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Safety and tolerability of once-daily extended release quetiapine fumarate in acute schizophrenia: pooled data from randomised, double-blind, placebo-controlled studies

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Introduction Extended release quetiapine fumarate (quetiapine XR) is a new formulation that allows once-daily dosing and a titration regimen that is simpler than that of immediate release quetiapine (quetiapine IR) and may potentially increase patients' adherence to their prescribed medication.
Methods The tolerability of quetiapine XR was examined in an analysis of pooled data from three Phase III, double-blind, placebo-controlled, randomised studies with quetiapine IR as a reference treatment.
Results The overall incidence of adverse events (AEs) was similar for quetiapine XR (69.5%) and quetiapine IR (72.5%). Most AEs were mild to moderate in severity and in line with those observed with quetiapine IR. The more rapid dose titration of quetiapine XR did not produce any new safety concerns and was as well tolerated as the regimen for quetiapine IR.
Conclusions The results of this pooled analysis show that quetiapine XR administered once daily is generally as well tolerated as quetiapine IR given twice daily. These data, together with the simpler dose-titration of quetiapine XR that allowed therapeutically effective doses to be reached by Day 2, suggest that this formulation potentially may improve adherence in patients with schizophrenia. Copyright © 2010 John Wiley & Sons, Ltd.

KEY WORDS — extended release quetiapine fumarate; schizophrenia; tolerability; pooled analysis; psychosis

INTRODUCTION

As many as 50% of patients with schizophrenia fail to adhere to their prescribed treatment regimens, behaviour that is associated with treatment failure, relapse and serious consequences such as hospitalisation and possibly suicide (Keith and Kane, 2003; Weiden *et al.*, 2004; Montross *et al.*, 2005; Ascher-Svanum *et al.*, 2006). A number of factors can affect adherence, which include a patient's lack of perception of treatment benefits, previous experience with adverse effects of antipsychotic medications, lack of self-awareness (leading, for example, to a failure to recognise that lifestyle has become unusual), lack of insight into the illness and the complexity of the dosing regimen, in particular multiple daily doses or complex treatment initiation (Fleischhacker *et al.*, 2003; Rettenbacher *et al.*, 2004; Osterberg and Blaschke, 2005).

Quetiapine is an atypical antipsychotic that has been shown to be effective against a broad range of schizophrenia symptoms, including positive, negative, cognitive and affective symptoms (Borison *et al.*, 1996; Arvanitis and Miller, 1997; Small *et al.*, 1997; Sax and Strakowski, 1998; Purdon *et al.*, 2001; Sajatovic *et al.*, 2002; Velligan *et al.*, 2002; De Nayer *et al.*, 2003; Emsley and Oosthuizen, 2003; Velligan *et al.*, 2003). It also has an established safety and tolerability profile (Arvanitis and Miller, 1997; Cheer and Wagstaff, 2004); in patients with schizophrenia, the level of extrapyramidal symptoms (EPS) associated with quetiapine is similar to that of placebo across the full approved dose range (Arvanitis and Miller, 1997). Prolactin levels are also indistinguishable from those in patients given placebo across the full dosage range (Arvanitis and Miller, 1997). In the short term, the most common adverse event (AE) associated with quetiapine is somnolence, which generally subsides over time (Arvanitis and Miller, 1997). During long-term treatment, moderate weight gain may occur (Brecher *et al.*, 2007).

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Quetiapine is currently available as immediate release (IR) tablets for twice or three-times daily dosing and requires 5 or more days to reach the recommended therapeutic dose range. The established clinical benefits of quetiapine IR, combined with the need to encourage adherence to the prescribed treatment, provided a strong rationale for simplifying the dose-titration regimen and reducing the dosing schedule. To this end, extended release quetiapine fumarate (quetiapine XR), a new, once-daily formulation, has been developed to provide patients and physicians with a more convenient dosing regimen and simpler dose titration so that patients can reach the therapeutic dose range by the second day of treatment. As of February 2008, quetiapine XR was approved for the treatment of schizophrenia in 17 countries including the USA and the Netherlands.

Quetiapine XR given once daily has been compared with placebo in three Phase III, randomised, double-blind studies (Studies 132, 133 and 41), in each of which quetiapine IR was included as a reference treatment. To date, two of these studies have been published, the results from Study 132 show that quetiapine XR 400, 600 and 800 mg/day are effective for the management of acute schizophrenia, with therapeutically effective doses attained as early as the second day of treatment (Kahn *et al.*, 2007) and results from Study 41, show that quetiapine XR 600 mg/day is significantly efficacious compared with placebo in the acute treatment of hospitalised patients with schizophrenia (Lindenmayer *et al.*, 2008). A long-term, placebo-controlled study has shown that quetiapine XR (400–800 mg/day) significantly reduces the risk of schizophrenia relapse (Peuskens *et al.*, 2007). In addition, two studies have further reported that efficacy is maintained without compromising tolerability when switching patients with schizophrenia from quetiapine IR or other antipsychotic treatment to quetiapine XR (Ganesan *et al.*, 2008, Möller *et al.*, 2008).

Due to the potentially severe impact that episodes of schizophrenia can have on patients, any advantages in terms of convenience must not be achieved at the expense of reduced safety and tolerability, which could lead to nonadherence. As there were no major differences in study design and patient inclusion criteria that might affect the safety profile of quetiapine XR in these three Phase III trials, data from these studies were pooled to allow a more comprehensive evaluation of the safety and tolerability of the new formulation. Here we report our analysis of these pooled tolerability data for quetiapine XR (compared with placebo and quetiapine IR) in patients experiencing acute exacerbations of schizophrenia.

MATERIALS AND METHODS

Study designs

The three studies (Studies 132, 133 and 41) included in this pooled analysis were multicentre, randomised, double-blind, double-dummy, placebo-controlled studies lasting 6 weeks. Study 132 was conducted in Eastern Europe, Asia, India and South Africa (39 centres), Study 133 in the United States (40 centres) and Study 41 in the United States (45 centres) and Canada (4 centres). The studies were performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference on Harmonisation/Good Clinical Practice. All patients (or their legal representatives) were required to provide written, informed consent before initiation of any study procedures.

Patients

The studies included male and female patients, aged 18–65 years, with a DSM-IV diagnosis of acute schizophrenia (catatonic (295.20), disorganised (295.10), paranoid (295.30) or undifferentiated (295.90)) (American Psychiatric Association, 1996), determined during a clinical interview with the patient. In Studies 132 and 133, patients could be inpatients or outpatients, while in Study 41 patients were required to be hospitalised for at least the first 10 days of the study. Key inclusion criteria included a Positive and Negative Syndrome Scale (PANSS) (Kay *et al.*, 1987) total score $\geq$70 (Studies 132 and 133) or $\geq$60 (Study 41); Clinical Global Impressions Severity of illness (CGI-S) score $\geq$4 (moderately to severely ill) and, in the opinion of the investigator, a worsening of the patient's condition in the previous 3 weeks; and a PANSS score $\geq$4 for at least one of the following items: delusions, conceptual disorganisation, hallucinatory behaviour or suspiciousness/persecution.

Key exclusion criteria included any DSM-IV Axis I condition other than schizophrenia; substance abuse or dependence; hospitalisation for the treatment of schizophrenia for more than a month immediately before the start of the study; evidence of other clinically relevant conditions (e.g. renal or hepatic impairment, significant coronary artery disease); known lack of response to two or more antipsychotics. In Studies 132 and 133, patients were excluded if they had unstable or untreated diabetes mellitus. In Study 41, patients were excluded if they had persistent tachycardia.

