

Quetiapine to Treat Agitation in Dementia: A Randomized, Double-Blind, Placebo-Controlled Study

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Abstract: In this 10-week, double-blind, fixed-dose study, elderly institutionalized patients with dementia and agitation were randomized (3:3:2) to quetiapine 200mg/day, 100mg/day, or placebo. The primary endpoint was change in Positive and Negative Syndrome Scale (PANSS)-Excitement Component (EC) scores at endpoint, analysed using last observation carried forward (LOCF) and observed cases (OC) approaches. Other efficacy measures were the Clinical Global Impression of Change (CGI-C), and response rates (percentage with 40% reduction [PANSS-EC]; "much" or "very much improved" [CGI-C]), Neuropsychiatric Inventory-Nursing Home version (NPI-NH), and Cohen-Mansfield Agitation Inventory (CMAI). The key safety measure was incidence of adverse events; change in Mini-Mental State Examination (MMSE) was also assessed. Baseline characteristics of 333 participants (quetiapine 200mg/day, n=117; quetiapine 100mg/day, n=124; placebo, n=92) and completion rates (63-65%) were comparable among groups. Compared with placebo, quetiapine 200mg/day was associated with clinically greater improvements in PANSS-EC (LOCF, p=0.065; OC, p=0.014 [ANCOVA]), CGI-C (LOCF, p=0.017; OC, p=0.002 [ANOVA]), and CGI-C response rates (LOCF, p=0.002; OC, p<0.001 [Chi-square test]). Quetiapine 100mg/day did not differentiate from placebo on these measures. There were no between-group differences in NPI-NH or CMAI. Incidences of cerebrovascular adverse events, postural hypotension, and falls were similar among groups. MMSE did not change in any group. Mortality was numerically higher in the quetiapine groups; rates were not statistically different from placebo. The results of this study suggest that quetiapine 200mg/day was effective and well-tolerated for treating agitation associated with dementia. However, caution should be exercised given the concerns regarding increased mortality with atypical antipsychotics in this vulnerable patient population.

Keywords: Quetiapine, atypical antipsychotic, efficacy, safety, tolerability, agitation, dementia, Alzheimer's disease.

INTRODUCTION

Behavioral disturbances including agitation are common in patients with dementia [1]. Their presence can have a major impact on the quality of life of patients and caregivers, accelerate cognitive decline, and often precipitate nursing home placement [2]. Management of agitation consists of non-pharmacologic and pharmacologic strategies. Currently, there is no Food and Drug Administration (FDA) approved medication for the treatment of persistent agitation in patients with dementia and effective treatment remains an unmet clinical need. Conventional antipsychotics were once the mainstay of pharmacological therapy for behavioral disturbances in dementia, but their use has declined while use of the atypical antipsychotics has increased [3]. Studies have indicated a modest benefit with these agents for treating psychosis and agitation (unpublished dataⁱ) [4-6]; however, results have not been consistently positive (unpublished dataⁱⁱ)

[7-9]. Although the atypical antipsychotics appear to be better tolerated than the traditional agents, concerns remain about sedation, falls, and the increased risk of cerebrovascular adverse events (CVAEs) and mortality (unpublished dataⁱⁱⁱ) [10-13].

Quetiapine is one of the newer members of this group of compounds. In an initial open-label study, in which 184 elderly patients with psychoses were treated with quetiapine (median dose 138 mg/day) for 52 weeks, there was a suggestion of possible behavioral benefits [14]. Based on these results, a double-blind, placebo-controlled, flexible-dose, 10-week study of quetiapine was conducted in 378 patients with dementia complicated with psychosis; the majority had a diagnosis of probable or possible AD (75%). Haloperidol (median dose = 1.9 mg) was used as an active comparator and the median dose of quetiapine was 113 mg/day. Psychotic symptoms were improved in both the quetiapine and haloperidol groups, but there were no significant differences for either active treatment versus placebo. Both treatments showed inconsistent evidence of reduced agitation in the patients with AD [15].

