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Original Paper

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Abstract

Identification of predictors of treatment response in patients with major depressive disorder (MDD) may facilitate improved disease management. Data were pooled from two 6-week, double-blind, placebo-controlled studies of extended-release quetiapine (quetiapine XR; 150 or 300 mg/day) as adjunct to ongoing antidepressant therapy. Effects of psychiatric history and baseline demographic and disease characteristics on efficacy outcomes (Week 6 Montgomery Åsberg Depression Rating Scale [MADRS] total score reduction) were evaluated in population subgroups (quetiapine XR both doses pooled, $n = 616$; placebo, $n = 303$). Baseline Clinical Global Impressions-Severity (CGI-S) score and previous depressive episodes on Week 6 MADRS total score change, and baseline MADRS individual item scores on Week 6 change in CGI-Improvement score, were also evaluated. No major differences between responders and non-responders to quetiapine XR were observed for patient characteristics or demographic and disease characteristics. No suggestion of a predictive association was found between baseline CGI-S score, number of depressive episodes, and baseline MADRS item scores and efficacy outcomes. These analyses showed no major differences between responders and non-responders, and no predictive association between the parameters assessed and efficacy outcomes for adjunct quetiapine XR in patients with MDD and an inadequate response to prior antidepressant therapy.

Keywords

Adjunct, atypical antipsychotic, extended-release quetiapine fumarate, major depressive disorder, predictive factors

Introduction

Major depressive disorder (MDD) is a global health concern and is associated with high levels of disability (Prince et al., 2007). First-line recommended treatment options for patients with MDD include an antidepressant (selective serotonin reuptake inhibitor [SSRI], serotonin norepinephrine reuptake inhibitor [SNRI], mirtazapine or bupropion) chosen on the basis of anticipated adverse events, individual tolerability and patient preference (American Psychiatric Association, 2010). However, many patients do not experience an adequate response to initial antidepressant treatment (Nemeroff, 2007). For example, in the open-label Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the rate of response to initial treatment with citalopram was 47% (Trivedi et al., 2006). Residual symptoms in unresponsive patients are associated with a chronic disease course, greater severity of illness and a higher risk of relapse (Bech et al., 2010; Judd et al., 2000; Thase et al., 1992). Strategies for treating patients who respond inadequately to first-line treatment include dose optimisation, combination therapy, augmentation or switching to another antidepressant (Bauer et al., 2007; Connolly and Thase, 2011).

Extended-release quetiapine fumarate (quetiapine XR) has been evaluated in an extensive clinical trial programme for the treatment of MDD both as a monotherapy for the acute treatment of adult (Bortnick et al., 2011; Cutler et al., 2009; Earley et al. 2008; Weisler et al., 2009) and elderly patients (Katila et al., 2013), as maintenance treatment as a monotherapy (Liebowitz et al., 2010) and as adjunct therapy to an antidepressant for the acute treatment of adult patients (Bauer et al., 2009; El-Khalili et al., 2010). As a consequence of these studies, quetiapine XR has been approved in Europe (AstraZeneca Pharmaceuticals (Ireland) Ltd, 2013), the USA (AstraZeneca Pharmaceuticals LP, 2013) and several other countries worldwide as an adjunct to antidepressant therapy in patients with an inadequate response to antidepressants and as monotherapy in a limited number of countries including Canada and Australia (please consult individual labels for each country).

In patients with MDD who have had an inadequate response to initial therapy, identification of potential predictors of response for subsequent medications may facilitate optimised treatment. The growing clinical interest in identifying predictors of response to

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treatment is reflected by the increasing number of reports on this topic in the literature (Friedman et al., 2012; Leuchter et al., 2009; Papakostas and Larsen, 2011; Porcelli et al., 2012; Serretti et al., 2007; Spronk et al., 2011; Steffens et al., 2011; Uher et al., 2012).

The *post hoc* analyses reported here used pooled data from the two adjunct studies of quetiapine XR (D1448C00006 and D1448C00007) to examine clinical and demographic characteristics of patients to identify any potential predictors of response.

Methods

Fully detailed methodologies for the two studies of adjunct quetiapine XR in MDD have been reported previously (Bauer et al., 2009; El-Khalili et al., 2010) and are summarised here.