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Treatment

Studies 132 and 133 had five treatment groups: quetiapine XR 400, 600 or 800 mg/day (both studies); quetiapine IR 400 mg/day (Study 132 only) or 800 mg/day (Study 133 only) or placebo (both studies). In Study 41, patients were randomised to one of six treatment groups: quetiapine XR 300, 600 or 800 mg/day; quetiapine IR 300 or 600 mg/day (in two divided doses) or placebo.

In Studies 132 and 133, target doses were reached by day 2 in the quetiapine XR 400 and 600 mg/day groups, by day 3 in the quetiapine XR 800 mg/day group and by day 5 and day 7 in the quetiapine IR 400 and 800 mg/day groups, respectively (Figure 1). In Study 41, target doses of quetiapine XR 300, 600 and 800 mg were reached by Days 1, 5 and 8, respectively, while target doses of quetiapine IR 300 and 600 mg were reached by days 4 and 6, respectively.

Quetiapine IR was given twice daily, with or without food, in the morning and evening. In Studies 132 and 133, the active dose of quetiapine XR was given in the evening with or without food, with placebo (dummy) in the morning. In Study 41, the active dose of quetiapine XR was given in the morning with food or without, with placebo (dummy) in the evening.

Patients' exposure to study medication was assessed using tablet counts, based on the difference between the number of dispensed and returned tablets. Patients were considered to have received the intended exposure if they took $\geq$70% and $\leq$120% of their prescribed doses.

Previous antipsychotic medications, as well as mood stabilisers, hypnotics, antidepressants, anxiolytics and anticholinergic medication, were discontinued at least 48 h before randomisation, and patients who had received a depot antipsychotic within one dosing interval before the start of the study were excluded. Lorazepam (up to 6 mg/day) or oxazepam (up to 60 mg/day) could be used to treat agitation during the first 6 days of the study. No other psychoactive medication was permitted during the study. Use of fluoxetine was prohibited from 14 days before randomisation until the end of the study. During the study, anticholinergic medication could only be used to treat emergent EPS.

Assessments

Tolerability measures were assessed at every visit and included reported AEs, electrocardiogram (ECG), vital signs, body weight, Barnes Akathisia Rating Scale (BARS) scores, Simpson-Angus Scale (SAS) scores and use of anticholinergic medication. In addition to individual MedDRA terms, certain AEs of interest were evaluated in more detail by clustering together appropriate MedDRA terms. These included AEs related to the following: somnolence (somnolence, sedation, lethargy and sluggishness); EPS (including,

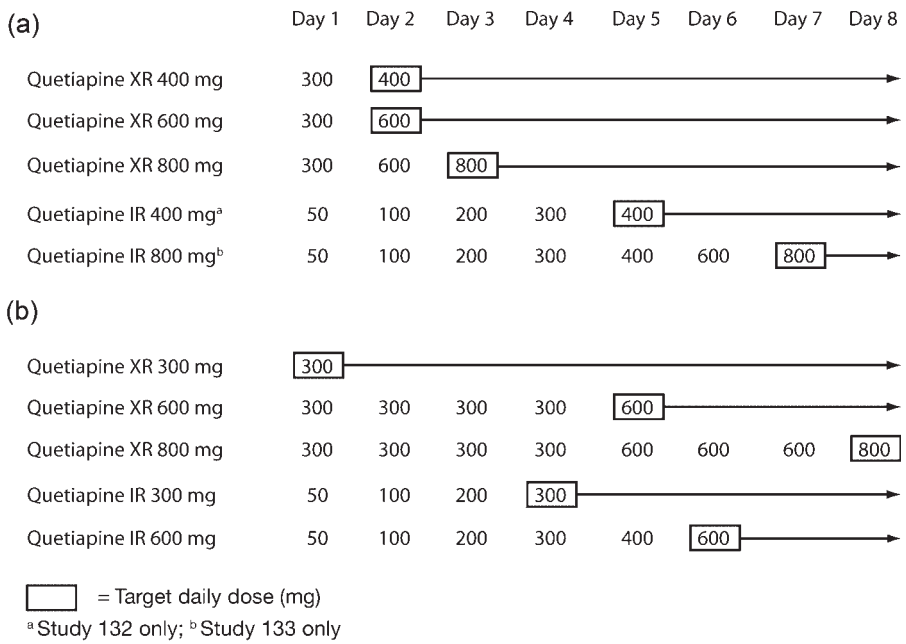

Figure 1. Dose titration regimens for (a) Studies 132, 133 and (b) Study 41. Quetiapine XR was given once daily in the evening and placebo once daily in the morning; quetiapine IR was given twice daily, morning and evening

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but not limited to, akathisia, dyskinesia, dystonia, extrapyramidal syndrome, muscle rigidity, parkinsonism, restlessness, tremor, cogwheel rigidity, hypertonia and hypokinesia); tachycardia (tachycardia and sinus tachycardia); postural hypotension (orthostatic hypotension, postural dizziness and postural orthostatic tachycardia syndrome) and QT prolongation (long QT syndrome, ECG QT corrected interval prolonged, ECG QT prolonged, long QT syndrome congenital, torsades de pointes, cardiac arrest, cardio-respiratory arrest, cardiac death, electromechanical dissociation, sinus arrest). The severity of AEs was rated by the investigator as mild (awareness of sign or symptom, but easily tolerated), moderate (discomfort sufficient to cause interference with normal activities) or severe (incapacitating with an inability to perform normal activities).

Any serious AEs occurring during any phase of the studies (run-in, treatment, washout, follow-up), were recorded. A serious AE was defined as an event that fulfilled one or more of the following criteria: resulted in death, was immediately life threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability or incapacity, was a congenital abnormality or birth defect, was an important medical event that could jeopardise the patient or require medical intervention to prevent one of the outcomes listed above.

Vital signs (pulse and diastolic and systolic blood pressure) were measured at every study visit. Laboratory measures (clinical chemistry, haematology and urinalysis) were assessed at baseline and at study completion or discontinuation. Clinical chemistry measurements included glucose and lipids (all studies), and insulin and HbA_{1C} (Studies 132 and 133 only). These parameters were measured under assumed fasting conditions (from midnight until the time of sampling the following morning), although a subgroup of patients was documented to have been fasting for at least 8 h (referred to as documented fasting patients).

Results are presented with descriptive statistics—medians (in which case no statistic of dispersion is presented) or means ± standard deviation. The safety population included all randomised patients who had taken at least one dose of study medication.

RESULTS

Patients

In total, 1685 patients were randomised to treatment in Studies 132, 133 and 41. Of these, one patient who did not receive investigational product was excluded, leaving 1684 patients who were included in the safety population (placebo, $n = 319$; quetiapine XR, $n = 951$; quetiapine IR, $n = 414$). Baseline demographic and clinical characteristics in each of the treatment groups were similar with the exception of race and weight (Table 1). PANSS total scores were lower in the quetiapine IR 300 and 600 mg/day groups, reflecting the slightly different inclusion criteria in Study 41.

