n = 667$) at 240 centres in the USA (Studies 9 and 10), Europe (Study 11 only), Argentina (Study 11 only), Canada (Study 11 only), Mexico (Study 11 only) and South Africa (Study 11 only). The pooled safety population comprised 2234 patients (14 patients did not receive treatment), and the pooled modified intent-to-treat population comprised 2171 patients (63 patients had no valid HAM-A score at or after randomisation). Demographic characteristics and baseline clinical characteristics were generally well matched across treatment groups (Table 1). Patients completing the studies and reasons for withdrawal are shown in Figure 2. Discontinuation rates were 25.8% (50 mg/day), 27.8% (150 mg/day), 37.6% (300 mg/day) and 22.2% (placebo).

The proportion of patients reporting sleep medication use at any time was 3.0% for placebo, 2.4% for quetiapine XR 50 mg/day, 1.9% for quetiapine XR 150 mg/day and 1.1% for quetiapine XR 300 mg/day. No patients received psychotherapy during the studies.

Efficacy

Least squares mean changes in HAM-A total scores from randomisation to Week 8 were significantly improved with quetiapine XR 50 (−13.31; $p < 0.001$), 150 (−14.39; $p < 0.001$) and 300 mg/day (−12.50; $p < 0.05$) compared with placebo (−11.30) (Figure 3a). At Week 1 and all subsequent time points, statistically significant improvements in HAM-A total score from randomisation were seen with quetiapine XR 50, 150 and 300 mg/day versus placebo, with the exception of quetiapine XR 300 mg/day at Week 6 (Figure 3b). Individual items of HAM-A were generally improved at Weeks 1 and 8 in the quetiapine XR groups compared with placebo.

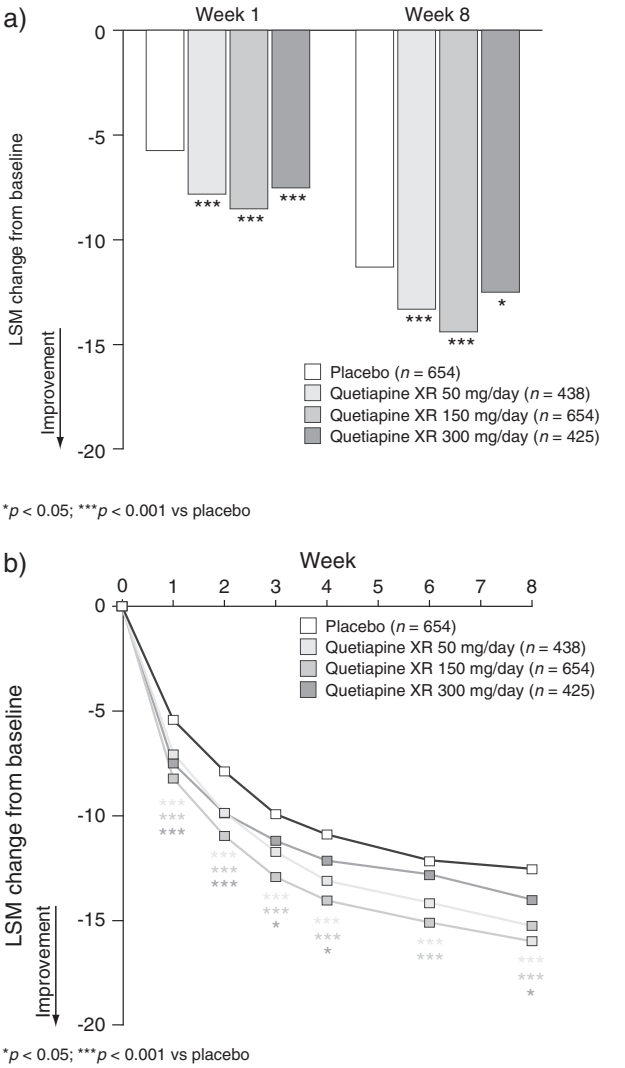

Figure 3. Change in Hamilton Anxiety Rating Scale total score a) from baseline at Weeks 1 and 8 (last observation carried forward) b) from baseline to Week 8 (mixed-model repeated measures) [pooled modified intent-to-treat analysis set]

The results for secondary efficacy variables are shown in Table 2. Week 1 HAM-A response rates were significantly greater with all quetiapine XR doses versus placebo. At Week 8, HAM-A response and remission rates were significantly greater with quetiapine XR 50 and 150 mg/day versus placebo; although response and remission rates with quetiapine XR 300 mg/day were greater than with placebo, they did not achieve significance.