Study design and treatment

Data were pooled from two similar, 6-week, double-blind, randomised, placebo-controlled studies of quetiapine XR (150 or 300 mg/day) as adjunct to ongoing antidepressant therapy in patients with MDD and an inadequate response to prior antidepressant therapy (Studies D1448C00006 [NCT00326105] (El-Khalili et al., 2010) and D1448C00007 [NCT00351910] (Bauer et al., 2009)). Written informed consent was provided by all patients prior to inclusion and the studies were conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation/Good Clinical Practice guidelines and applicable regulatory requirements.

Outpatients (aged 18–65 years) were required to have a Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (American Psychiatric Association, 1994) diagnosis of MDD (single episode or recurrent; confirmed by Mini-International Neuropsychiatric Interview), a Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960) total score ≥20 and a HAM-D Item 1 (depressed mood) score ≥2 at enrolment and randomisation. Eligible patients also had a history of inadequate response to an antidepressant during the current episode of MDD, defined as continuing depressive symptoms following at least minimum effective antidepressant treatment for 6 weeks (including ≥1 dose increase) according to their respective labels.

Key exclusion criteria were: a DSM-IV Axis I disorder other than MDD within 6 months of enrolment; a DSM-IV Axis II disorder that significantly impacted their current psychiatric status; a current episode of MDD >12 months or <4 weeks in duration prior to enrolment; history of substance or alcohol abuse; evidence of clinically relevant disease; or serious risk of homicide or suicide.

Both studies consisted of an enrolment period (≤14 days) and a 6-week randomised treatment period. Study D1448C00006 had an additional 2-week drug-discontinuation/follow-up period. During enrolment, all prohibited medication was discontinued. Patients continued to maintain their previous antidepressant therapy at the same dose from enrolment until the end of double-blind treatment. Permitted antidepressants in these studies were amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline or venlafaxine. In both studies, patients were randomised (using a computer-based system) to receive either quetiapine XR 150 mg/day, quetiapine XR 300 mg/day or placebo adjunct to ongoing antidepressant treatment in a 1:1:1 ratio. The dose of quetiapine XR was 50 mg/day on Days 1–2, 150 mg/day on Days 3–4 and 300 mg/day on Day 5 according to randomisation group. Study treatment was administered once daily in the evening. Quetiapine XR tablets were identical in appearance, smell and taste to their respective placebo tablets. Use of mood stabilisers, other than those allowed in the study protocol, or other antipsychotics or psychoactive drugs in the 7 days prior to randomisation was not permitted. No concomitant psychotherapy was permitted (other than supportive psychotherapy) during the study period, unless psychotherapy had been ongoing for a minimum of 3 months before randomisation.

The primary efficacy endpoint in both studies was change from randomisation to Week 6 in Montgomery Åsberg Depression Rating Scale (MADRS) total score. MADRS response (≥50% reduction in MADRS total score from randomisation) rate at Week 6 was included as a secondary endpoint.

Statistical analysis

The treatment groups included in the present analyses were quetiapine XR (both the 150 mg/day and 300 mg/day doses pooled) plus antidepressant and placebo plus antidepressant.

All analyses examining potential predictors of response were performed *post hoc* using the pooled modified intent-to-treat (MITT) population, defined as all patients assigned to randomised treatment who took the investigational product, had a randomisation MADRS assessment and had at least one valid MADRS assessment after randomisation. A last observation carried forward (LOCF) approach was used. Descriptive statistics were provided for all analyses.

The effects of baseline psychiatric history, demographic and disease characteristics (variables analysed are listed in Table 1) on efficacy outcomes were evaluated in three sets of patient subgroups according to MADRS response/study completion status: 1) patients categorised as having a reduction in MADRS total score at Week 6 of ≥50% (responders) or <50% (non-responders); 2) patients categorised as having a reduction in MADRS total score at Week 6 of ≥75% (responders) or <25% (non-responders); and 3) patients categorised as having a reduction in MADRS total score at Week 6 of ≥50% (responders) or <50% or were non-completers (non-responders). This third analysis provided an alternative approach to the LOCF analysis.

A further analysis evaluated the number and proportion of patients in categories of percentage reduction in MADRS total score from baseline to Week 6 (<0%, 0–<15%, 15–<30%, 30–<45%, 45–<60%, 60–<75%, ≥75%) according to the number of depressive episodes (0, 1, 2–3, 4–<10, ≥10) both in the previous year and lifetime.