The mean duration of exposure to drug was similar across groups: 30.6 days for placebo, 31.8 days for quetiapine XR and 29.4 days for quetiapine IR. Adherence in patients treated with quetiapine XR and quetiapine IR was comparable across doses. The majority of patients in each treatment group were fully adherent, taking between 70 and 120% of the prescribed doses (96.7, 92.1, 94.8 and 95.4% for quetiapine XR at doses of 300, 400, 600 and 800 mg, respectively, and 94.4, 96.7, 95.3 and 90.4% for quetiapine IR at doses of 300, 400, 600 and 800 mg, respectively); however, it must be noted that these figures are based on tablet counts and do not take account of patients intentionally discarding or not returning tablets in order to increase the numbers of used tablets.

After Day 6, the proportion of patients receiving lorazepam was 7.0% for placebo, 5.9% for quetiapine XR and 5.0% for quetiapine IR. The percentage of patients taking at least one dose of sleep medication during the study was higher in the placebo group than in the quetiapine groups: 44.8% for placebo versus 34.4 and 35.0% for quetiapine XR and IR, respectively.

Tolerability

Adverse events. The overall incidence of AEs was slightly higher for patients randomised to quetiapine XR (69.5%) compared with placebo (61.4%), but was comparable with that for quetiapine IR (72.5%) (Table 2). Most AEs were mild to moderate in severity, and there was no evidence of a dose effect with quetiapine. The incidence of serious AEs was low for the quetiapine XR group (4.4%) and similar to the incidence for those randomised to placebo (4.4%) and quetiapine IR (3.9%) (Table 2). One death from unknown causes was reported in Study 132 in a patient treated with quetiapine IR 400 mg/day. The investigator did not consider the death to be related to treatment. The incidence of AEs that were considered by the investigator to be related to study medication was 43.3% for quetiapine XR, compared with 45.9% for quetiapine IR and 30.7% for placebo. The

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Table 1. Baseline demography and disease characteristics of patients in Studies 132, 133 and 41. Results are presented as mean (SD) unless otherwise stated

		Quetiapine XR					Quetiapine IR			
Characteristic	Placebo $n=319$	300 mg $n=91$	400 mg $n=227$	600 mg $n=310$	800 mg $n=323$	Total $n=951$	300 mg $n=90$	400 mg $n=123$	600 mg $n=86$	800 mg $n=115$	Total $n=414$
Male, *n* (%)	216 (67.7)	67 (73.6)	159 (70.0)	213 (68.7)	231 (71.5)	670 (70.5)	68 (75.6)	73 (59.3)	63 (73.3)	74 (64.3)	278 (67.1)
Age, years	38.1 (11.7)	38.9 (11.0)	38.1 (10.6)	38.0 (10.4)	37.5 (10.2)	38.0 (10.4)	39.2 (10.7)	34.4 (10.1)	40.4 (9.5)	40.6 (10.5)	38.4 (10.5)
Weight, kg	78.6 (22.8)	82.7 (20.0)	78.7 (24.6)	80.6 (25.1)	81.2 (24.0)	80.6 (24.2)	86.7 (20.3)	66.1 (18.4)	87.0 (20.3)	89.4 (21.3)	81.4 (22.4)
PANSS score	93.0 (13.8)	92.4 (19.5)	93.6 (14.0)	94.3 (15.0)	93.5 (14.7)	93.7 (15.1)	89.7 (15.5)	96.4 (16.0)	89.5 (17.7)	93.0 (13.5)	92.5 (15.9)
CGI-S score	4.7 (0.7)	4.8 (0.7)	4.7 (0.7)	4.7 (0.7)	4.8 (0.7)	4.7 (0.7)	4.8 (0.7)	4.9 (0.6)	4.8 (0.7)	4.5 (0.6)	4.8 (0.7)
Race/ethnicity, *n* (%)											
White	145 (45.5)	47 (51.6)	103 (45.4)	148 (47.7)	164 (50.8)	462 (48.6)	43 (47.8)	73 (59.3)	38 (44.2)	31 (27.0)	185 (44.7)
Black	101 (31.7)	33 (36.3)	72 (31.7)	104 (33.5)	98 (30.3)	307 (32.3)	35 (38.9)	7 (5.7)	32 (37.2)	71 (61.7)	145 (35.0)
Asian	46 (14.4)	3 (3.3)	44 (19.4)	44 (14.2)	43 (13.3)	134 (14.1)	1 (1.1)	43 (35.0)	2 (2.3)	2 (1.7)	48 (11.6)
Hispanic	11 (3.4)	7 (7.7)	0	8 (2.6)	9 (2.8)	24 (2.5)	11 (12.2)	0	13 (15.1)	0	24 (5.8)
Other	16 (5.0)	1 (1.1)	8 (3.5)	6 (1.9)	9 (2.8)	24 (2.5)	0	0	1 (1.2)	11 (9.6)	12 (2.9)
DSM-IV schizophrenia subtype, *n* (%)											
Disorganised	8 (2.5)	3 (3.3)	10 (4.4)	8 (2.6)	9 (2.8)	30 (3.2)	3 (3.3)	2 (1.6)	0 (0.0)	8 (7.0)	13 (3.1)
Catatonic	1 (0.3)	0 (0.0)	2 (0.9)	2 (0.6)	0 (0.0)	4 (0.4)	1 (1.1)	1 (0.8)	0 (0.0)	0 (0.0)	2 (0.5)
Paranoid	241 (75.5)	81 (89.0)	165 (72.7)	232 (74.8)	241 (74.6)	719 (75.6)	73 (81.1)	91 (74.0)	69 (80.2)	96 (83.5)	329 (79.5)
Undifferentiated	69 (21.6)	7 (7.7)	50 (22.0)	68 (21.9)	73 (22.6)	198 (20.8)	13 (14.4)	29 (23.6)	17 (19.8)	11 (9.6)	70 (16.9)

CGI-S, Clinical Global Impressions Severity of Illness scale; IR, immediate release; PANSS, Positive and Negative Syndrome Scale; XR, extended release.

incidences of AEs leading to discontinuation in the quetiapine groups were similar to placebo (7.5% placebo, 6.4% quetiapine XR, 7.7% quetiapine IR).

The most common AEs are shown in Table 2. For patients randomised to quetiapine XR the most common AEs were sedation (12.7%), dry mouth (12.1%) and somnolence (12.1%) (Table 2), findings consistent with quetiapine IR (15.7, 9.2 and 13.3%, respectively). The incidence of somnolence-related AEs (somnolence, sedation, lethargy and sluggishness) ranged from 22.5 to 28.6% in patients treated with quetiapine XR, compared with 10.3% in the placebo group and from 8.1 to 43.0% in the quetiapine IR group (Table 3). Somnolence-related AEs were mild to moderate in all patients in the placebo group and in >96% of patients in both quetiapine XR and quetiapine IR groups. The median time to onset was similar in all treatment groups; 4.0 days for placebo, 3.0 days for quetiapine XR and 2.0 days for quetiapine IR; and the mean (SD) duration of somnolence which started during treatment was 9.8 (11.6) days, 18.1 (15.1) days and 17.2 (15.6) days, respectively.

The overall incidence of tachycardia was 2.9% for quetiapine XR, compared with 6.5% for quetiapine IR and 1.3% for placebo (Table 3). The median time to first onset of tachycardia was 4.5 days for quetiapine XR, 5.0 days for quetiapine IR and 11.5 days for placebo.

The incidence of syncope was very low and comparable between the quetiapine XR and quetiapine IR formulations: one report in patients randomised to placebo (after 28 days of treatment); three reports in patients randomised to take quetiapine XR (one on day 2 and one on day 13 in the 600 mg/day group; one on day 7 in the 800 mg/day group); and one report in patients treated with quetiapine IR 800 mg (on Day 5).