DOI: 10.1002/hup

Table 2. Secondary efficacy variables (last observation carried forward, pooled modified intent-to-treat population)

LSM score change from randomisation (95% CI versus placebo)	Placebo ($n=654$)	Quetiapine XR 50 mg/day ($n=438$)	Quetiapine XR 150 mg/day ($n=654$)	Quetiapine XR 300 mg/day ($n=425$)
Week 1[a]				
HAM-A total	−5.74	−7.82 (−2.73, −1.43) $p<0.001$	−8.52 (−3.34, −2.22) $p<0.001$	−7.52 (−2.44, −1.13) $p<0.001$
HAM-A response rate, %[b,c]	12.5	17.9 (1.44, 2.98) $p<0.001$	21.7 (1.44, 2.65) $p<0.001$	21.4 (1.13, 2.24) $p<0.01$
HAM-A psychic symptom subscale	−3.21	−4.57 (−1.75, −0.97) $p<0.001$	−5.20 (−2.33, −1.66) $p<0.001$	−4.67 (−1.85, −1.06) $p<0.001$
HAM-A somatic symptom subscale	−2.50	−3.23 (−1.09, −0.37) $p<0.001$	−3.32 (−1.13, −0.51) $p<0.001$	−2.86 (−0.72, 0.01) $p=0.0552$
Week 8				
HAM-A total	−11.30	−13.31 (−2.92, −1.11) $p<0.001$	−14.39 (−3.87, −2.31) $p<0.001$	−12.50 (−2.12, −0.29) $p<0.05$
HAM-A response rate, %[b,c]	49.7	61.4 (1.18, 1.96) $p<0.01$	65.0 (1.51, 2.35) $p<0.001$	53.9 (0.99, 1.64) $p=0.062$
HAM-A remission rate, %[c,d]	27.4	34.2 (1.02, 1.76) $p<0.05$	39.0 (1.31, 2.10) $p<0.001$	28.5 (0.79, 1.40) $p=0.722$
HAM-A psychic symptom subscale	−6.24	−7.45 (−1.75, −0.68) $p<0.001$	−8.27 (−2.49, −1.57) $p<0.001$	−7.22 (−1.52, −0.44) $p<0.001$
HAM-A somatic symptom subscale	−5.04	−5.86 (−1.26, −0.38) $p<0.001$	−6.14 (−1.48, −0.72) $p<0.001$	−5.31 (−0.71, 0.18) $p=0.243$
CGI-S total	−1.41	−1.67 (−0.41, −0.11) $p<0.001$	−1.84 (−0.56, −0.31) $p<0.001$	−1.52 (−0.26, 0.04) $p=0.140$
CGI-I, % 'very much/much improved'[c]	54.7	65.1 (1.13, 1.90) $p<0.01$	67.9 (1.40, 2.19) $p<0.001$	57.6 (0.90, 1.50) $p=0.242$
MADRS total	−3.07	−4.43 (−2.05, −0.67) $p<0.001$	−5.38 (−2.90, −1.72) $p<0.001$	−3.94 (−1.56, −0.17) $p<0.05$
Q-LES-Q % maximum total	8.82	9.50 (−1.13, 2.50) $p=0.461$	11.90 (1.51, 4.66) $p<0.001$	8.15 (−2.51, 1.17) $p=0.473$
PSQI global	−3.53	−5.00 (−1.85, −1.08) $p<0.001$	−5.25 (−2.06, −1.37) $p<0.001$	−4.60 (−1.47, −0.67) $p<0.001$

p values are versus change from randomisation to the corresponding time point (Weeks 1 or 8) for placebo.
LSM, least squares means; CI, confidence interval; HAM-A, Hamilton Anxiety Rating Scale; CGI-S, Clinical Global Impression-Severity of Illness; CGI-I, CGI-Improvement; MADRS, Montgomery-Åsberg Depression Rating Scale; Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire; PSQI, Pittsburgh Sleep Quality Index.
[a]The Day 4 (D1448C00010 and D1448C00011) and Week 1 (D1448C00009) assessments were combined (Week 1) in the pooled analysis;
[b]≥50% reduction from randomisation;
[c]95% CI for odds ratio versus placebo;
[d]HAM-A total score ≤7.

The number needed to treat values based on HAM-A response rates for quetiapine XR 50, 150 and 300 mg/day were 10.0, 6.9 and 19.6, respectively. At Week 8, the effect sizes for HAM-A change from baseline were 0.25 for quetiapine XR 50 mg/day, 0.39 for 150 mg/day and 0.14 for 300 mg/day.

At Weeks 1 and 8, significant improvements versus placebo were observed in HAM-A psychic symptom subscale score for quetiapine XR 50, 150 and 300 mg/day. At these time points, significant improvements in HAM-A somatic symptom subscale score were observed for quetiapine XR 50 and 150 mg/day versus placebo but not for quetiapine XR 300 mg/day.