To evaluate the effect of baseline disease severity on efficacy outcomes, the number and proportion of patients in categories of percentage reduction in MADRS total score from baseline to Week 6 were also analysed according to baseline Clinical Global Impressions-Severity (CGI-S) (National Institute of Mental Health, 1976) score categories (Mildly, Moderately, Markedly, Severely, Amongst the most severely ill).

The effect of baseline MADRS individual item (Items 1–10) scores (0–6) on CGI-Improvement (CGI-I) score at Week 6 (number and proportion of patients in CGI-I score categories of 'Very much', 'Much', 'Minimally' improved, No change and

Table 1. Variables of baseline psychiatric history, demographic and disease characteristics investigated in the *post hoc* analyses of responders and non-responders.

Psychiatric history	Demographic characteristics	Disease characteristics
Years since first depressive episode	Gender	MADRS total score
Years since first depressive episode group (<10, ≥10 years)	Age	MADRS severity (total score <28, ≥28)
	Age group (18–39, 40–65 years)	HAM-D total score
Depressive episodes over lifetime	Ethnicity	HAM-D severity (total score <28, ≥28)
Depressive episodes over lifetime group (<4, ≥4)	Region: Australia, Europe, North America, South Africa	HAM-D Item 1 score
Depressive episodes over past year		CGI-S total score
Number of hospitalisations	Weight	CGI-S severity (total score <5, ≥5)
Number of hospitalisations group (0, ≥1)	Weight group (<78 kg, ≥78 kg)	HAM-A total score
Family members with MDD	Waist circumference	HAM-A severity (total score <19, ≥19)
Number of family members with MDD (0–1, ≥2)	BMI	Q-LES-Q total score
Biological father with MDD	BMI group (<18.5, 18.5–<25, 25–<30, 30–<40, ≥40 kg/m^2)	Q-LES-Q severity (total score <45, ≥45)
Biological mother with MDD		Q-LES-Q Item 16 score
Number of biological brothers		PSQI global score
Number of biological brothers with MDD		PSQI severity (global score <12, ≥12)
Number of biological sisters		BARS total score
Number of biological sisters with MDD		SAS total score
Number of biological children		DSM-IV diagnosis (single episode or recurrent)
Number of biological children with MDD		
Any suicide attempt		
Number of suicide attempts over lifetime		
Hospitalised for suicide attempt		
Current or prior exposure (yes, no) to: aripiprazole clozapine, olanzapine, quetiapine, risperidone, ziprasidone		

BARS: Barnes Akathisia Rating Scale; BMI: body mass index; CGI-S: Clinical Global Impressions-Severity; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale; MADRS: Montgomery Åsberg Depression Rating Scale; MDD: major depressive disorder; PSQI: Pittsburgh Sleep Quality Index; Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire; SAS: Simpson-Angus Scale.

'Very much', 'Much', 'Minimally' worse at Week 6) was also assessed.

Stepwise model selection was used to identify correlations between outcome variables of interest (MADRS response, MADRS percentage change from baseline and MADRS total score) and potential predictors of outcome (gender, age, weight, body mass index [BMI], baseline HAM-D total score, baseline MADRS score, baseline CGI-S total score, baseline Hamilton Anxiety Rating Scale total score, baseline Quality of Life Enjoyment and Satisfaction Questionnaire total score, baseline Pittsburgh Sleep Quality Index global score, baseline Simpson-Angus Scale [SAS] total score, Barnes Akathisia Rating Scale global assessment score, baseline depressive mood, baseline satisfaction/content score, DSM-IV diagnosis [single episode or recurrent MDD], number of hospitalisations, family members with MDD, ever attempted suicide, hospitalised for a suicide attempt, total number of major depressive episodes in the previous year, lifetime total number of depressive episodes, treatment with an SSRI as adjunctive treatment, treatment with an SNRI as adjunctive treatment, years since first diagnosis of MDD, years since first depressive episode, years since onset of present depressive episode and 10 baseline MADRS item scores [apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts and suicidal thoughts]).

Model selection was performed on MADRS percentage change and MADRS total score at Week 6 using PROC REG stepwise, forward and backward selection methods and on responders at Week 6 using PROC LOGISTIC stepwise, forward and backward selection models. Statistical analyses were performed using SAS® Version 8.2 (Cary, NC, USA).

Results

Patient population

The pooled patient population has been described previously (Bauer et al., 2010a). The pooled MITT population comprised 616 patients in the quetiapine XR plus antidepressant group (both doses pooled) and 303 patients in the placebo plus antidepressant group.

