RESEARCH ARTICLE

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Tolerability of extended-release quetiapine fumarate compared with immediate-release quetiapine fumarate in older patients with Alzheimer's disease with symptoms of psychosis and/or agitation: a randomised, double-blind, parallel-group study

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Objective: The objective of this study was to assess the safety and tolerability of extended-release quetiapine fumarate (quetiapine XR) compared with quetiapine immediate-release (quetiapine IR) in older patients with Alzheimer's disease with symptoms of psychosis and/or agitation.

Methods: This was a 6-week, double-blind, double-dummy, randomised study. Of the 109 patients screened, 100 were randomised to receive quetiapine XR ($n = 68$) or quetiapine IR ($n = 32$), at doses of 50 and 25 mg/day, respectively. Treatment was escalated to 100 mg/day by Day 4. At Day 8, a flexible-dose (50-300 mg/day) period began when dose adjustment was made at the investigator's discretion. The primary variable was incidence and type of adverse events (AEs). Secondary variables included efficacy and other safety assessments.

Results: Mean daily doses were 143.6 and 142.0 mg in the quetiapine XR and quetiapine IR groups, respectively. Ninety patients completed the study; only one withdrew (in the quetiapine XR group) because of an AE. Laboratory evaluations identified severe neutropaenia (one patient), mild neutropaenia (three patients) and eosinophilia (five patients); however, these were not reported, as AEs and confounding factors, such as patient age, concomitant illness and medication, made it difficult to determine any relationship to quetiapine treatment. Numerical improvements from baseline were seen across both treatment groups in Neuropsychiatric Inventory frequency × severity total, Neuropsychiatric Inventory-Nursing Home version, Cohen–Mansfield Agitation Inventory, Clinical Global Impression-Severity of Illness and Clinical Global Impression-Improvement scores.

Conclusion: Quetiapine XR dosed up to 300 mg/day was generally well tolerated, with a similar profile to that of quetiapine IR. Copyright © 2011 John Wiley & Sons, Ltd.

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Introduction

Up to 90% of patients with Alzheimer's disease (AD) experience behavioural changes, which may be due to co-existing medical illnesses or co-morbid psychiatric ailments. Clinical examinations frequently reveal that psychotic symptoms form the basis of these abnormal behaviours seen in AD (Tariot *et al.*, 2006). Proper assessment and management of these conditions often leads to resolution; however, there is an identifiable

need for better classification and measurement of psychiatric symptoms in patients with AD and for effective and well-tolerated treatment options to manage those symptoms (Lyketsos, 2007).

An early open-label trial of quetiapine immediate-release (quetiapine IR) focusing on dosing and tolerability in older patients with psychosis demonstrated acceptable tolerability results and suggested a possible behavioural benefit (Tariot *et al.*, 2000). Thereafter, two randomised, double-blind, placebo-controlled studies showed some benefits of quetiapine IR in older patients with dementia (Tariot *et al.*, 2006; Zhong *et al.*, 2007). Extended-release quetiapine fumarate (quetiapine XR) has subsequently been developed to allow a more convenient once-daily dosing regimen and simpler dose initiation.

In 2005, the Food and Drug Administration issued a black box warning that atypical antipsychotics are associated with an increased risk of death in older patients with dementia. Although atypical antipsychotics including quetiapine are not approved in either the USA or Europe for use in this population, their effectiveness in this setting has been the subject of debate (Sink *et al.*, 2005).

In this study, conducted outside of the approved indication and before the black box warning was issued, older patients with AD received either quetiapine XR or quetiapine IR to evaluate the tolerability of quetiapine XR compared with quetiapine IR.

Materials and methods

The study was performed in accordance with the Declaration of Helsinki, the International Conference of Harmonisation and Good Clinical Practice Guidelines and the Institutional Review Board or Independent Ethics Committee affiliated with each centre. Written informed consent was obtained from all patients (or their legal representatives). Where patients were unable to give legally valid consent for themselves, they were asked to assent to the study and to sign a form (when feasible) indicating their wish to participate.

Patient population

Patients with AD, aged ≥65 years, residing in nursing homes or equivalent institutions and requiring antipsychotic medication for symptoms of psychosis and/or agitation were enrolled.