At Week 8, Q-LES-Q-SF % maximum total score significantly improved with quetiapine XR 150 mg/day versus placebo; Q-LES-Q-SF % maximum total score improved with quetiapine XR 50 and 300 mg/day versus placebo but did not reach statistical significance. Significant improvements in MADRS total and PSQI global scores were observed with all three quetiapine XR doses versus placebo. CGI-S total scores and the proportion of patients with a CGI-I score of 1 or 2 ('very much/much improved') were significantly improved compared with placebo, with quetiapine XR 50 and 150 mg/day but did not reach significance in the quetiapine XR 300 mg/day group (Table 2).

The Jonckheere–Terpstra test did not reveal a dose response (of increased treatment effect with increasing dose) for either HAM-A total score or the Q-LES-Q-SF % maximum total score across the dose range investigated (50, 150 and 300 mg/day).

Patient subgroup analyses of the change from randomisation to Week 8 in HAM-A total score by age, gender, ethnicity and severity of anxiety are shown in Table 3. Across the patient subgroups, the data were generally consistent with the general pattern of results seen in the total study population. However, some differences were observed; for

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Table 3. Hamilton Anxiety Rating Scale total score change from randomisation to Week 8 by subgroup (last observation carried forward, pooled modified intent-to-treat population)

LSM score change from randomisation (95% CI versus placebo)	Placebo ($n=654$)	Quetiapine XR 50 mg/day ($n=438$)	Quetiapine XR 150 mg/day ($n=654$)	Quetiapine XR 300 mg/day ($n=425$)
Gender				
Male	−11.47	−13.66 (−3.68, −0.72) $p<0.01$	−14.03 (−3.90, −1.22) $p<0.001$	−12.87 (−2.94, 0.12) $p=0.072$
Female	−11.20	−13.10 (−3.04, −0.76) $p<0.01$	−14.58 (−4.36, −2.40) $p<0.001$	−12.31 (−2.24, 0.01) $p=0.053$
Age, years				
18–39	−11.88	−13.03 (−2.42, 0.12) $p=0.075$	−14.55 (−3.78, −1.55) $p<0.001$	−12.54 (−1.95, 0.62) $p=0.311$
40–65	−10.65	−13.53 (−4.16, −1.60) $p<0.001$	−14.24 (−4.72, −2.47) $p<0.001$	−12.51 (−3.15, −0.57) $p<0.01$
Ethnicity				
White	−11.06	−13.17 (−3.09, −1.14) $p<0.001$	−14.27 (−4.05, −2.36) $p<0.001$	−12.29 (−2.24, −0.22) $p<0.05$
Black	−13.39	−13.86 (−3.21, 2.27) $p=0.736$	−15.15 (−4.23, 0.17) $p=0.163$	−14.25 (−3.50, 1.78) $p=0.522$
Asian and other	−11.11	−15.16 (−8.74, 0.62) $p=0.089$	−15.77 (−8.82, −0.51) $p<0.05$	−12.74 (−5.51, 2.24) $p=0.409$
Baseline HAM-A score				
<29	−11.87	−12.99 (−2.15, −0.10) $p<0.05$	−14.31 (−3.32, −1.56) $p<0.001$	−12.66 (−1.79, 0.22) $p=0.125$
≥29	−9.31	−14.35 (−6.90, −3.16) $p<0.001$	−14.74 (−7.16, −3.69) $p<0.001$	−11.82 (−4.61, −0.41) $p<0.05$

p values are versus change from randomisation to Week 8 for placebo.
HAM-A, Hamilton Anxiety Rating Scale; LSM, least squares means; CI, confidence interval.

example, the treatment effect appeared to be reduced in black patients, and a greater treatment effect was seen in patients with a HAM-A total score ≥29 at baseline.

Safety and tolerability

The overall incidence of AEs was 75.4%, 85.6%, 88.1% and 69.3% with quetiapine XR 50, 150 and 300 mg/day and placebo, respectively; serious AEs occurred with an incidence of 0.7%, 0.6%, 1.6% and 0.6%, respectively. A total of three patients had four serious AEs that were considered possibly related to the study drug, three in the quetiapine XR 300 mg/day group (diabetes mellitus and acute renal failure [one patient] and suicidal ideation) and one in the quetiapine XR 150 mg/day group (syncope). There were no deaths during any of the studies. The most frequently reported AEs in patients receiving quetiapine XR were dry mouth, somnolence, sedation and constipation.