Efficacy in the overall pooled population

Efficacy results for the pooled population have been reported previously (Bauer et al., 2010a); in brief, least squares means changes in MADRS total score from randomisation to Week 6 were –14.5 for quetiapine XR 150 mg/day plus antidepressant, –14.8 for quetiapine XR 300 mg/day plus antidepressant and –12.0 for placebo plus antidepressant ($p < 0.001$ *vs.* placebo for both doses). At Week 6, MADRS response (≥50% reduction in MADRS total score) rates were 53.7% for quetiapine XR 150 mg/day plus antidepressant, 58.3% for quetiapine XR 300 mg/day plus antidepressant and 46.2% for placebo ($p = 0.063$ and $p < 0.01$ *vs.* placebo, respectively).

Table 2. Analyses of patients' baseline psychiatric history, demographic and disease characteristics in responders and non-responders defined using the cut-offs of ≥50% and <50% reduction in MADRS total score at Week 6, respectively (LOCF; pooled MITT).

	Responders[a]		Non-responders[b]	
	Quetiapine XR + AD (*n* = 345)	Placebo + AD (*n* = 140)	Quetiapine XR + AD (*n* = 271)	Placebo + AD (*n* = 163)
Psychiatric history				
Years since first depressive episode, mean	13.1	13.6	12.9	15.4
Depressive episodes over lifetime, mean	9.5	10.0	9.3	9.5
Depressive episodes over past year, mean	1.3	1.6	1.7	1.3
Number of hospitalisations, mean	0.5	0.4	0.5	0.6
Demographic characteristics				
Gender, %				
Male	29.6	30.0	27.3	36.2
Female	70.4	70.0	72.7	63.8
Ethnicity, %				
White	93.0	94.3	96.3	93.9
Black	4.3	5.0	3.0	5.5
Asian	0.6	0.7	0	0
Other	2.0	0	0.7	0.6
Region, %				
Australia	5.8	5.7	3.0	4.3
Europe	40.3	38.6	44.6	45.4
North America	48.1	50.0	49.8	49.1
South Africa	5.8	5.7	2.6	1.2
Disease characteristics				
MADRS total score, %				
<28	46.1	40.0	48.7	49.1
≥28	53.9	60.0	51.3	50.9
HAM-D total score, %				
<28	81.7	81.4	85.2	84.0
≥28	18.3	18.6	14.8	16.0
CGI-S total score, %				
<5	54.5	55.7	52.0	58.9
≥5	45.5	44.3	48.0	41.1
HAM-A total score, %				
<19	47.0	48.6	39.9	50.3
≥19	53.0	51.4	60.1	49.7

AD: antidepressant; CGI-S: Clinical Global Impressions-Severity; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale; LOCF: last observation carried forward; MADRS: Montgomery Åsberg Depression Rating Scale; MITT: modified intent-to-treat; XR: extended release.
[a]≥50% reduction in MADRS total score at Week 6.
[b]<50% reduction in MADRS total score at Week 6.

Effect of psychiatric history and demographic and disease characteristics on efficacy outcomes. Results of the evaluation of the key variables of patients' psychiatric history and baseline demographic and disease characteristics in responders and non-responders (defined by ≥50% and <50% reduction in MADRS total score, respectively) are presented in Table 2 and did not reveal any definitive predictive factors for any of the variables evaluated in either the quetiapine XR plus antidepressant group or placebo plus antidepressant group.

Similarly, using the alternative definitions for responders or non-responders (≥75%/<25% reduction in MADRS total score, respectively), evaluation of the key variables of patients' psychiatric history and baseline demographic and disease characteristics did not reveal any definitive predictive factors in either the quetiapine XR or placebo groups (Table 3). The inclusion of non-completers as part of the non-responder group as an alternative to the LOCF approach did not show any major differences between the results of the two methods of analysis (Table 4).

In addition, no definitive predictive factors were revealed in either of the patient populations through the analyses of reduction in MADRS total score by number of depressive episodes in the previous year and the lifetime number of depressive episodes (Table 5).

Effect of disease severity on efficacy outcomes. There was no suggestion that baseline disease severity was a predictive factor in either the quetiapine XR or placebo groups, as evaluated by the

Table 3. Analyses of patients' baseline psychiatric history, demographic and disease characteristics in responders and non-responders defined using the cut-offs of ≥75% and <25% reduction in MADRS total score at Week 6, respectively (LOCF; pooled MITT[a]).