Key inclusion criteria included the following: diagnosis of dementia of the Alzheimer's type with early onset or with late onset dementia by Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, 1994 classification, or diagnosis of dementia in AD with early onset; late onset; atypical or mixed type; or unspecified, plus other symptoms that were predominantly delusional, hallucinatory, depressive or mixed according to the International Statistical Classification of Diseases-10th revision Research Diagnostic Criteria; a Mini-Mental State Examination (MMSE) score of 23 or less at screening and baseline; a Neuropsychiatric Inventory (NPI) score [frequency multiplied by severity (NPI freq*sev)] of ≥3 at screening and baseline, for any of the following items: agitation, delusions and hallucinations; stable general health appropriate for age; willingness and ability to comply with the safety monitoring guidelines and to adhere to the schedule of assessments.

Key exclusion criteria included the following: evidence of a clinically significant or unstable disease that could affect symptom presentation or assessments of study drug or could render the patient unable to complete the study; known intolerance or lack of response to previous treatment with quetiapine; use of clozapine within 30 days, depot/long-acting injectable antipsychotic drugs within one dosage interval, other antipsychotics within 4 days or mood stabilisers within 14 days prior to randomisation; uncontrolled hypertension, history of antihypertensive-medication adjustments within 30 days prior to randomisation, history of idiopathic orthostatic hypotension or known history of sensitivity to the hypotensive effects of antipsychotic or antidepressant medication; persistent tachycardia, electrocardiogram (ECG) evidence of myocardial infarction in 3 months prior to randomisation or ECG results revealing a clinically significant abnormality; use of potent CYP 3A4 inhibitors or CYP 3A4 inducers in 14 days preceding randomisation; clinical laboratory values outside normal range and considered clinically significant and relevant by the investigator; risk of transmitting HIV or hepatitis B; history of participation in a clinical study or compassionate-use programme in the 30 days preceding randomisation.

Study design

This was a 6-week, double-blind, double-dummy, randomised, parallel-group, controlled Phase III study in older patients with AD that was conducted at 14 sites in five countries: Australia, Belgium, Canada, Norway and South Africa.

The study consisted of a 7-day run-in period prior to randomisation, a 7-day fixed-dose titration period and a flexible-dose adjustment period for the remainder of the trial. Randomisation was strictly sequential and was in blocks, with a treatment balance of quetiapine XR: quetiapine IR of 2:1. During the fixed-dose titration period (Days 1–7), quetiapine XR was initiated at a dosage of 50 mg/day and quetiapine IR at 25 mg/day, given at approximately 15:00 h once daily. On Day 2, quetiapine IR was increased to 50 mg/day (25 mg BID). Both quetiapine XR and quetiapine IR were escalated to 100 mg/day on Day 4, and this dosage was continued for the remainder of the fixed-dose titration period (Figure 1). During the flexible-dose adjustment period, the dose of either study treatment could be adjusted in steps of 50 mg/day at least 3 days apart and up to a maximum daily dose of 300 mg, assuming acceptable tolerability of the preceding dose. If necessary, the dose could be decreased at any time to a minimum of 50 mg/day. AstraZeneca provided tablets of quetiapine IR 25 and 100 mg and quetiapine XR 50 and 200 mg, along with matching placebos. Study medication was administered orally under the supervision of study personnel. Quetiapine IR was administered at approximately 8:00 h and 15:00 h, whereas quetiapine XR was administered at approximately 15:00 h only. The tablets had to be swallowed whole.

The patients enrolled in the study were required to stop taking all antipsychotic medication at least 4 days prior to randomisation. If more time was needed for discontinuation of previous medications as specified in the exclusion criteria, the screening for the study was conducted, and informed consent was obtained before discontinuation of those medications.

Assessments

The primary variable for this study was the incidence and type of adverse events (AEs) in the quetiapine XR group compared with the quetiapine IR group.

Secondary tolerability variables were the following: proportion of patients withdrawn because of an AE; proportion of patients with AEs related to orthostatic hypotension; clinically significant abnormalities during treatment in vital signs, ECG, chemistry and haematology; change from baseline up to Day 42 in the modified Simpson–Angus Scale (SAS), the Barnes Akathisia Rating Scale (BARS) and the Abnormal Involuntary Movements Scale (AIMS) scores; proportion of patients using anticholinergic medication; change in weight from screening to Day 42.