Postural hypotension was reported in 8.5% of patients randomised to quetiapine XR compared with 10.1% of those patients randomised to quetiapine IR, and 5.6% in those randomised to placebo (Table 3). The median time to first onset of postural hypotension was 2.0 days for quetiapine XR, 5.0 days for quetiapine IR and 2.0 days for placebo.

No AEs associated with QT prolongation were reported in these studies, and no evidence of increases in mean Fridericia corrected QTc was observed in any treatment groups. The percentage of patients with shifts to a QTc ≥450 ms was 0.8% for placebo, 0.6% for quetiapine XR and 0.6% for quetiapine IR. Small dose-related increases in mean heart rate were observed in the quetiapine-treated groups at the end of treatment.

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Table 2. Overall adverse event (AE) profile. Values presented are *n* (%)

		Quetiapine XR					Quetiapine IR				
	Placebo $n=319$	300 mg $n=91$	400 mg $n=227$	600 mg $n=310$	800 mg $n=323$	Total $n=951$	300 mg $n=90$	400 mg $n=123$	600 mg $n=86$	800 mg $n=115$	Total $n=414$
AEsa	196 (61.4)	78 (85.7)	141 (62.1)	228 (73.5)	214 (66.3)	661 (69.5)	75 (83.3)	66 (53.7)	73 (84.9)	86 (74.8)	300 (72.5)
Serious AEs[a]	14 (4.4)	2 (2.2)	12 (5.3)	17 (5.5)	11 (3.4)	42 (4.4)	1 (1.1)	6 (4.9)	2 (2.3)	7 (6.1)	16 (3.9)
Drug-related AEsa[b]	98 (30.7)	53 (58.2)	87 (38.3)	145 (46.8)	127 (39.3)	412 (43.3)	47 (52.2)	27 (22.0)	54 (62.8)	62 (53.9)	190 (45.9)
AEs leading to discontinuation[c]	24 (7.5)	5 (5.5)	17 (7.5)	23 (7.4)	16 (5.0)	61 (6.4)	6 (6.7)	6 (4.9)	7 (8.1)	13 (11.3)	32 (7.7)
Common AEs[d] (MedDRA preferred term[a])											
Sedation	21 (6.6)	14 (15.4)	24 (10.6)	42 (13.5)	41 (12.7)	121 (12.7)	17 (18.9)	1 (0.8)	22 (25.6)	25 (21.7)	65 (15.7)
Dry mouth	4 (1.3)	12 (13.2)	26 (11.5)	39 (12.6)	38 (11.8)	115 (12.1)	8 (8.9)	2 (1.6)	9 (10.5)	19 (16.5)	38 (9.2)
Somnolence	12 (3.8)	11 (12.1)	27 (11.9)	36 (11.6)	41 (12.7)	115 (12.1)	18 (20.0)	9 (7.3)	11 (12.8)	17 (14.8)	55 (13.3)
Dizziness	12 (3.8)	9 (9.9)	20 (8.8)	37 (11.9)	27 (8.4)	93 (9.8)	9 (10.0)	7 (5.7)	10 (11.6)	11 (9.6)	37 (8.9)
Headache	47 (14.7)	15 (16.5)	18 (7.9)	29 (9.4)	30 (9.3)	92 (9.7)	17 (18.9)	2 (1.6)	13 (15.1)	10 (8.7)	42 (10.1)
Insomnia	46 (14.4)	6 (6.6)	22 (9.7)	22 (7.1)	21 (6.5)	71 (7.5)	8 (8.9)	13 (10.6)	6 (7.0)	1 (0.9)	28 (6.8)
Orthostatic hypotension	15 (4.7)	21 (23.1)	1 (0.4)	21 (6.8)	27 (8.4)	70 (7.4)	16 (17.8)	2 (1.6)	19 (22.1)	2 (1.7)	39 (9.4)
Constipation	15 (4.7)	10 (11.0)	11 (4.8)	19 (6.1)	21 (6.5)	61 (6.4)	3 (3.3)	1 (0.8)	12 (14.0)	9 (7.8)	25 (6.0)
Nausea	22 (6.9)	5 (5.5)	9 (4.0)	22 (7.1)	16 (5.0)	52 (5.5)	4 (4.4)	2 (1.6)	8 (9.3)	5 (4.3)	19 (4.6)
Dyspepsia	7 (2.2)	5 (5.5)	11 (4.8)	15 (4.8)	13 (4.0)	44 (4.6)	2 (2.2)	0	8 (9.3)	10 (8.7)	20 (4.8)
Agitation	16 (5.0)	5 (5.5)	9 (4.0)	14 (4.5)	7 (2.2)	35 (3.7)	2 (2.2)	5 (4.1)	3 (3.5)	4 (3.5)	14 (3.4)
Heart rate increased	4 (1.3)	6 (6.6)	1 (0.4)	14 (4.5)	13 (4.0)	34 (3.6)	5 (5.6)	0	10 (11.6)	1 (0.9)	16 (3.9)
Vomiting	13 (4.1)	2 (2.2)	4 (1.8)	16 (5.2)	10 (3.1)	32 (3.4)	3 (3.3)	0	1 (1.2)	3 (2.6)	7 (1.7)
Fatigue	6 (1.9)	7 (7.7)	5 (2.2)	10 (3.2)	6 (1.9)	28 (2.9)	3 (3.3)	2 (1.6)	5 (5.8)	6 (5.2)	16 (3.9)
Tachycardia	3 (0.9)	7 (7.7)	3 (1.3)	9 (2.9)	8 (2.5)	27 (2.8)	10 (11.1)	3 (2.4)	13 (15.1)	0	26 (6.3)
Hypotension	3 (0.9)	9 (9.9)	3 (1.3)	7 (2.3)	7 (2.2)	26 (2.7)	6 (6.7)	2 (1.6)	9 (10.5)	0	17 (4.1)
Weight increased	5 (1.6)	4 (4.4)	1 (0.4)	8 (2.6)	10 (3.1)	23 (2.4)	8 (8.9)	1 (0.8)	8 (9.3)	3 (2.6)	20 (4.8)
Diarrhoea	10 (3.1)	0	3 (1.3)	2 (0.6)	11 (3.4)	16 (1.7)	2 (2.2)	1 (0.8)	2 (2.3)	7 (6.1)	12 (2.9)
Blood pressure diastolic decreased	2 (0.6)	7 (7.7)	0	2 (0.6)	4 (1.2)	13 (1.4)	3 (3.3)	0	7 (8.1)	0	10 (2.4)
Stomach discomfort	5 (1.6)	2 (2.2)	2 (0.9)	4 (1.3)	5 (1.5)	13 (1.4)	4 (4.4)	0	1 (1.2)	6 (5.2)	11 (2.7)
Blood pressure systolic decreased	3 (0.9)	4 (4.4)	0	1 (0.3)	5 (1.5)	10 (1.1)	3 (3.3)	0	5 (5.8)	0	8 (1.9)
Lethargy	0	1 (1.1)	0	2 (0.6)	3 (0.9)	6 (0.6)	1 (1.1)	0	5 (5.8)	0	6 (1.4)

[a]Patients with more than one event in the same category are counted only once in that category.
[b]As judged by the investigator.
[c]In addition, one patient in the placebo group was discontinued in the randomisation period owing to an AE that started before the day of the first dose of study medication.
[d]Common AEs were defined as AEs occurring in any quetiapine treatment group at an incidence of $\geq$5%.