	Responders[b]		Non-responders[c]	
	Quetiapine XR + AD (*n* = 175)	Placebo + AD (*n* = 60)	Quetiapine XR + AD (*n* = 125)	Placebo + AD (*n* = 89)
Psychiatric history				
Years since first depressive episode, mean	12.9	13.0	14.6	17.7
Depressive episodes over lifetime, mean	8.8	9.9	10.5	11.1
Depressive episodes over past year, mean	1.5	1.6	1.8	1.4
Number of hospitalisations, mean	0.5	0.2	0.6	0.6
Demographic characteristics				
Gender, %				
Male	26.3	26.7	28.8	33.7
Female	73.7	73.3	71.2	66.3
Ethnicity, %				
White	92.0	93.3	95.2	94.4
Black	5.7	5.0	4.0	5.6
Asian	0.6	1.7	0	0
Other	1.7	0	0.8	0
Region, %				
Australia	7.4	10.0	2.4	5.6
Europe	35.4	35.0	38.4	43.8
North America	49.1	48.3	56.0	49.4
South Africa	8.0	6.7	3.2	1.1
Disease characteristics				
MADRS severity, %				
<28	47.4	41.7	46.4	49.4
≥28	52.6	58.3	53.6	50.6
HAM-D total score, %				
<28	83.4	76.7	83.2	82.0
≥28	16.6	23.3	16.8	18.0
CGI-S total score, %				
<5	54.9	60.0	47.2	50.6
≥5	45.1	40.0	52.8	49.4
HAM-A total score, %				
<19	48.0	48.3	40.8	52.8
≥19	52.0	51.7	59.2	47.2

AD: antidepressant; CGI-S: Clinical Global Impressions-Severity HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale; LOCF; last observation carried forward; MADRS: Montgomery Åsberg Depression Rating Scale; MITT: modified intent-to-treat; XR: extended release.

[a]The total pooled MITT population comprised 616 patients in the quetiapine XR + AD group and 303 patients in the placebo group; not all patients were included in the responders and non-responders categories (≥75% and <25% reduction in MADRS total score at Week 6, respectively).

[b]≥75% reduction in MADRS total score at Week 6.

[c]<25% reduction in MADRS total score at Week 6.

analyses of percentage change from baseline to Week 6 in MADRS total score by baseline CGI-S score category (Mildly, Moderately, Markedly, Severely, Amongst the most severely ill) (Table 4).

MADRS individual items. The investigation of the effect of MADRS individual item scores at baseline on CGI-I category score at Week 6 also did not show any clear predictive factors for either patient population (data not shown).

Stepwise model selection. Predictive correlations revealed using stepwise model selection for MADRS (observed) total score and percent change from baseline at Week 6 are shown in Table 6. Predictive correlations revealed using stepwise model selection for responders (observed) at Week 6 are shown in Table 7.

Safety and tolerability

Safety and tolerability outcomes have been reported previously for these two studies separately and in a pooled analysis (Bauer et al., 2009, 2010a; El-Khalili et al., 2010) and were consistent with the known tolerability profile for quetiapine.

Table 4. Analyses of patients' baseline psychiatric history, demographic and disease characteristics using an alternative approach to the LOCF method (responders defined as patients with ≥50% reduction in MADRS total score at Week 6; non-responders defined as study non-completers or patients with <50% reduction in MADRS total score at Week 6) (pooled MITT).

	Responders[a]		Non-responders[b]	
	Quetiapine XR + AD (*n* = 316)	Placebo + AD (*n* = 133)	Quetiapine XR + AD (*n* = 300)	Placebo + AD (*n* = 170)
Psychiatric history				
Years since first depressive episode, mean	12.9	13.9	13.2	15.1
Depressive episodes over lifetime, mean	7.8	10.3	11.1	9.2
Depressive episodes over past year, mean	1.3	1.6	1.7	1.3
Number of hospitalisations, mean	0.5	0.4	0.6	0.6
Demographic characteristics				
Gender, %				
Male	29.4	28.6	27.7	37.1
Female	70.6	71.4	72.3	62.9
Ethnicity, %				
White	93.7	94.0	95.3	94.1
Black	4.1	5.3	3.3	5.3
Asian	0.3	0.8	0.3	0
Other	1.9	0	1.0	0.6
Region, %				
Australia	5.4	6.0	3.7	4.1
Europe	41.5	37.6	43.0	45.9
North America	47.2	50.4	50.7	48.8
South Africa	6.0	6.0	2.7	1.2
Disease characteristics				
MADRS total score, %				
<28	45.3	40.6	49.3	48.2
≥28	54.7	59.4	50.7	51.8
HAM-D total score, %				
<28	82.3	82.0	84.3	83.5
≥28	17.7	18.0	15.7	16.5
CGI-S total score, %				
<5	56.3	56.4	50.3	58.2
≥5	43.7	43.6	49.7	41.8
HAM-A total score, %				
<19	46.2	49.6	41.3	49.4
≥19	53.8	50.4	58.7	50.6