Secondary efficacy variables were the following: change from baseline to Day 42 in NPI, Cohen–Mansfield Agitation Inventory (CMAI), MMSE and Clinical Global Impression-Severity of Illness (CGI-S) scores; and CGI-Improvement (CGI-I) score on Day 42.

The CMAI measures the frequency of agitated behaviours, and the outcome variable was changed in total score from baseline to Days 8, 15, 22, 29 and 42, when the CMAI was obtained.

The MMSE was used to assess several cognitive domains that may be impaired in patients with AD (memory, orientation, language, praxis and attention/concentration). The MMSE score was not calculated if any of the 11 subitems were missing. The key outcome variable was the change from baseline to Day 42 [last observation carried forward (LOCF)].

Treatment adherence was assessed on the timing of medication intake. Patients were considered nonadherent and were withdrawn from further treatment if the study medication was missed for 96 h or more.

Statistical analysis

The safety population was used for all safety and tolerability analyses and included all patients who were randomised and received at least one study treatment. The modified intent-to-treat (MITT) population was used for all efficacy analyses and included all enrolled patients who took trial medication and who had a

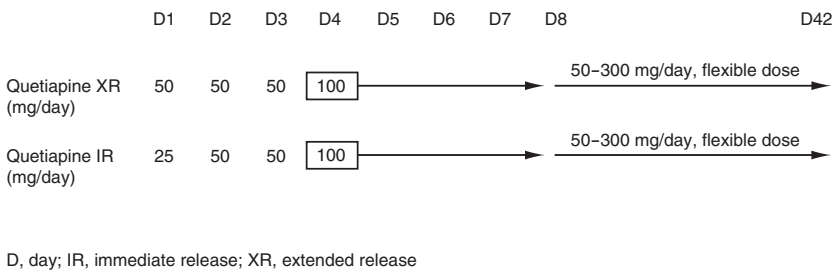

Figure 1 Study dosing schedule.

baseline value of NPI freq*sev total score, plus at least one post-baseline assessment of NPI freq*sev total score.

The LOCF principle was used to handle missing data due to discontinuation from the study. The last post-baseline assessment was used; baseline values were not carried forward into the treatment phase.

The number of patients was not based on formal power calculations. An enrolment of ≥90 patients randomised to either quetiapine XR or quetiapine IR in the proportion of 2:1 was considered sufficient to assess the tolerability of quetiapine XR in this population but not powered for any statistical analysis. Therefore, all data are presented as descriptive statistics only with the associated inherent limitations.

Results

Patient disposition

Between May 2002 and February 2003, 109 patients were enrolled and screened. Of these, 100 patients were randomised (quetiapine XR, 68 patients; quetiapine IR, 32 patients). Overall, 90% of patients who were randomised completed the study (quetiapine XR, 59 patients; quetiapine IR, 31 patients). Ten patients discontinued from the study, nine (13.2%) from the quetiapine XR group and one (3.1%) from the quetiapine IR group (Figure 2).

Four patients in the quetiapine XR group were discontinued from the study owing to protocol deviations or violations. Two of these patients had not taken the study drug for ≥4 days, another patient refused multiple doses of evening medication and the fourth patient discontinued the study drug treatment on Day 31 by leaving the centre. For population analysis and according to definitions, these patients were included in the safety and MITT populations.

Six minor protocol deviations (quetiapine XR, five patients; quetiapine IR, one patient) were reported. These deviations did not lead to discontinuation and resulted from vital signs not being collected on the day of and the day following a dose escalation (two patients); a patient not fasting prior to collection of blood (Visit 1); an extra sample needing to be collected; a patient missing a morning dose and being given an incorrect afternoon dose; a patient missing an afternoon dose; and a morning and an afternoon dose being withheld from the sixth patient because of an AE.

The safety population included 68 patients in the quetiapine XR group and 32 patients in the quetiapine IR group. The two treatment groups were similar with regard to demographics and key baseline characteristics (Table 1). Mean age was approximately 80 years. Overall, there were more female than male patients, distributed similarly between the two treatment groups.

The two groups were similar in terms of exposure: mean exposure was 39.1 [standard deviation (SD) 8.15] days in the quetiapine XR group and 41.8 (SD 1.26) days in the quetiapine IR group. Mean daily doses were 143.6 mg (SD 46.42) in the quetiapine XR group and 142.0 mg (SD 42.65) in the quetiapine IR group.