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Table 3. Adverse events (AEs) related to somnolence, tachycardia, postural hypotension and EPS. Values presented are *n* (%)

	Patients reporting AEs *n* (%)										
		Quetiapine XR					Quetiapine IR				
MedDRA preferred term[a]	Placebo *n* = 319	300 mg *n* = 91	400 mg *n* = 227	600 mg *n* = 310	800 mg *n* = 323	Total *n* = 951	300 mg *n* = 90	400 mg *n* = 123	600 mg *n* = 86	800 mg *n* = 115	Total *n* = 414
Any somnolence-related AE[b]	33 (10.3)	26 (28.6)	51 (22.5)	78 (25.2)	83 (25.7)	238 (25.0)	35 (38.9)	10 (8.1)	37 (43.0)	40 (34.8)	122 (29.5)
Sedation	21 (6.6)	14 (15.4)	24 (10.6)	42 (13.5)	41 (12.7)	121 (12.7)	17 (18.9)	1 (0.8)	22 (25.6)	25 (21.7)	65 (15.7)
Somnolence	12 (3.8)	11 (12.1)	27 (11.9)	36 (11.6)	41 (12.7)	115 (12.1)	18 (20.0)	9 (7.3)	11 (12.8)	17 (14.8)	55 (13.3)
Lethargy	0	1 (1.1)	0	2 (0.6)	3 (0.9)	6 (0.6)	1 (1.1)	0	5 (5.8)	0	6 (1.4)
Sluggishness	0	0	0	0	1 (0.3)	1 (0.1)	0	0	2 (2.3)	0	2 (0.5)
Any tachycardia-related AE[b]	4 (1.3)	7 (7.7)	3 (1.3)	10 (3.2)	8 (2.5)	28 (2.9)	10 (11.1)	4 (3.3)	13 (15.1)	0	27 (6.5)
Tachycardia	3 (0.9)	7 (7.7)	3 (1.3)	9 (2.9)	8 (2.5)	27 (2.8)	10 (11.1)	3 (2.4)	13 (15.1)	0	26 (6.3)
Sinus tachycardia	1 (0.3)	0	0	1 (0.3)	0	1 (0.1)	0	1 (0.8)	0	0	1 (0.2)
Any postural hypotension-related AE[b]	18 (5.6)	22 (24.2)	3 (1.3)	27 (8.7)	29 (9.0)	81 (8.5)	17 (18.9)	2 (1.6)	21 (24.4)	2 (1.7)	42 (10.1)
Orthostatic hypotension	15 (4.7)	21 (23.1)	1 (0.4)	21 (6.8)	27 (8.4)	70 (7.4)	16 (17.8)	2 (1.6)	19 (22.1)	2 (1.7)	39 (9.4)
Dizziness (postural)	2 (0.6)	3 (3.3)	1 (0.4)	5 (1.6)	4 (1.2)	13 (1.4)	1 (1.1)	1 (0.8)	4 (4.7)	0	6 (1.4)
Postural orthostatic tachycardia syndrome	2 (0.6)	1 (1.1)	1 (0.4)	3 (1.0)	0	5 (0.5)	0	0	1 (1.2)	0	1 (0.2)
Any EPS-related AE[b]	15 (4.7)	9 (9.9)	10 (4.4)	25 (8.1)	27 (8.4)	71 (7.5)	8 (8.9)	6 (4.9)	9 (10.5)	9 (7.8)	32 (7.7)
Tremor	3 (0.9)	1 (1.1)	3 (1.3)	9 (2.9)	6 (1.9)	19 (2.0)	1 (1.1)	2 (1.6)	4 (4.7)	4 (3.5)	11 (2.7)
Akathisia	4 (1.3)	0	3 (1.3)	7 (2.3)	7 (2.2)	17 (1.8)	3 (3.3)	2 (1.6)	4 (4.7)	1 (0.9)	10 (2.4)
Restlessness	2 (0.6)	2 (2.2)	2 (0.9)	2 (0.6)	9 (2.8)	15 (1.6)	0	0	0	1 (0.9)	1 (0.2)
Extrapyramidal disorder	5 (1.6)	1 (1.1)	2 (0.9)	4 (1.3)	4 (1.2)	11 (1.2)	0	1 (0.8)	0	3 (2.6)	4 (1.0)
Dystonia	0	2 (2.2)	0	2 (0.6)	1 (0.3)	5 (0.5)	2 (2.2)	0	0	0	2 (0.5)
Drooling	0	0	0	1 (0.3)	2 (0.6)	3 (0.3)	0	0	0	0	0
Dyskinesia	1 (0.3)	1 (1.1)	1 (0.4)	1 (0.3)	0	3 (0.3)	2 (2.2)	0	2 (2.3)	0	4 (1.0)
Muscle rigidity	0	0	0	2 (0.6)	0	2 (0.2)	0	0	0	0	0
Tardive dyskinesia	1 (0.3)	1 (1.1)	0	0	1 (0.3)	2 (0.2)	0	1 (0.8)	1 (1.2)	0	2 (0.5)
Cogwheel rigidity	1 (0.3)	0	0	1 (0.3)	0	1 (0.1)	0	0	0	1 (0.9)	1 (0.2)
Hypertonia	0	1 (1.1)	0	0	0	1 (0.1)	0	0	0	0	0
Movement disorder	0	0	0	1 (0.3)	0	1 (0.1)	0	0	0	0	0
Parkinsonism	0	0	0	0	1 (0.3)	1 (0.1)	0	0	1 (1.2)	0	1 (0.2)
Oculogyration	0	0	0	0	0	0	0	1 (0.8)	0	0	1 (0.2)
Parkinsonian gait	1 (0.3)	0	0	0	0	0	0	0	0	0	0
Psychomotor hyperactivity	0	0	0	0	0	0	0	1 (0.8)	0	0	1 (0.2)

[a]Patients with more than one AE falling under the same term are counted only once in that term.
[b]Patients with more than one AE are counted only once.

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One AE of neutropenia was reported for quetiapine XR 800 mg/day.

Extrapyramidal symptoms. The incidences of AEs potentially related to EPS were 7.5% for quetiapine XR, 7.7% for quetiapine IR and 4.7% for placebo. No individual AE potentially related to EPS exceeded 3% in any treatment group (Table 3). All but one of the AEs potentially related to EPS were mild or moderate in severity (one case of psychomotor hyperactivity in a patient receiving quetiapine IR 400 mg was rated as severe), and there was no discernable relationship between severity and dose. The incidence of akathisia was 1.8% for quetiapine XR, which was similar to that for placebo (1.3%). Akathisia was reported more often with quetiapine IR, but the incidence was still generally low (2.4% overall; 3.3, 1.6, 4.7 and 0.9% for doses of 300, 400, 600 and 800 mg, respectively).

There was no difference between the treatment groups in mean change from baseline in either SAS total score or BARS Global Assessment score. Mean (SD) changes in SAS scores were −0.90 (3.41), −0.72 (2.22), −0.51 (2.22) and −0.68 (2.35) for quetiapine XR 300, 400, 600 and 800 mg/day; −0.08 (4.09), −1.19 (3.25), −0.53 (2.36) and −0.34 (1.52) for quetiapine IR 300, 400, 600 and 800 mg/day and −0.56 (2.35) for placebo. Mean (SD) changes in BARS scores were −0.18 (0.82), −0.13 (0.60), −0.10 (0.63) and −0.11 (0.65) for quetiapine XR 300, 400, 600 and 800 mg/day; −0.20 (0.80), −0.10 (0.62), −0.22 (0.95) and −0.06 (0.81) for quetiapine IR 300, 400, 600 and 800 mg/day and −0.12 (0.70) for placebo. In all treatment groups, the majority of the patients had no change in SAS total score and BARS Global Assessment score, and the proportion of patients improving was greater than the proportion of patients worsening.