AD: antidepressant; CGI-S: Clinical Global Impressions-Severity; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale; LOCF; last observation carried forward; MADRS: Montgomery Åsberg Depression Rating Scale; MITT: modified intent-to-treat; XR: extended release.
[a]≥50% reduction in MADRS total score at Week 6.
[b]<50% reduction in MADRS total score at Week 6.

Discussion

Approximately 50% of patients with MDD do not respond to treatment with initial first-line antidepressants (Trivedi et al., 2006). Also, MDD is associated with substantial morbidity and mortality and, thus, the consequences are severe if symptoms of MDD remain untreated (due to a lack of response) or patients experience residual depressive symptoms (due to partial response/lack of remission). Therefore, it would be advantageous to be able to predict which treatment would be more likely to achieve a favourable outcome in order to optimise treatment for each patient.

In this analysis of pooled data from two acute studies of adjunct quetiapine XR (150–300 mg/day) in patients with MDD and an inadequate response to prior antidepressant treatment, no major differences between responders and non-responders with regard to psychiatric history and baseline demographic and disease characteristics were observed. Furthermore, there was no suggestion of a predictive association between the number of depressive episodes, disease severity at baseline, or baseline MADRS item scores and efficacy outcomes (assessed by change from randomisation in MADRS total score at Week 6). These data showing that baseline severity scores are not predictors of efficacy are not unexpected, since quetiapine XR monotherapy

Table 5. Number and proportion of patients in categories based on percentage change from baseline to Week 6 in MADRS total score by number of depressive episodes in the last year or over the patient's lifetime and by treatment group (pooled MITT).