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ⁱ Breder C, Swanink R, Marcus RN, *et al.* Dose-ranging study of aripiprazole in patients with Alzheimer's dementia. Proceedings of the 157th Annual Meeting of the American Psychiatric Association, New York, NY, USA, 1-6 May, 2004; 243. Abstract.

ⁱⁱ De Deyn PP, Jeste D, Mintzer J. Aripiprazole in dementia of the Alzheimer's type. Presented at the 16th Annual Meeting of the American Association of Geriatric Psychiatry, Waikiki, Oahu, HI, USA, 1-4 March, 2003.

ⁱⁱⁱ Schneider LS, Dagerman K. Meta-analysis of atypical antipsychotics for aggression and psychosis in Alzheimer's disease: likelihood of helping versus harming. Presented at the 9th International Conference on Alzheimer's Disease and Related Disorders, Philadelphia, PA, USA, 17-22 July, 2004.

The primary objective of this study was to evaluate the efficacy of two fixed doses of quetiapine (200 mg/day and 100 mg/day) compared with placebo in treating agitation in patients with dementia. The two fixed doses of 100 and 200 mg/day were chosen based on previous studies that indicated at least 100 mg/day may be required for efficacy [14, 15]. The titration rate used in the study (quetiapine 100 mg by Day 4 and 200 mg by Day 8) was based on evidence that faster titration of quetiapine does not result in an increased incidence of adverse events (AEs) [16]. The primary hypothesis was that at least one dose of quetiapine would be superior to placebo in change from baseline Positive and Negative Syndrome Scale-Excitement Component (PANSS-EC), [17, 18] at Week 10. Secondary objectives were to assess other measures of efficacy, tolerability, and safety, and to clarify dosing and titration considerations for quetiapine in this population.

METHODS

Participants

Participants were residents of nursing homes and assisted living facilities, enrolled between September 2002 and November 2003 from 53 centers in the United States. They had diagnoses of probable or possible AD or vascular dementia according to Diagnostic and Statistical Manual of Mental Disorders – fourth edition [DSM-IV] or the National Institute of Neurological and Communicative Disorders and Stroke/the Alzheimer's Disease and Related Disorders Association [NINCDS/ADRDA] criteria. Other inclusion criteria were as follows: minimum age of 55 years, ambulatory or ambulatory with assistance, documented clinical symptoms of agitation that did not result directly from the participant's medical condition and required treatment with antipsychotic medication in the opinion of the investigator, a total score of ≥ 14 on the PANSS-EC and a score of ≥ 4 on one of the 5 PANSS-EC items (hostility, tension, uncooperativeness, excitement, poor impulse control) both at screening and at randomization. Key exclusion criteria included a history of schizophrenia, schizoaffective disorder or bipolar disorder, agitation that was judged not to be related to dementia, failure to respond to a prior adequate trial of atypical antipsychotics for the treatment of agitation, and unstable medical illness (this included but was not limited to: cardiovascular, renal, hepatic, hematological, endocrine, and cerebrovascular disorders). Any participants with abnormal ECG results that were considered clinically significant were also excluded from the study.

Institutional Review Boards or Independent Ethics Committees at each site approved the informed consent procedure and study protocol. Written informed consent was obtained from the caregiver or legally authorized representative prior to the initiation of any study specific procedures.

Study Design and Treatment

This was a 10-week, randomized, multicenter, double-blind, placebo-controlled, fixed-dose study. Screening assessments were conducted within 14 days prior to randomization to determine eligibility. At baseline, participants who met enrollment criteria were randomly assigned in a 3:3:2 ratio to one of three fixed-dose treatment groups:

quetiapine 200 mg/day, 100 mg/day, or placebo. The centralized randomization schedule was generated using a random block size of 8 and was created using random seed and treatment allocation ratios of 3:3:2 and maintained blinded by the sponsor's randomization group. Medication was distributed to centers in randomization blocks of 8. Each kit contained 10 blister wallets with the same number of tablets and the same configuration of color, size, and shape. Study medication was administered twice daily from blister wallets.