Anticholinergic medication to control EPS was used infrequently during the studies. The percentage of patients who used anticholinergic medication at some point during a study was 4.3% for quetiapine XR (7.7, 4.0, 4.5 and 3.4% for doses of 300, 400, 600 and 800 mg, respectively), 4.8% for quetiapine IR (6.7, 4.1, 3.5 and 5.2 for doses of 300, 400, 600 and 800, respectively) and 6.3% for placebo. The use of anticholinergic medication was not dose related and decreased in all treatment groups during the course of the study.

Laboratory data and vital signs. The mean change from baseline in serum prolactin levels was comparable between treatment groups: −12.96 ng/ml quetiapine XR, −13.33 ng/ml quetiapine IR and −13.69 ng/ml placebo. The incidence of AEs potentially associated with prolactin in the quetiapine XR or quetiapine IR groups was low and comparable with placebo. There were two reports of erectile dysfunction and one report of delayed ejaculation in the quetiapine XR group, one report of decreased libido in the quetiapine IR group and one report of sexual dysfunction in both the placebo and quetiapine IR groups (all male patients).

Changes in plasma glucose and HbA_{1C} for those who completed the study and insulin concentrations in patients who were documented to have been fasting for at least 8 h at the time of the blood test and who had completed the 6-week treatment period are shown in Table 4. There was a high degree of inter-individual variability in these parameters, but overall there was a small increase in the quetiapine groups relative to placebo. Results were similar for the quetiapine XR and IR groups, and there was no dose–response relationship. The percentage of patients who experienced a clinically important shift in fasting plasma glucose level ($\geq$6.99 mmol/L) at any time was similar for the quetiapine XR (8.7%, $n = 67$) and quetiapine IR (6.7%, $n = 22$) groups.

Mean body weight changes from baseline to end of study in patients who completed the studies are presented in Table 4. The percentages of patients with weight increases $\geq$7% who completed the studies were higher for the quetiapine XR (13.7%) and quetiapine IR (19.5%) groups than for placebo (6.7%).

No clinically relevant changes in mean total plasma cholesterol, HDL or LDL were reported for quetiapine in patients who completed the studies. Mean changes (SD) in plasma triglyceride concentrations were −0.11 (0.89) mmol/L for placebo, 0.17 (1.07) mmol/L for quetiapine XR and 0.38 (1.06) mmol/L for quetiapine IR. The increase in triglycerides did not show a dose–response relationship for either of the quetiapine formulations (Table 4). Furthermore, the percentage of patients who experienced a clinically important shift in fasting triglycerides ($\geq$2.26 mmol/L) at any time was comparable for the quetiapine XR (17.9%, $n = 118$) and quetiapine IR (15.6%, $n = 43$) groups. Changes in orthostatic pulse rate and blood pressure are reported in Table 4.

Tolerability during the first week of treatment

The tolerability of quetiapine XR during the rapid dose-titration period (first week of treatment) was assessed by pooling the findings Studies 132 and 133. Results from Study 41 were presented separately in this

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Table 4. Changes from baseline in glucose, haemoglobin A_{1C} (HbA_{1C}), insulin, body weight, lipids and vital signs in patients completing the studies. Documented fasting for insulin only; completer data for glucose, HbA_{1C}, weight and lipids. Mean changes from baseline (SD)

		Quetiapine XR					Quetiapine IR				
	Placebo $n=319$	300 mg $n=91$	400 mg $n=227$	600 mg $n=310$	800 mg $n=323$	Total $n=951$	300 mg $n=90$	400 mg $n=123$	600 mg $n=86$	800 mg $n=115$	Total $n=414$
Glucose (mmol/L)											
n[a]	156	34	141	178	185	538	38	86	32	57	213
Change	−0.01 (1.16)	0.01 (1.26)	0.18 (0.96)	0.20 (1.13)	0.01 (1.15)	0.12 (1.10)	0.08 (1.47)	−0.02 (0.85)	0.59 (1.33)	0.65 (2.03)	0.27 (1.45)
HbA_{1C} (%)[b]											
n[a]	136	–	143	143	146	432	–	89	–	56	145
Change	−0.02 (0.31)	–	0.04 (0.30)	0.03 (0.31)	0.06 (0.30)	0.05 (0.31)	–	−0.02 (0.26)	–	0.10 (0.48)	0.03 (0.37)
Insulin (μIU/mL)[b]											
n[a]	173	–	183	170	182	535	–	108	–	74	182
Change	−0.04 (15.43)	–	6.08 (24.06)	1.98 (28.77)	3.80 (30.89)	4.00 (28.03)	–	3.37 (22.76)	–	4.15 (15.45)	3.69 (20.07)
Body weight (kg)											
n[a]	163	34	144	184	193	555	39	87	31	58	215
Change	0.26 (3.65)	2.37 (3.77)	1.36 (2.82)	1.93 (4.06)	1.43 (4.65)	1.63 (3.99)	1.90 (3.76)	1.78 (2.59)	3.69 (4.46)	2.19 (4.46)	2.19 (3.70)
Total cholesterol (mmol/L)											
n[a]	160	34	145	179	187	545	38	89	32	56	215
Change	−0.12 (0.76)	0.20 (0.94)	0.15 (0.75)	0.10 (0.88)	0.12 (0.82)	0.13 (0.83)	0.20 (0.86)	0.39 (0.83)	0.22 (0.73)	0.20 (0.78)	0.28 (0.81)
LDL-cholesterol (mmol/L)											
n[a]	156	33	138	171	178	520	35	87	30	52	204
Change[b]	−0.06 (0.64)	0.14 (0.62)	0.02 (0.63)	0.08 (0.73)	0.05 (0.72)	0.06 (0.69)	0.07 (0.66)	0.25 (0.65)	0.07 (0.67)	0.09 (0.66)	0.15 (0.66)
HDL-cholesterol (mmol/L)											
n[a]	160	34	145	179	187	545	38	89	32	56	215
Change[b]	−0.02 (0.24)	−0.01 (0.26)	−0.01 (0.23)	−0.02 (0.25)	0.00 (0.25)	−0.01 (0.24)	−0.01 (0.37)	0.00 (0.29)	0.05 (0.30)	0.00 (0.27)	0.00 (0.30)
Triglycerides (mmol/L)											
n[a]	160	34	145	179	187	545	38	89	32	56	215
Change[b]	−0.11 (0.89)	−0.02 (0.70)	0.28 (0.94)	0.14 (1.22)	0.16 (1.05)	0.17 (1.07)	0.53 (1.37)	0.39 (0.89)	0.35 (0.92)	0.27 (1.16)	0.38 (1.06)
Pulse (bpm)											
n[a]	225	NA	221	210	227	658	NA	119	NA	108	227
Change[b]	0.10 (8.78)	NA	0.27 (8.34)	0.42 (9.44)	−0.04 (8.31)	0.21 (8.69)	NA	0.14 (8.14))	NA	0.77 (8.57)	0.44 (8.34)
Systolic blood pressure (mmHg)											
n[a]	226	NA	221	210	227	658	NA	119	NA	107	226
Change[b]	−0.67 (10.98)	NA	−1.42 (11.43)	−1.80 (9.75)	−1.09 (10.82)	−1.43 (10.69)	NA	−0.84 (8.43)	NA	−2.22 (13.32)	−1.50 (11.01)
Diastolic blood pressure (mmHg)											
n[a]	226	NA	221	210	227	658	NA	119	NA	107	226
Change[b]	−0.36 (7.93)	NA	−1.14 (9.16)	−0.20 (8.07)	−1.05 (7.57))	−0.81 (8.29)	NA	−0.92 (8.06)	NA	−1.31 (10.10)	−1.10 (9.07)

[a]Number of patients with non-missing observations.
[b]Data from a pooled analysis of Studies 132 and 133 only.

part of the analysis owing to the different dose titration regimen.