Treatment	Depressive episodes	Total	% change from baseline in MADRS total score						
			<0% reduction, *n* (%)	0%–<15% reduction, *n* (%)	15%–<30% reduction, *n* (%)	30%–<45% reduction, *n* (%)	45%–<60% reduction, *n* (%)	60%–<75% reduction, *n* (%)	≥75% reduction, *n* (%)
Depressive episodes in the last year									
Quetiapine XR + AD (*n* = 616)	0	162	7 (4.3)	14 (8.6)	15 (9.3)	30 (18.5)	21 (13.0)	31 (19.1)	44 (27.2)
	1	296	9 (3.0)	36 (12.2)	34 (11.5)	41 (13.9)	38 (12.8)	55 (18.6)	83 (28.0)
	2–3	114	6 (5.3)	7 (6.1)	9 (7.9)	22 (19.3)	17 (14.9)	23 (20.2)	30 (26.3)
	4–<10	32	2 (6.3)	3 (9.4)	3 (9.4)	4 (12.5)	1 (3.1)	5 (15.6)	14 (43.8)
	≥10	12	1 (8.3)	1 (8.3)	2 (16.7)	1 (8.3)	2 (16.7)	1 (8.3)	4 (33.3)
	Total	616	25 (4.1)	61 (9.9)	63 (10.7)	98 (15.9)	79 (12.8)	115 (18.7)	175 (28.4)
Placebo + AD (*n* = 303)	0	101	8 (7.9)	12 (11.9)	16 (15.8)	16 (15.8)	21 (20.8)	8 (7.9)	20 (19.8)
	1	116	10 (8.6)	22 (19.0)	16 (13.8)	12 (10.3)	23 (19.8)	13 (11.2)	20 (17.2)
	2–3	64	5 (7.8)	6 (9.4)	8 (12.5)	10 (15.6)	7 (10.9)	14 (21.9)	14 (21.9)
	4–<10	15	1 (6.7)	0	0	1 (6.7)	6 (40.0)	3 (20.0)	4 (26.7)
	≥10	7	2 (28.6)	1 (14.3)	0	1 (14.3)	1 (14.3)	0	2 (28.6)
	Total	303	26 (8.6)	41 (13.5)	40 (13.2)	40 (13.2)	58 (19.1)	38 (12.5)	60 (19.8)
Depressive episodes over the patient's lifetime									
Quetiapine XR + AD (*n* = 616)	Missing	10	1 (10.0)	3 (30.0)	1 (10.0)	2 (20.0)	1 (10.0)	2 (20.0)	0
	0	35	1 (2.9)	3 (8.6)	2 (5.7)	4 (11.4)	8 (22.9)	6 (17.1)	11 (31.4)
	1	60	0	6 (10.0)	7 (11.7)	12 (20.0)	6 (10.0)	16 (26.7)	13 (21.7)
	2–3	178	10 (5.6)	16 (9.0)	21 (11.8)	24 (13.5)	20 (11.2)	28 (15.7)	59 (33.1)
	4–<10	180	4 (2.2)	18 (10.0)	20 (11.1)	35 (19.4)	20 (11.1)	33 (18.3)	50 (27.8)
	≥10	153	9 (5.9)	15 (9.8)	12 (7.8)	21 (13.7)	24 (15.7)	30 (19.6)	42 (27.5)
	Total	616	25 (4.1)	61 (9.9)	63 (10.2)	98 (15.9)	79 (12.8)	115 (18.7)	175 (28.4)
Placebo + AD (*n* = 303)	Missing	2	0	1 (50.0)	1 (50.0)	0	0	0	0
	0	17	3 (17.6)	2 (11.8)	1 (5.9)	4 (23.5)	3 (17.6)	2 (11.8)	2 (11.8)
	1	27	1 (3.7)	4 (14.8)	3 (11.1)	3 (11.1)	6 (22.2)	3 (11.1)	7 (25.9)
	2–3	87	6 (6.9)	16 (18.4)	9 (10.3)	13 (14.9)	18 (20.7)	12 (13.8)	13 (14.9)
	4–<10	81	7 (8.6)	9 (11.1)	13 (16.0)	10 (12.3)	15 (18.5)	9 (11.1)	18 (22.2)
	≥10	89	9 (10.1)	9 (10.1)	13 (14.6)	10 (11.2)	16 (18.0)	12 (13.5)	20 (22.5)
	Total	303	26 (8.6)	41 (13.5)	40 (13.2)	40 (13.2)	58 (19.1)	38 (12.5)	60 (19.8)

AD: antidepressant; MADRS: Montgomery Åsberg Depression Rating Scale; MITT: modified intent-to-treat; XR: extended release.

Table 6. Stepwise model selection results in predicting absolute and percent change in MADRS total score at Week 6.

Parameter	Estimated absolute change in MADRS total score at Week 6	*p* value
Treatment with quetiapine XR *vs.* placebo	−3.5	0.0002
Increase of 1 in baseline Q-LES-Q score	−0.1	<0.0001
Increase of 1 in baseline CGI-S score	+2.5	0.0005
Increase of 1 in baseline number of lifetime suicide attempts	+0.6	0.0066
1-year increase in time since first episode of depression	+0.1	0.0209
Increase of 1 in baseline reduced sleep score	+0.9	0.0231
Increase of 1 in baseline pessimistic thoughts score	−0.7	0.1099
	Estimated percentage change in MADRS total score at Week 6	
Treatment with quetiapine XR *vs.* placebo	−14.1	<0.0001
Increase of 1 in baseline Q-LES-Q score	−0.5	<0.0001
Increase of 1 in baseline CGI-S score	+7.5	0.0057
Increase of 1 in baseline number of lifetime suicide attempts	+2.2	0.0057
1-year increase in time since first episode of depression	+0.1	0.3072
Increase of 1 in total number of major depressive episodes in the previous year	+0.7	0.1743
Increase of 1 in baseline MADRS total score	−1.4	<0.0001

CGI-S: Clinical Global Impressions-Severity; MADRS: Montgomery Åsberg Depression Rating Scale; Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire; XR: extended release.

Table 7. Stepwise model selection results in predicting Week 6 responder status.