Tolerability assessments

Adverse events. Quetiapine XR and quetiapine IR were generally well tolerated; 69.1% of patients in the quetiapine XR group and 71.9% of patients in the quetiapine IR group experienced an AE.

The two treatment groups were generally similar with respect to the type of AEs reported (Table 2). Somnolence was the most common AE with an onset within the first 7 days of treatment (fixed-dose titration period), and approximately 50% of patients who reported this AE had an onset during the first week (7.4% and 9.4% in the quetiapine XR and IR groups, respectively). Sedation occurring during the first 7 days of treatment was less common in quetiapine XR patients than in quetiapine IR patients (2.9% and 9.4%, respectively).

Vomiting was observed more frequently in the quetiapine XR group, and nausea was reported more frequently in the quetiapine IR group. The majority of events of vomiting were of mild intensity; there were no events of severe intensity, whereas the events of nausea were mild to moderate.

Urinary tract infection was reported in a higher percentage of patients receiving quetiapine XR (8.8%) than quetiapine IR (3.1%).

There were five serious AEs (SAEs); three (4.4%) in the quetiapine XR group and two (6.3%) in the quetiapine IR group. One patient in the quetiapine IR group who experienced a complete atrioventricular block died from terminal phase of metastatic carcinoma of the prostate, and his death was considered unrelated to the study treatment. An 88-year-old female patient (randomised to quetiapine XR during the study and subsequently treated with quetiapine IR following the study period) developed pneumonia during the follow-up period, 4 weeks after the last quetiapine XR dose, and died the following day. The

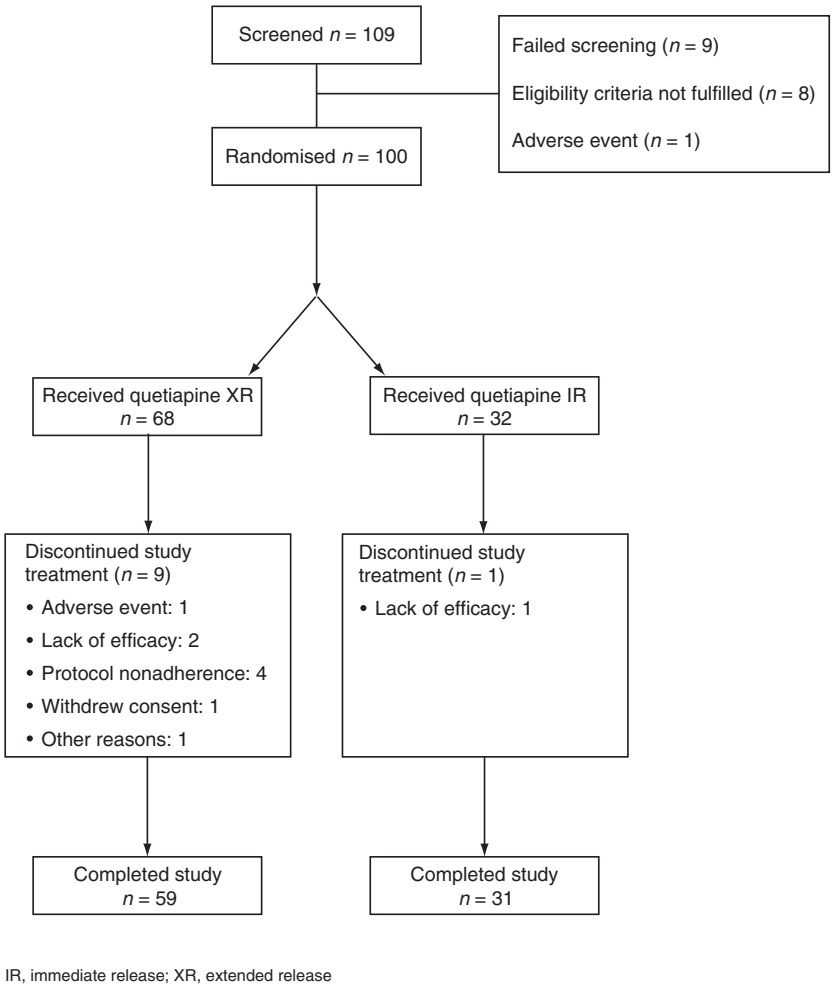

Figure 2 Patient disposition (completion or discontinuation).

pneumonia and death were considered to be not related to the study treatment.