Quetiapine XR was generally well tolerated during the first week of treatment. In Studies 132 and 133, the incidences of AEs during the first week of treatment in patients receiving quetiapine XR (43.0%) were almost identical to the incidences of AEs in patients taking quetiapine IR (42.0%) (Table 5a). The incidence was higher in patients taking quetiapine XR or quetiapine IR than in those taking placebo (31.9%). There were 14 discontinuations due to AEs during the first week of treatment: 2 (0.9%) in the placebo group, 10 (1.5%) for quetiapine XR and 2 (0.8%) for quetiapine IR. Similar results were shown for Study 41 (Table 5b).

For patients taking quetiapine XR, quetiapine IR or placebo, the most commonly reported AEs during the first week of treatment mirrored the overall AE profile in these studies. In Studies 132 and 133, these were somnolence (9.0, 8.8 and 1.3%, respectively), sedation (7.4, 9.2 and 3.4%, respectively), dry mouth (6.8, 6.3 and 0.9%, respectively), dizziness (5.9, 4.2 and 2.6%, respectively), headache (3.4, 2.5 and 6.4%, respectively) and insomnia (2.8, 2.9 and 7.2%, respectively). There were no AEs associated only with quetiapine XR treatment, and there was no apparent dose relationship. For quetiapine XR, there were two reports of syncope (Day 2 in the quetiapine XR 600 mg/day group; day 7 in the quetiapine XR 800 mg/day group) and five reports of tachycardia (three in the quetiapine XR 400 mg/day group, one in the quetiapine XR 600 mg/day group and one in the quetiapine XR 800 mg/day group) during the first week of treatment. The incidence rates for postural hypotension during the first week were similar for placebo, quetiapine XR and quetiapine IR (5.3, 7.8 and 7.5%, respectively).

The most commonly reported AEs reported during the first week of treatment with quetiapine XR, quetiapine IR and placebo in Study 41 are shown in Table 5b. These include orthostatic hypotension (22.4, 15.3 and 16.7%, respectively), sedation (20.6, 19.3 and 11.9%, respectively), somnolence (12.5, 14.8 and 8.3%, respectively), dry mouth (11.4, 6.8 and 0%, respectively) and headache (9.6, 11.9 and 15.5%, respectively). During the first week of treatment dry mouth and constipation were the only AEs reported with quetiapine XR and quetiapine IR which were not recorded in the placebo cohort. Similar to Studies 132 and 133, no obvious dose relationship was observed for quetiapine IR or quetiapine XR therapy in Study 41.

DISCUSSION

Quetiapine XR is a new formulation that allows once daily dosing and has been shown to be effective in the dose range 400–800 mg/day for a broad range of schizophrenia symptoms. The data from Studies 132, 133 and 41 demonstrate that treatment with quetiapine XR once daily for up to 42 days at doses between 400 mg/day and 800 mg/day is generally as well tolerated and with a similar AE profile as equivalent

Table 5a. Adverse events (AEs) occurring during the first week of treatment. Data in this table are pooled from Studies 132 and 133 only; data from Study 41 are excluded because this study used a different dose-titration regimen. Values presented are *n* (%).

	Patients reporting AEs *n* (%)							
		Quetiapine XR				Quetiapine IR		
	Placebo *n* = 235	400 mg *n* = 227	600 mg *n* = 218	800 mg *n* = 234	Total *n* = 679	400 mg *n* = 123	800 mg *n* = 115	Total *n* = 238
AEs[a]	75 (31.9)	96 (42.3)	109 (50.0)	87 (37.2)	292 (43.0)	35 (28.5)	65 (56.5)	100 (42.0)
Serious AEs[a]	1 (0.4)	3 (1.3)	3 (1.4)	2 (0.9)	8 (1.2)	1 (0.8)	2 (1.7)	3 (1.3)
Drug-related AEs[ab]	37 (15.7)	66 (29.1)	67 (30.7)	55 (23.5)	188 (27.7)	18 (14.6)	50 (43.5)	68 (28.6)
Discontinuations due to AEs[c]	2 (0.9)	1 (0.4)	5 (2.3)	4 (1.7)	10 (1.5)	1 (0.8)	1 (0.9)	2 (0.8)
Common AEs[d] (MedDRA preferred term[a])								
Somnolence	3 (1.3)	22 (9.7)	16 (7.3)	23 (9.8)	61 (9.0)	9 (7.3)	12 (10.4)	21 (8.8)
Sedation	8 (3.4)	22 (9.7)	16 (7.3)	12 (5.1)	50 (7.4)	1 (0.8)	21 (18.3)	22 (9.2)
Dry mouth	2 (0.9)	18 (7.9)	14 (6.4)	14 (6.0)	46 (6.8)	2 (1.6)	13 (11.3)	15 (6.3)
Dizziness	6 (2.6)	12 (5.3)	16 (7.3)	12 (5.1)	40 (5.9)	5 (4.1)	5 (4.3)	10 (4.2)
Headache	15 (6.4)	10 (4.4)	4 (1.8)	9 (3.8)	23 (3.4)	0	6 (5.2)	6 (2.5)
Insomnia	17 (7.2)	8 (3.5)	7 (3.2)	4 (1.7)	19 (2.8)	6 (4.9)	1 (0.9)	7 (2.9)

[a]Patients with more than one AE falling under the same term are counted only once in that term.
[b]As judged by the investigator.
[c]Patients withdrawn up to and including Day 7. In addition, one patient in the placebo group was discontinued in the randomisation period due to an adverse event starting before the day of the first dose.
[d]Common AEs associated with study drug were defined as AEs occurring in any quetiapine treatment group at an incidence of ≥5% and observed at a rate of at least twice that of placebo.

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Table 5b. Adverse events (AEs) occurring during the first week of treatment. Data in this table are from Study 41. Values presented are *n* (%).