Parameter	Estimated odds ratio	95% CI	*p* value
Responder (≥50% reduction in MADRS total score at Week 6)			
Treatment with quetiapine XR *vs.* placebo	1.8	1.33, 2.50	0.0002
Increase of 1 in baseline Q-LES-Q score	1.0	1.03, 1.05	<0.0001
Increase of 1 in baseline MADRS score	1.1	1.03, 1.09	0.0001
Increase of 1 in BARS score	0.7	0.48, 0.98	0.0364
Years since first diagnosis of depression	1.0	0.97, 1.00	0.2986

BARS: Barnes Akathisia Rating Scale; CI: confidence interval; MADRS: Montgomery Åsberg Depression Rating Scale; Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire; XR: extended release.

was shown to be effective for the treatment of MDD across a broad range of disease severities (Thase et al., 2013). However, a number of correlations between the outcome variables response, MADRS change from baseline, and MADRS total score and a small number of predictors were identified, although the clinical relevance of these relationships is unclear.

To our knowledge, no other studies have investigated predictors of response for atypical antipsychotics as adjunct therapy in MDD. However, a limited number of studies have looked at predictors of remission. In a 6-week, open-label randomised study, patients with MDD and an inadequate response to an SSRI or venlafaxine received either quetiapine XR as adjunct to an antidepressant, lithium as adjunct to an antidepressant or quetiapine XR monotherapy (Bauer et al., 2010b); time variables were predictive for symptomatic remission. For example, time since first known psychiatric disorder was 3.7 years shorter in patients who achieved symptomatic remission compared with non-remitters ($p < 0.0001$). Other time variables that were significant predictors of symptomatic remission in this study included time since first known depressive episode, time since first diagnosis of MDD, time with the present depressive episode, and a number of anxiety and physical variables (such as lower supine and standing pulse rate) (Bauer et al., 2010b).

In the prospectively randomised COmbining Medications to Enhance Depression outcomes (CO-MED) study in outpatients with MDD, response rates in patients with more severe MDD were similar to those reported in patients with mild MDD, suggesting that severity of disease at baseline is not predictive of response (Friedman et al., 2012). However, in a multicentre, randomised controlled trial, factors indicative of more severe and/or persistent levels of MDD were found to be predictive of treatment response with duloxetine (Howland et al., 2008). Similarly, the Genome Based Therapeutic Drugs for Depression (GENDEP) study reported that, for nortriptyline, higher BMI and obesity predicted poor response whereas for escitalopram, neither of these factors significantly affected response (Uher et al., 2009). Taken together, these findings suggest that different predictors of response may be specific to different treatments, highlighting the importance of investigating predictors of response for each therapy.

Although we did not find any predictive value prior to adjunctive treatment with quetiapine XR, it is possible that early

improvement during adjunctive therapy, as reported by Muzina et al. (2011), may herald better outcomes. An analysis of pooled data from three large, randomised, double-blind, placebo-controlled trials of aripiprazole as adjunct to an antidepressant found ≥20% improvement in MADRS total score at Week 2 to be highly predictive of remission at Week 6 (Muzina et al., 2011).

The strengths of the current analyses include the large, multinational patient population and the large range of clinical parameters investigated. A limitation of these analyses is that the data were obtained under randomised clinical trial conditions and so the patient population was restricted according to the study protocol (adhering to strict inclusion and exclusion criteria); therefore, any conclusions drawn may not be generalisable beyond the specific population studied. In addition, these studies used fixed dosing, which is not reflective of clinical practice, and were of short (6-week) duration so these findings are applicable only to acute therapy. A further potential limitation is that we do not have any genetic/biomarker data from the present studies to analyse for prediction of treatment response. Although no biomarkers are currently suitable for clinical application, brain functional measures, genetic biomarkers, proteomic measures and metabolomic measures are currently being investigated and have demonstrated various levels of reliability to predict treatment response in MDD (Leuchter et al., 2009; Porcelli et al., 2012; Spronk et al., 2011).

In summary, in these analyses of pooled data from the two acute studies of adjunct quetiapine XR (150 and 300 mg/day) in patients with MDD and an inadequate response to prior antidepressant treatment, no predictive factors of treatment response were identified. Furthermore, no major differences between responders and non-responders were observed with regard to psychiatric history and baseline demographic and disease characteristics, and there was no suggestion of a predictive association between baseline CGI-S score, number of depressive episodes or MADRS item scores and efficacy outcomes. Therefore, our findings do not support reserving adjunct quetiapine XR therapy for a particular clinical subset of patients with MDD and an inadequate response to prior antidepressant treatment. Further investigation may be required to fully understand any predictive factors for response with adjunct quetiapine XR in MDD.

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