The remaining three SAEs did not lead to death and were considered to be not related to treatment by the investigator. Two were urinary tract infections, one reported in a 78-year-old male patient during the treatment period with quetiapine XR and the other in an 89-year-old female patient after the treatment period with quetiapine IR. The third was a subdural haematoma following a fall in a 78-year-old male patient, 12 days

Table 1 Patient demographics and key baseline characteristics by treatment group (safety population)

		Quetiapine XR (*n* = 68)	Quetiapine IR (*n* = 32)	Total (*n* = 100)
Gender: *n* (%)	Male	24 (35.3)	10 (31.3)	34 (34.0)
	Female	44 (64.7)	22 (68.8)	66 (66.0)
Age (years)	Mean (SD)	80.5 (6.4)	79.3 (6.9)	80.1 (6.5)
	Range	65–94	67–90	65–94
Race: *n* (%)	Caucasian	68 (100)	32 (100)	100 (100)
Weight (kg)	*n* (%)	68 (100)	32 (100)	100 (100)
	Mean (SD)	61.2 (12.0)	61.5 (13.0)	61.3 (12.2)
BMI (kg/m^2)	*n* (%)	68 (100)	32 (100)	100 (100)
	Mean (SD)	23.4 (3.6)	23.0 (4.0)	23.3 (3.7)

BMI, body mass index; IR, immediate release; SD, standard deviation; XR, extended release.

Table 2 Most common treatment-emergent adverse events occurring in at least 5% of patients in either treatment group (safety population)

MedDRA preferred term	Quetiapine XR ($n = 68$)	Quetiapine IR ($n = 32$)
	n (%)	*n* (%)
Somnolence	10 (14.7)	6 (18.8)
Vomiting NOS	7 (10.3)	2 (6.3)
Headache	6 (8.8)	3 (9.4)
Urinary tract infection NOS	6 (8.8)	1 (3.1)
Sedation	5 (7.4)	4 (12.5)
Dry mouth	4 (5.9)	1 (3.1)
Fatigue	4 (5.9)	1 (3.1)
Nausea	4 (5.9)	3 (9.4)
Chest pain	1 (1.5)	2 (6.3)
Dizziness	1 (1.5)	3 (9.4)
Orthostatic hypotension	1 (1.5)	2 (6.3)
Haemorrhage NOS	0	3 (9.4)

IR, immediate release; MedDRA, Medical Dictionary for Regulatory Activities; NOS, not otherwise specified; XR, extended release.

after the last dose of quetiapine XR (300 mg/day). This patient had several co-morbidities and was receiving a number of concomitant medications.

One patient withdrew owing to an AE (aggression), which began during screening (5 days prior to randomisation) and continued during the treatment phase. The last dose of quetiapine XR was administered to this patient on Day 14, and the patient was discontinued from the study the same day.

Haematology results. There were no clinically important differences between quetiapine XR and quetiapine IR with respect to changes in haematology and clinical chemistry parameters from screening to Day 42.

Eosinophilia ($\geq 460 \times 10^6$/L) was reported in four patients in the quetiapine XR group and one patient in the quetiapine IR group. Laboratory investigations identified three patients with neutropaenia ($\leq 1.5 \times 10^9$/L) and one patient with severe neutropaenia ($\leq 0.5 \times 10^9$/L), all in the quetiapine XR group; none of these were reported as AEs.

In previous studies of quetiapine IR, an effect on thyroid function has been indicated without the development of the clinical signs of disease (Kelly and Conley, 2005). In the present study, some decreases in the concentrations of free thyroxine without accompanying increases in thyroid stimulating hormone, or increase in thyroid stimulating hormone concentrations without concurrent changes in free thyroxine were seen. These changes were considered to be not clinically significant.

Metabolic risk factors. Small increases in mean (SD) fasting blood glucose levels from screening to Day 42 in both treatment groups were considered to be not clinically significant. There were no AEs associated with diabetes mellitus. Blood glucose data by diabetic status was inappropriate for interpretation owing to the small number of patients in the diabetic and diabetic-at-risk subcategories within each group. At the end of treatment, high glucose levels (≥7 mmol/L) were observed in four patients treated with quetiapine IR; all four patients had normal glucose levels at baseline (<6.1 mmol/L), indicating a shift in concentration.