	Patients reporting AEs *n* (%)							
		Quetiapine XR				Quetiapine IR		
	Placebo *n* = 84	300 mg *n* = 91	600 mg *n* = 92	800 mg *n* = 89	Total *n* = 272	300 mg *n* = 90	600 mg *n* = 86	Total *n* = 176
AEs	57 (67.9)	74 (81.3)	80 (87.0)	68 (76.4)	222 (81.6)	69 (76.7)	69 (80.2)	138 (78.4)
Serious AEs	0	1 (1.1)	1 (1.1)	0	2 (0.7)	2 (0.7)	0	0
Drug-related AEs[a]	37 (44.0)	47 (51.6)	58 (63.0)	46 (51.7)	151 (55.5)	41 (45.6)	48 (55.8)	59 (50.6)
Discontinuations due to AEs	5 (6.0)	3 (3.3)	6 (6.5)	1 (1.1)	10 (3.7)	4 (4.4)	4 (4.7)	8 (4.5)
Common AEs[b] (MedDRA preferred term[c])								
Orthostatic hypotension	14 (16.7)	19 (20.9)	18 (19.6)	24 (27.0)	61 (22.4)	13 (14.4)	14 (16.3)	27 (15.3)
Sedation	10 (11.9)	12 (13.2)	21 (22.8)	23 (25.8)	56 (20.6)	15(16.7)	19 (22.1)	34 (19.3)
Somnolence	7 (8.3)	11 (12.1)	13 (14.1)	10 (11.2)	34 (12.5)	16 (17.8)	10 (11.6)	26 (14.8)
Dry mouth	0	10 (11.0)	10 (10.9)	11 (12.4)	31 (11.4)	6 (6.7)	6 (7.0)	12 (6.8)
Headache	13 (15.5)	10 (11.0)	6 (6.5)	10 (11.2)	26 (9.6)	12 (13.3)	9 (10.5)	21 (11.9)
Dizziness	2 (2.4)	8 (8.8)	11 (12.0)	5 (5.6)	24 (8.8)	8 (8.9)	7 (8.1)	15 (8.5)
Constipation	0	7 (7.7)	6 (6.5)	3 (3.4)	16 (5.9)	3 (3.3)	9 (10.5)	12 (6.8)
Heart rate increased	3 (3.6)	6 (6.6)	10 (10.9)	11 (12.4)	27 (9.9)	4 (4.4)	8 (9.3)	12 (6.8)
Tachycardia	1 (1.2)	6 (6.6)	8 (8.7)	5 (5.6)	19 (7.0)	7 (7.8)	8 (9.3)	15 (8.5)
Hypotension	2 (2.4)	6 (6.6)	5 (5.4)	4 (4.5)	15 (5.5)	6 (6.7)	9 (10.5)	15 (8.5)
Fatigue	5 (6.0)	5 (5.5)	2 (2.2)	2 (2.2)	9 (3.3)	2 (2.2)	4 (4.7)	6 (3.4)
Blood pressure diastolic decreased	2 (2.4)	5 (5.5)	1 (1.1)	3 (3.4)	9 (3.3)	3 (3.3)	7 (8.1)	10 (5.7)
Insomnia	10 (11.9)	4 (4.4)	7 (7.6)	4 (4.5)	15 (5.5)	8 (8.9)	5 (5.8)	13 (7.4)
Agitation	6 (7.1)	4 (4.4)	5 (5.4)	1 (1.1)	10 (3.7)	1 (1.1)	3 (3.5)	4 (2.3)
Dyspepsia	4 (4.8)	3 (3.3)	5 (5.4)	2 (2.2)	10 (3.7)	1 (1.1)	4 (4.7)	5 (2.8)
Nausea	4 (4.8)	2 (2.2)	5 (5.4)	1 (1.1)	8 (2.9)	3 (3.3)	6 (7.0)	9 (5.1)
Blood pressure systolic decreased	2 (2.4)	1 (1.1)	0	2 (2.2)	3 (1.1)	3 (3.3)	5 (5.8)	8 (4.5)

[a]As judged by the investigator.
[b]Common AEs associated with study drug were defined as AEs occurring in any quetiapine treatment group at an incidence of ≥5%.
[c]Patients with more than one AE falling under the same term are counted only once in that term.

total daily doses of quetiapine IR given twice daily. The incidence of AEs in patients taking quetiapine XR was not dose related.

Most AEs reported during quetiapine XR treatment were rated as mild or moderate in intensity. The incidence, type and severity of AEs observed with quetiapine XR were similar to those observed with equivalent doses of quetiapine IR and are well described by the current label for quetiapine IR. Somnolence/sedation, dry mouth, dizziness, headache, insomnia, orthostatic hypotension and constipation were the most commonly reported AEs for quetiapine XR, but these were generally mild to moderate in intensity. Reports of somnolence with quetiapine XR are consistent with the established safety profile of quetiapine IR and studies have shown that somnolence is usually mild and transient, occurring early in treatment (Goldstein *et al.*, 2005). Moreover, here we report no substantial difference in the duration of somnolence experienced by patients treated with quetiapine XR or IR preparations.

The incidence of AEs associated with EPS was low for both quetiapine XR and quetiapine IR, although slightly higher than that observed with placebo; and all but one of the AEs related to EPS were of mild or moderate severity. The incidence of individual EPS-related AEs did not exceed 3% in any of the treatment arms and all were mild-moderate in intensity. The incidence of akathisia for quetiapine XR was also low and similar to placebo. There were overall mean decreases in scores on the two scales used to assess EPS-related adverse effects (SAS and BARS) that were similar to those associated with placebo. Most patients showed either an improvement or no change in scores throughout the study.

Vital signs did not reveal any clinically important effects of quetiapine XR. A small mean increase in pulse rate was observed in patients treated with quetiapine XR compared with patients taking placebo. In most cases, the individual changes seen were not associated with reports of dizziness, orthostatic hypotension or tachycardia. The changes in vital signs were similar for quetiapine XR and quetiapine IR and consistent with the established profile of quetiapine. Tachycardia, orthostatic hypotension and syncope occurred infrequently for quetiapine XR and were similar in frequency to those in patients randomised to quetiapine IR or placebo. In Studies 132 and 133, the incidences of these AEs in patients taking quetiapine XR were low during the first week and similar to those

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in patients taking placebo. Therefore, rapid dose titration of quetiapine XR during the first week raised no concerns over these AEs. This is supported by results from Study 41 which report no syncope with quetiapine XR (or quetiapine IR). The incidences of orthostatic hypotension and tachycardia were slightly larger than placebo for quetiapine XR, but were similar to quetiapine IR in this study.

Patients taking quetiapine XR had a greater mean increase in body weight than those taking placebo (1.77 ± 5.22 kg vs. 0.26 ± 3.65 kg), and this change was similar for those taking quetiapine IR (2.19 ± 3.70 kg). In previous long-term studies with the IR formulation a mean change in body weight of +3.19 kg has been observed over 52 weeks' treatment (Brecher *et al.*, 2007). Laboratory data on blood lipids revealed no clinically relevant changes in plasma total cholesterol, HDL or LDL in patients treated with quetiapine XR or quetiapine IR. Glucose and triglyceride values were slightly increased for those taking quetiapine XR compared with placebo, and tended to be lower than for those taking quetiapine IR.

Overall, clinically effective doses of quetiapine XR were generally safe and well tolerated in the treatment of patients with schizophrenia, with no additional safety concerns observed at the higher doses of 600 and 800 mg/day compared with 400 mg/day. These results are consistent with those seen in clinical trials of quetiapine IR at the same daily dosages. The rapid dose titration with quetiapine XR was not associated with any increase in AEs, and no new safety concerns emerged with respect to quetiapine XR compared with quetiapine IR. Furthermore, these tolerability results complement those reported in other quetiapine XR studies (Ganesan *et al.*, 2008, Möller *et al.*, 2008).

These tolerability data for quetiapine XR, together with the simplified treatment regimen, imply that patient adherence could be potentially improved by treatment with quetiapine XR instead of quetiapine IR. These characteristics of quetiapine XR are of clinical relevance because adherence to the prescribed antipsychotic medication regimen is a significant factor in preventing psychotic relapse (Kane, 1996; Robinson *et al.*, 1999; Csernansky and Schuchart, 2002; Fleischhacker *et al.*, 2003; Citrome and Volavka, 2004; Leucht and Heres, 2006).

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