The most common (≥1.5%) AEs leading to discontinuation with quetiapine XR 50, 150, 300 mg/day and placebo were sedation (2.4%, 5.1%, 10.1% and 0.5%, respectively); somnolence (3.8%, 5.1%, 6.5% and 0.3%, respectively); fatigue (2.4%, 1.9%, 1.8% and 0.2%, respectively) and dizziness (1.5%, 1.2%, 1.6% and 0.6%, respectively). AEs potentially related to extrapyramidal symptoms (EPS), sexual dysfunction and somnolence and AEs reported during the TDSS period are shown in Table 4.

The incidences of AEs potentially related to somnolence and sedation with quetiapine XR 50, 150, 300 mg/day and placebo were 38.1%, 52.3%, 63.1% and 16.5%, respectively (Table 4). The majority of AEs potentially related to somnolence were reported by Day 2 for all active treatment groups. AEs of somnolence, sedation, lethargy and sluggishness led to the discontinuation of 6.2%, 10.4%, 17.1% and 0.9% of patients from the quetiapine XR 50, 150 and 300 mg/day and placebo groups.

The incidences of AEs potentially related to EPS with quetiapine XR 50, 150, 300 mg/day and placebo were 3.8%, 5.1%, 5.9% and 3.2%, respectively. There was no clinically important difference in the intensity of AEs potentially associated with EPS across treatment groups, the majority of which were either mild or moderate. There were five severe AEs potentially associated with EPS, one extrapyramidal disorder (quetiapine XR 150 mg/day group), one psychomotor hyperactivity (quetiapine XR 300 mg/day group) and three tremor (one in the placebo group and two in the quetiapine XR 150 mg/day group). Five patients (0.7%) in the quetiapine XR 150 mg/day group and seven (1.6%) in the 300 mg/day group withdrew because of AEs potentially associated with EPS. The proportion of patients who experienced

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Table 4. Most frequently reported adverse events of special interest (extrapyramidal symptoms, sexual dysfunction and somnolence/sedation occurring at an incidence of ≥1% in any group) and adverse effects reported during the treatment discontinuation signs and symptoms period (occurring at an incidence of ≥2% in any group) [All from pooled safety population]

	Placebo ($n = 665$)	Quetiapine XR 50 mg/day ($n = 452$)	Quetiapine XR 150 mg/day ($n = 673$)	Quetiapine XR 300 mg/day ($n = 444$)
EPS, *n* (%)				
Total	21 (3.2)	17 (3.8)	34 (5.1)	26 (5.9)
Akathisia	3 (0.5)	4 (0.9)	11 (1.6)	8 (1.8)
Restlessness	2 (0.3)	6 (1.3)	12 (1.8)	6 (1.4)
Tremor	12 (1.8)	4 (0.9)	8 (1.2)	8 (1.8)
Sexual dysfunction, *n* (%)				
Total	14 (2.1)	6 (1.3)	17 (2.5)	17 (3.8)
Libido decreased	6 (0.9)	1 (0.2)	12 (1.8)	7 (1.6)
Somnolence and sedation, *n* (%)				
Total	110 (16.5)	172 (38.1)	352 (52.3)	280 (63.1)
Lethargy	5 (0.8)	0	9 (1.3)	8 (1.8)
Sedation	33 (5.0)	56 (12.4)	133 (19.8)	131 (29.5)
Sluggishness	2 (0.3)	0	6 (0.9)	8 (1.8)
Somnolence	70 (10.5)	117 (25.9)	214 (31.8)	146 (32.9)
Most frequently reported AEs during TDSS period, *n* (%)				
Nausea	15 (2.3)	10 (2.2)	38 (5.6)	24 (5.4)
Insomnia	12 (1.8)	13 (2.9)	41 (6.1)	23 (5.2)
Headache	21 (3.2)	11 (2.4)	20 (3.0)	14 (3.2)
Diarrhoea	7 (1.1)	5 (1.1)	7 (1.0)	12 (2.7)
Vomiting	3 (0.5)	3 (0.7)	9 (1.3)	10 (2.3)
Dizziness	8 (1.2)	13 (2.9)	7 (1.0)	6 (1.4)

EPS, extrapyramidal symptoms; AE, adverse event; TDSS, treatment discontinuation signs and symptoms.

worsening in Barnes Akathisia Rating Scale global score (3.0%–4.4%) and Simpson-Angus Scale total score (7.1%–8.1%) was similar in each group.

The incidences of AEs potentially associated with sexual dysfunction with quetiapine XR 50, 150, 300 mg/day and placebo were 1.3%, 2.5%, 3.8% and 2.1%, respectively. One patient (0.2%) in the quetiapine XR 50 mg/day group, three (0.4%) in the 150 mg/day and two (0.5%) in the 300 mg/day group withdrew because of AEs potentially associated with sexual dysfunction. At the end of treatment, mean change in CSFQ total score was 1.78 for quetiapine XR (pooled doses) and 1.71 for placebo; the least squares mean change (95% confidence interval) for quetiapine versus placebo was 0.07 (−0.53, 0.68), thus establishing the non-inferiority of quetiapine XR to placebo. CSFQ total scores increased with quetiapine XR (pooled doses) and placebo for females (1.30 and 0.72; $n = 1402$) and for males (2.13 and 2.99; $n = 800$); differences versus placebo were not statistically significant.