Investigation of the shifts in metabolic syndrome risk factors considered blood pressure, body mass index (BMI), triglyceride and glucose concentrations (high-density lipoprotein and low-density lipoprotein were not measured in this study). When considering those patients who did not meet ≥3 of these risk factors at baseline, two patients (in the quetiapine XR group) met criteria for an aggregate of ≥3 metabolic syndrome risk factors under confirmed fasting glucose conditions.

Weight. Mean changes in body weight and BMI were similar between the two quetiapine groups, with an increase observed in both groups by Day 42. Mean (SD) weight increases were 0.3 (3.41) kg versus 0.4 (3.29) kg in the quetiapine XR and IR groups, respectively. Mean (SD) BMI increases were 0.1 (1.29) and 0.1 (1.35) kg/m^2 in the quetiapine XR and IR groups, respectively. The percentage of patients with ≥7% weight gain was 6.3% and 15.6% in the quetiapine XR and quetiapine IR groups, respectively.

Vital signs. There was a small increase in mean heart rate (3.2 and 3.6 bpm for quetiapine XR and IR, respectively). One patient in each treatment group had a potentially clinically significant drop in heart rate to <50 bpm at Day 42. There were no AEs related to dizziness, postural dizziness, orthostatic hypotension and falls or accidental injuries reported in these patients. No heart rates >120 bpm were recorded.

Although a small elevation in heart rate and small decrease in systolic and diastolic blood pressure was observed in both treatment groups, there was a low incidence of orthostatic events (Table 3). There were no concurrent events of falls, accidental injuries or injuries related to falls in patients reporting these events. Dizziness and light-headedness were not reported.

Extrapyramidal symptoms. Parkinsonian and akathisia symptoms as assessed by SAS, BARS and AIMS scores indicated either slight improvement or

Table 3 Adverse events potentially related to hypotension (safety population)

MedDRA preferred term	Quetiapine XR ($n = 68$)	Quetiapine IR ($n = 32$)
	n (%)	*n* (%)
Any event potentially related to hypotension	3 (4.4)	4 (12.5)
Hypotension NOS	2 (2.9)	1 (3.1)
Orthostatic hypotension	1 (1.5)	2 (6.3)
Hypotension postural, aggravated	0	0
Blood pressure orthostatic	0	0
Blood pressure orthostatic, abnormal	0	0
Syncope	0	1 (3.1)

AE, adverse event; IR, immediate release; MedDRA, Medical Dictionary for Regulatory Activities; NOS, not otherwise specified; XR, extended release.

absence of deterioration with quetiapine XR and quetiapine IR. Anticholinergic medication was not used during the study.

Efficacy assessments

Baseline and mean change from baseline at Day 42 for the efficacy assessments are shown in Table 4. Similar and steady patterns of improvement in mean NPI freq*sev total score and NPI-Nursing Home disruption score were observed in the two treatment groups.

The two treatment groups showed progressive improvements in CMAI and CGI-S scores. Similarly, CGI-I scores showed the majority of patients achieving 'very much' or 'much' improved in both treatment groups, respectively. There was no deterioration of cognition in either treatment group, as measured by the mean MMSE scores.

Discussion

This study investigated the incidence and type of AEs observed in older patients with AD with symptoms of psychosis and/or agitation treated with quetiapine XR or quetiapine IR, a use for which quetiapine is not approved. Quetiapine XR and quetiapine IR were generally well tolerated. The only patient who discontinued because of an AE had symptom onset prior to receiving study treatment. Two deaths were reported, neither of which were judged to be due to study treatment.