Participants randomized to treatment with quetiapine initially received 25 mg/day. The dose was titrated in 25 mg increments every day to reach 100 mg/day on Day 4 for both quetiapine treatment groups; those assigned to 100 mg/day were maintained on this dose, those randomized to 200 mg/day continued the titration in 25 mg increments daily to reach the target dose of 200 mg on Day 8, after which the dose was held constant. Participants unable to tolerate the assigned treatment were discontinued from the study.

Psychotropic medications were prohibited with the following exceptions: as-needed use of sedative-hypnotics for insomnia; use of lorazepam (up to 4 mg/day) or an equivalent benzodiazepine during the first 14 days of the study as needed for agitation; stable doses of antidepressants, benzodiazepines, and cholinesterase inhibitors, which were to be maintained throughout the study.

Assessments

The primary efficacy outcome measure was change from baseline to endpoint on the PANSS-EC score. PANSS-EC is a reliable and validated 5-item subscale of the PANSS that includes ratings of excitement, poor impulse control, tension, hostility, and uncooperativeness [18]. Although there is no clinical consensus regarding clinically meaningful changes in PANSS-EC, this measure has been used in previous studies of intramuscular olanzapine in agitated patients with dementia, and the magnitude of effect relative to placebo was 2.5 units [19].

A key secondary outcome measure was the Alzheimer's Disease Cooperative Study Clinical Global Impression of Change (ADCS-CGI-C) [20], which was used to assess the participant's overall clinical condition and to address the clinical significance of changes in other psychometric measures. Several other secondary outcome measures were also used. The Neuropsychiatric Inventory-Nursing Home (NPI-NH) [21] is a 12-item scale assessing neuropsychiatric symptoms in patients with dementia residing in nursing homes. For each item, the Occupational Disruptiveness score was obtained to assess the work, effort, time or distress that the particular behavior caused staff caregivers [22]. The Cohen-Mansfield Agitation Inventory (CMAI) [23] is a 29-item instrument assessing frequency of manifestations of agitation in the elderly.

All efficacy assessments were administered at baseline and at Weeks 1, 2, 4, 6, and 10 or at study withdrawal; the PANSS-EC and CGI-C were also assessed at Week 8.

Safety and tolerability assessments included treatment-emergent AEs, clinically significant changes in laboratory tests, electrocardiograms (ECGs), and vital signs. AEs were

recorded using the MedDRA system of nomenclature and incidence rates tabulated by system organ class and preferred term. Treatment-emergent extrapyramidal symptoms (EPS) were also assessed using the Simpson-Angus Scale (SAS) [24] and the Abnormal Involuntary Movement Scale (AIMS) [25]. Effects on cognition were assessed using the Mini Mental State Examination (MMSE) [26]. Because of special concern about falling in this vulnerable population, falls were assessed at each occurrence using a modified Hendrich Fall Scale [27].

Statistical Analysis

Assuming a Bonferroni type I error rate of 2.5% to allow for multiple comparisons with placebo, power 80%, randomization ratio of 3:3:2, and estimated 10% dropout rate, the sample size required for each quetiapine arm was 115, and 77 for placebo, with an estimated total of 308 participants. A Simes-Hommel approach was used for the primary analysis and the comparison of quetiapine 200 mg/day to placebo was tested at $p = 0.025$. Only nominal p values were reported for secondary variables or secondary analyses, with no adjustments for multiplicity. Secondary efficacy measures were the CGI-C scores; the percentage of participants achieving at least a 40% reduction in PANSS-EC scores; the proportion of participants who were rated <3 on CGI-C; mean change from baseline to endpoint on the total and subscale scores for NPI-NH and CMAI.