There were no clinically relevant mean changes from baseline in electrocardiogram, haematology assessments, vital signs or clinical laboratory data; however, an increase from baseline in mean supine pulse was observed in the quetiapine XR 150 (1.1 beats per minute [bpm]) and 300 mg/day (2.2 bpm) groups compared with a decrease in the quetiapine XR 50 mg/day (−0.6 bpm) and placebo (−0.2 bpm) groups. Mean increases in heart rate were observed in quetiapine XR-treated patients (1.2, 3.1, 5.6 and 0.6 bpm for quetiapine XR 50, 150, 300 mg/day and placebo, respectively), and mean QT intervals decreased with increasing quetiapine XR dose (−4.2, −6.4, −12.3 and −3.1 msec for quetiapine XR 50, 150, 300 mg/day and placebo, respectively). The proportions of patients with clinically relevant shifts from normal values in weight, fasting glucose and fasting lipid parameters are shown in Table 5. A greater proportion of patients receiving quetiapine XR than placebo showed a clinically important shift in glucose levels; the highest incidence of clinically important shifts occurred in the quetiapine XR 300 mg/day group. A greater proportion of patients receiving quetiapine XR 150 and 300 mg/day showed clinically important shifts in levels of triglycerides, and a greater proportion of patients receiving quetiapine XR 300 mg/day showed clinically important shifts in levels of high-density lipoprotein compared with those receiving placebo. At the end of the treatment period, mean increases in body weight were recorded in all groups, with the greatest increases being in the quetiapine XR 300 mg/day group.

Drug-discontinuation/tapering phase. Mean TDSS total scores are shown in Table 6. TDSS total scores in the quetiapine XR groups were numerically higher than the placebo group throughout the drug-discontinuation/tapering phase, and higher scores

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Table 5. Patients with shifts from normal to clinically significant values in clinical laboratory parameters and body weight from randomisation to end of treatment in patients with fasting status confirmed[a] (last observation carried forward, pooled safety population)

	Placebo ($n=665$)	Quetiapine XR 50 mg/day ($n=452$)	Quetiapine XR 150 mg/day ($n=673$)	Quetiapine XR 300 mg/day ($n=444$)
Glucose (mg/dl)				
Patients with fasting glucose ≥126 mg/dl at end of treatment, *n* (%)	8 (1.8) [$n=449$]	6 (1.9) [$n=319$]	6 (1.4) [$n=436$]	10 (3.7) [$n=272$]
Total cholesterol (mg/dl)				
Patients with fasting total cholesterol ≥240 mg/dl at end of treatment, *n* (%)	15 (3.9) [$n=381$]	15 (6.2) [$n=242$]	25 (7.1) [$n=350$]	10 (4.3) [$n=231$]
HDL cholesterol (mg/dl)				
Patients with fasting HDL cholesterol ≤40 mg/dl at end of treatment, *n* (%)	32 (8.7) [$n=367$]	20 (8.2) [$n=244$]	29 (8.2) [$n=352$]	27 (13.0) [$n=207$]
LDL cholesterol (mg/dl)				
Patients with fasting LDL cholesterol ≥160 mg/dl at end of treatment, *n* (%)	14 (3.6) [$n=389$]	12 (4.7) [$n=253$]	20 (5.4) [$n=367$]	5 (2.1) [$n=237$]
Triglycerides (mg/dl)				
Patients with fasting triglycerides ≥200 mg/dl at end of treatment, *n* (%)	20 (5.4) [$n=371$]	12 (4.9) [$n=245$]	36 (10.1) [$n=358$]	35 (16.3) [$n=215$]
Prolactin (ng/ml)[b]				
Mean (SD) at randomisation	8.5 (7.0)	9.0 (7.7)	8.5 (8.9)	7.6 (4.9)
Mean (SD) change	0.2 (7.6)	0.2 (5.2)	0.4 (7.4)	0.8 (5.1)
Weight				
≥7% increase in weight at end of treatment, *n* (%)	11 (1.7) [$n=656$]	14 (3.2) [$n=438$]	29 (4.4) [$n=655$]	17 (4.0) [$n=428$]

HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation.
[a]Fasting status was determined based upon a documented report from the patient that last meal was ≥8 h before blood sample was taken for randomisation and post-randomisation laboratory measurements. However, not all samples could be confirmed as fasted despite there being an 8-h interval since the last meal, as patients could have had caloric intake.
[b]Patients with fasting status assumed. Normal prolactin range: 2–20 ng/ml (males); 2–29 ng/ml (females).