The pattern of AEs was similar in the two quetiapine treatment groups, with somnolence being the most commonly reported AE in each. There were no clinically important changes in mean haematological and clinical chemistry parameters, vital signs measurements or weight. The magnitude of weight gain recorded in this study was comparable to that observed in two studies of quetiapine XR (50–300 mg/day flexible dosing) in older patients with major depressive disorder (0.7 kg at Week 9) (Katila *et al.*, 2009) and generalised anxiety disorder (0.6 kg at Week 9) (Magi *et al.*, 2009). Although laboratory investigations identified a small number of patients with eosinophilia and neutropaenia, the advanced age of the patients and other factors (concomitant illnesses, including infections; prior and concomitant medication) made it difficult to clarify any relationship between the haematological events and study

Table 4 Change from baseline to Day 42 in secondary efficacy variables (MITT population, LOCF)

	Quetiapine XR ($n = 67$)		Quetiapine IR ($n = 32$)	
	Baseline	Change from baseline at Day 42	Baseline	Change from baseline at Day 42
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
NPI freq*sev total score	41.8 (21.9)	–20.0 (26.4)	40.9 (19.2)	–25.0 (16.7)
NPI disruption score	15.7 (8.9)	–7.3 (10.4)	17.1 (8.1)	–10.7 (6.4)
CMAI score	30.7 (19.7)	–14.0 (18.1)	30.8 (16.6)	–16.1 (12.5)
MMSE score	12.9 (6.6)	–0.4 (3.2)	12.8 (5.7)	0.0 (2.98)
CGI-S score	4.7 (1.0)	–1.0 (1.5)	5.0 (1.3)	–1.3 (1.5)
	Very much improved	Much improved	Very much improved	Much improved
	n (%)	*n* (%)	*n* (%)	*n* (%)
CGI-I	21 (31.3)	20 (29.9)	13 (40.6)	10 (31.3)

CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity of Illness; CMAI, Cohen–Mansfield Agitation Inventory; IR, immediate release; LOCF, last observation carried forward; MITT, modified intent-to-treat; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; NPI freq*sev, NPI frequency × severity; XR, extended release.

medication. The evaluation of vital signs did not reveal any new findings with quetiapine XR. There were small elevations of heart rate and a small decrease in systolic and diastolic blood pressure. These effects were generally similar for quetiapine XR and quetiapine IR. There was no increase in parkinsonian and akathisia symptoms in either quetiapine treatment group as measured by SAS, BARS and AIMS, and no patient required anticholinergic medication.

Assessment of efficacy suggested some improvement in the symptoms of psychosis and agitation in both treatment groups, as measured by NPI-Nursing Home, CMAI, CGI-S scores and CGI-I score. There was no clinically significant change in MMSE score over the study period, contrary to the results seen in a study by Ballard *et al.* (2005).

The study results indicate that quetiapine XR is associated with a safety profile similar to that observed with quetiapine IR in patients with dementia-related psychosis and/or agitation, as demonstrated in other studies (Tariot *et al.*, 2006; Zhong *et al.*, 2007), and there were no unexpected safety outcomes. However, there is no licensed indication for the use of quetiapine in this population, and as for other members of the atypical antipsychotic class, quetiapine has a Food and Drug Administration black box warning for use in older patients with dementia.

Strengths of the study derive from its randomised, double-blind and controlled design; these factors contribute to balance, accuracy and reliability of the study data and their interpretation. The multicentre nature of the study may also be an advantage, as it shows consistency of data across a variety of cultural and clinical settings.

Limitations of the study include the following: short-term design; small patient sample of a single ethnicity; lack of a placebo control group; and lack of formal statistical considerations in design. The study did not include examinations of possible rater bias, inter-rater consistency/reliability and interview quality. All these factors may affect the outcome of clinical trials (Kobak *et al.*, 2007) and are particularly important in multinational/multicentre studies.

Finally, the study population had identifiable vulnerabilities that could potentially interfere with this kind of study and a number of confounding factors, which may have derived from the characteristics of such a population. These included the age and physical fragility of the patients and the number and nature of co-morbidities and associated treatments, which could possibly have interfered with symptomatic manifestations. In addition, dementia frequently manifests in a lack of cooperation and difficulty with reporting symptoms. These factors coupled with the institutionalised nature of the patients may have impacted on assessment.

In conclusion, in older patients with AD with symptoms of psychosis and/or agitation, quetiapine XR and quetiapine IR have similar tolerability and efficacy profiles. Neither drug is approved for use in this population.

Key points

- Patients with Alzheimer's disease frequently experience behavioural changes, which may be due to co-morbid medical or psychiatric illness.
- In older patients with AD, quetiapine IR and quetiapine XR were generally well tolerated, and there was some improvement in the symptoms of psychosis.

There is no licensed indication for quetiapine in this population.

Conflict of interest

None declared.

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