Table 6. Mean treatment discontinuation signs and symptoms total scores (pooled treatment discontinuation signs and symptoms population)

	TDSS total score, mean (SD)				
Post-treatment day	Placebo ($n=416$)	Quetiapine XR 50 mg/day ($n=263$)	Quetiapine XR 150 mg/day ($n=385$)	Quetiapine XR 300 mg/day ($n=108$)[a]	Quetiapine XR 300 mg/day ($n=117$)[b]
1	1.6 (1.9)	2.2 (2.7)	2.0 (2.0)	2.9 (2.9)	1.5 (1.8)
3	2.3 (2.5)	2.8 (3.1)	3.2 (3.1)	4.9 (4.0)	2.2 (2.3)
5	2.2 (2.4)	2.8 (3.0)	3.0 (3.2)	4.2 (3.4)	2.0 (2.2)
7	2.4 (2.7)	2.7 (3.0)	3.1 (3.1)	4.1 (3.6)	1.9 (2.1)
14	2.7 (3.0)	3.0 (3.0)	3.1 (3.1)	3.9 (3.5)	3.1 (3.0)

TDSS, treatment discontinuation signs and symptoms, SD, standard deviation
[a]Patients with no down-titration;
[b]patients with down-titration.

were observed with increasing dose. However, in the subset of patients receiving quetiapine XR 300 mg/day who had their dose down-titrated at the end of treatment, TDSS total scores were similar to placebo. Throughout the first week of the 2-week follow-up period, the proportion of patients recording worsened chills, nausea, sweating, insomnia and vomiting, as assessed by TDSS items/symptoms, was higher in patients in the quetiapine XR groups than the placebo group. The most frequently reported AEs during the TDSS period are shown in Table 4.

DISCUSSION

This prospectively planned pooled analysis of three large, placebo-controlled, randomised studies shows quetiapine XR at doses of 50, 150 and 300 mg/day to be significantly more effective than placebo at reducing symptoms in GAD over 8 weeks, with response seen as early as Week 1. This finding is in line with the results from the individual acute monotherapy studies in which quetiapine XR has been shown to be effective in reducing GAD symptoms (Bandelow *et al*., 2010; Khan *et al*., 2011; Merideth *et al*.,). The pooled

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data from the three studies described here provided a greater sample size for evaluation of the primary and secondary efficacy variables and allowed efficacy and tolerability analyses across patient subgroups to be performed and any dose–response relationship to be determined.

The improvement in HAM-A total score achieved with quetiapine XR was significant as early as Week 1 for all three doses; this reflects the outcome observed in each individual trial. In addition, the HAM-A response rate was significantly greater for all three quetiapine XR doses compared with placebo at Week 1. This fast onset of action provides a potential advantage over current first-line treatment options for GAD, SSRIs and SNRIs, which in some studies have required 2–4 weeks of treatment before a significant decrease in anxiety symptoms is observed (Pollack, 2001), during which time benzodiazepines are often prescribed as adjunct therapy. Similarly, the effect size noted here for quetiapine XR 150 mg/day was 0.39, whereas effect sizes of 0.17 for buspirone, 0.36 for SSRIs, 0.38 for benzodiazepines, 0.42 for venlafaxine XR and 0.50 for pregabalin have been reported (Hidalgo *et al*., 2007).

Treatment with quetiapine XR resulted in significant improvements across a range of anxiety symptoms as demonstrated by HAM-A response and remission, HAM-A psychic and somatic symptom subscale scores and CGI-I and CGI-S scores. In addition to the presence of anxiety, GAD is characterised by somatic symptoms and pain, and in one study, almost 50% of patients with GAD reported impairment in occupational functioning due to physical symptoms (Wittchen *et al*., 2002). In some studies, SSRIs and SNRIs, such as paroxetine, escitalopram and venlafaxine, have shown greater efficacy in improving the psychic symptoms of anxiety than the somatic symptoms (Davidson *et al*., 1999; Pollack *et al*., 2001; Stein *et al*., 2005). This was also the case in the studies reported here at Week 8; in Study 10, escitalopram 10 mg/day significantly improved HAM-A psychic symptom subscale score versus placebo ($p < 0.01$) but not HAM-A somatic symptom subscale score ($p = 0.305$) (Merideth *et al*.,), and in Study 11, paroxetine 20 mg/day significantly improved HAM-A psychic and somatic symptom subscale scores versus placebo ($p < 0.001$ and $p = 0.050$, respectively) (Bandelow *et al*., 2010). In contrast, in this analysis, quetiapine XR significantly improved HAM-A psychic (50, 150, 300 mg/day) and somatic (50, 150 mg/day) symptom subscale scores at Weeks 1 and 8.

Analysis of the primary efficacy variable by patient subgroup showed that the improvement from randomisation to Week 8 in HAM-A total score with quetiapine XR was generally consistent across the subgroups examined, with the exception of analysis by ethnicity. Although some differences were observed in the magnitude of change in HAM-A total score between subgroups, improvements occurred in all subgroups and no particular subgroup was responsible for the differences seen between placebo and quetiapine XR in the overall pooled population. The apparently greater treatment effect in patients with a HAM-A total score ≥ 29 at entry appeared to be mostly driven by the reduced effect of placebo in this subgroup of patients with more severe disease. These findings are consistent with results from other studies of anxiety disorders and MDD, which have reported that patients with less severe disease often respond to placebo treatment with a similar magnitude to that seen with active treatment; conversely, patients with more severe disease often show a smaller placebo response (Glassman *et al*., 2006). Subgroup analysis by ethnicity indicated an apparent smaller treatment effect of quetiapine XR in black patients; however, the majority of patients enrolled in these three studies were white, and thus, the small patient numbers in the other subgroups may have limited the statistical power of the analyses. Further work is required to determine whether this effect is replicable and, if so, whether it reflects underlying pharmacogenetic, socioeconomic or other factors (Cohen *et al*., 2006).

A limitation of this pooled study is that the patient population excluded patients with comorbid depression and hence may not represent patients with GAD and comorbid depression, who are common in clinical practise. However, all three doses of quetiapine XR reduced depressive symptoms, as demonstrated by statistically significant improvements in MADRS total scores at Week 8 compared with placebo. Quetiapine XR has also shown efficacy in treating depressive symptoms in MDD (Bauer *et al*., 2009; Cutler *et al*., 2009; Weisler *et al*., 2009; El-Khalili *et al*., 2010; Bortnick *et al*., 2011), and consequently, it would be anticipated to show efficacy in comorbid GAD and MDD. Furthermore, all three doses of quetiapine XR significantly improved sleep quality as measured by the PSQI global score. As sleep disturbance is a core symptom of GAD and MDD (Belanger *et al*., 2005; Mendlewicz, 2009), improvements in sleep quality would also be expected to contribute to treatment effect in patients with comorbid GAD and MDD.

Although quetiapine XR was investigated at doses of 50, 150 and 300 mg/day, significant effects were observed across the greatest number of outcome measures with the quetiapine XR 150 mg/day dose, and this dose was associated with the lowest number

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needed to treat. An example of these outcome measures is improved health-related quality of life, a key goal when treating patients with GAD (Ninan, 2001), as assessed by mean change in Q-LES-Q-SF % maximum score from randomisation at Week 8, which was only significant for 150 mg/day. With the exception of Q-LES-Q-SF % maximum total score, quetiapine XR 50 mg/day was associated with significant improvements in all primary and secondary outcome measures, with the magnitude of effect being less than for quetiapine XR 150 mg/day. Furthermore, the magnitude of improvements in several outcome measures was less in the 300 mg/day group compared with the 50 and 150 mg/day groups. The possible reasons for the lack of a dose–response relationship remain speculative; however, one possible explanation is an increased withdrawal rate (>35%) from the higher dose arm due to reduced tolerability of this dose compared with lower doses. The maximum quetiapine XR dose investigated in these studies, 300 mg/day, has proven to be effective as monotherapy in an acute study of bipolar depression. On the basis of the change in MADRS total score at Week 8, the effect size with quetiapine XR was 0.61; rates of discontinuation due to AEs were lower in the quetiapine XR arm (12.1% [17/140]) (Suppes *et al*., 2010) than the equivalent dose group in the GAD studies, which may suggest that patients with bipolar disorder may be more willing to tolerate AEs than those with GAD.

The majority of pharmacological therapies currently utilised to treat anxiety disorders enhance serotonin and/or noradrenaline neurotransmission. Quetiapine and norquetiapine (active human metabolite) have moderate-to-high affinity for histamine (Jensen *et al*., 2008), serotonin $5HT_{2A}$ and dopamine D_2 receptors, and norquetiapine is also a potent inhibitor of $5HT_{2C}$ receptors and the norepinephrine transporter (NET) (Jensen *et al*., 2008; Nyberg and Widzowski, 2010). The clinical relevance of NET inhibition is further supported by positron emission tomography data showing NET occupancy in quetiapine-treated subjects (Nyberg *et al*., 2008). NET inhibition has not been demonstrated by other atypical antipsychotics at clinically relevant doses (Nyberg and Widzowski, 2010); however, it is a property shared by a number of antidepressants, such as SNRIs, and may be an important mechanism contributing to the therapeutic effect.

In this pooled analysis, quetiapine XR at doses of 50, 150 and 300 mg/day was generally well tolerated, with a tolerability profile consistent with the known profile of quetiapine (Arvanitis *et al*., 1997; Kahn *et al*., 2007; Timdahl *et al*., 2007). Overall, a greater number of AEs were reported by patients who received quetiapine XR compared with those who received placebo; this incidence was higher in the quetiapine XR 150 and 300 mg/day groups than in the 50 mg/day group. This increased incidence of AEs is reflected in the higher discontinuation rates in the quetiapine XR 150 and 300 mg/day groups. The incidences of AEs potentially associated with EPS were greater in the quetiapine XR groups than the placebo group; however, overall, the incidence was low and the majority of events were mild to moderate in intensity. There were no reports of tardive dyskinesia in any of the three acute studies. Patients receiving treatment with atypical antipsychotics should be monitored for the emergence of EPS (Casey, 2006) as the occurrence of these events in the short term may be associated with a greater risk for the development of tardive dyskinesia in the long term (Barnes and McPhillips, 1998; Sachdev, 2004).

The CSFQ scores were not statistically significantly different from placebo for male or female patients with quetiapine XR, and the incidence of AEs potentially related to sexual dysfunction was similarly low for all treatment groups. This is of interest as SSRIs are known to be associated with an increased risk of AEs related to sexual dysfunction (Ferguson, 2001), and such AEs often lead to treatment discontinuation (Fleischhacker *et al*., 1994; Hu *et al*., 2004).

With the exception of a mean increase in supine pulse in the quetiapine XR 150 and 300 mg/day groups, there were no clinically relevant changes in vital signs for any quetiapine XR dose. A greater proportion of patients in the quetiapine XR groups showed shifts to elevated glucose and triglycerides and to lowered high-density lipoprotein compared with those receiving placebo. Mean increases in body weight were recorded in all treatment groups, with the greatest increases in the quetiapine XR 300 mg/day group. Clinical guidelines recommend that serum glucose, lipid and insulin levels, and weight/body mass index should be monitored at regular intervals following the initiation of antipsychotic treatment (American Diabetes Association *et al*., 2004).

The tolerability data indicate that the rate of AEs remains relatively low with the 300 mg/day dose. It seems likely that the majority (approximately 75%) of patients requiring this dose will be able to tolerate it, although an increased withdrawal rate compared with lower doses may occur. Although no dose–response relationship was found here, some patients may experience greater efficacy with higher doses, and the dose of quetiapine XR should be individualised for each patient to achieve the optimal balance of efficacy with safety and tolerability.

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This pooled analysis included data from a large number of patients and used robust statistical analyses. However, it should be noted that the studies did not allow flexibility in quetiapine XR dosing; consequently, they are not reflective of clinical practice where the dose can be adjusted on the basis of efficacy and tolerability in the individual patient. Additionally, onset of somnolence and sedation during the first 7 days of treatment may have presented a potential unblinding bias, thus enhancing the observed efficacy of quetiapine XR. GAD is a chronic disorder, and the findings from these acute studies should not be extrapolated to make conclusions about long-term efficacy. However, data from a maintenance study show that quetiapine XR effectively increases the time to recurrence of anxiety in patients with GAD (Katzman *et al*., 2011).

In summary, this pooled analysis of three large, placebo-controlled, randomised studies demonstrates that quetiapine XR monotherapy at low doses of 50–300 mg/day is effective for the treatment of GAD, with improvements in GAD symptoms seen as early as Week 1. Quetiapine XR was generally well-tolerated in patients with GAD, and the safety profile was consistent with the known safety profile of quetiapine.

CONFLICT OF INTEREST

Dan Stein has received research grants and/or consultancy honoraria from Abbott, AstraZeneca, Eli-Lilly, GlaxoSmithKline, Johnson & Johnson, Lundbeck, Orion, Pfizer, Pharmacia, Roche, Servier, Solvay, Sumitomo, Tikvah and Wyeth.

In the last 5 years and in the near future, Borwin Bandelow has been/will be on the speaker's board or advisory board or acts as a consultant for AstraZeneca, Bristol-Myers Squibb, Cephalon, Dainippon Sumitomo, Essex, GlaxoSmithKline, Janssen-Cilag, Lilly, Lundbeck, Pfizer, Solvay, Wyeth and Xian-Janssen.

Charles Merideth serves as Principal Investigator and Medical Director/CEO of Affiliated Research Institute.

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The investigators involved in these studies have been listed previously (Bandelow *et al*., 2010; Khan *et al*., 2011; Merideth *et al*., in press).

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