Differences between quetiapine and placebo on the mean change scores in PANSS-EC, NPI-NH, and CMAI were evaluated using analysis of covariance (ANCOVA) with treatment group, geographic region, dementia diagnosis, and baseline score as covariates. Differences in CGI-C scores were evaluated using analysis of variance (ANOVA) with a model including treatment group, geographic region, and dementia diagnosis. Both ANCOVA and ANOVA analysis were performed at each study visit as well as at end of study. Adjustments were made for multiple comparisons with placebo at the final assessment, with nominal p values reported for secondary efficacy measures, including the time-dependent assessments at each study visit. The percentage of participants who achieved 40% reduction in baseline PANSS-EC score and the proportion of participants rated <3 on CGI-C were analyzed using Cochran-Mantel-Haenszel Chi-square techniques with treatment group and dementia diagnosis as factors in the analysis. Pre-planned exploratory analyses included evaluation of two other definitions of response based on a 30% and 50% decrease in PANSS scores from baseline.

Analyses of all efficacy assessments were conducted on the modified intention-to-treat (ITT) population, defined as randomized participants who received at least one dose of study medication and had at least one post-baseline assessment. Primary efficacy analyses were done using the LOCF approach for imputing missing data. Supportive analyses were conducted using the OC approach with no imputation for missing data; only those participants with an observation in a 7-day window centered around Week 10 were included in the endpoint analysis. A post hoc longitudinal analysis was also performed for the PANSS-EC using the Mixed Model Repeat Measure (MMRM) approach, incorporating a

banded Toeplitz covariance structure and fixed effects for time (visit) and treatment by time added to those for the ANCOVA. This approach incorporates in a single analysis all available data across time, assuming that missing data points are missing at random and estimate the Week 10 change from baseline based on the model and observed data at Week 10.

Safety and tolerability data, including SAS, AIMS, and MMSE change from baseline, were assessed using descriptive statistics.

Although subgroups based on diagnosis were incorporated as a factor in the analysis model and evaluated with the response to treatment Cochran-Mantel-Haenszel test, the formal analysis of the AD subgroup was a post hoc analysis to explore the effect in this subgroup of interest.

RESULTS

Participants

A total of 435 participants consented and were screened, 333 were randomized to quetiapine 200 mg/day ($n=117$), quetiapine 100 mg/day ($n=124$), or placebo ($n=92$) Fig. (1); all received treatment. Two hundred and fifteen participants (65%) completed the study; the completion rates were comparable among the three groups Fig. (1). The completion rates at the end of titration (Day 8) were also similar: 96% (quetiapine 200 mg/day), 95% (quetiapine 100 mg/day), and 98% (placebo). Seven participants were excluded from the efficacy analysis due to the absence of either baseline or post-baseline PANSS-EC scores; thus the modified ITT population consisted of 114 participants on quetiapine 200 mg/day, 120 on quetiapine 100 mg/day, and 92 on placebo.

The demographic and baseline characteristics were similar among the three treatment groups (Table 1). Participants were predominantly women (74%) and Caucasian (84%), with a mean age of 83 years; the majority (79%) had AD; the range of MMSE scores was 0-16 with a mean of 5.3. The mean scores for the behavioral measures at baseline were comparable among the three groups (Table 2). Additional baseline information is presented in Table 3.

Treatment

The mean duration of exposure to study medication was similar among the three groups (54 to 56 days). The use of concomitant medications was comparable across the three treatment groups: the percentage of patients who received benzodiazepines was 34% in the quetiapine 200 mg/day group, 35% in the quetiapine 100 mg/day group, and 42% in the placebo group. For antidepressants, the corresponding values were 44%, 44% and 47%, respectively, and for cholinesterase inhibitors, 39%, 32% and 34%, respectively.

Efficacy

Primary. Results for the primary endpoint showed a greater reduction from baseline to endpoint in the mean PANSS-EC score with quetiapine 200 mg/day compared with placebo. This difference was not significant using the LOCF analysis ($p=0.065$), but was significant using the OC analysis ($p=0.014$) [Table 2; Fig. (2)]. The reduction in

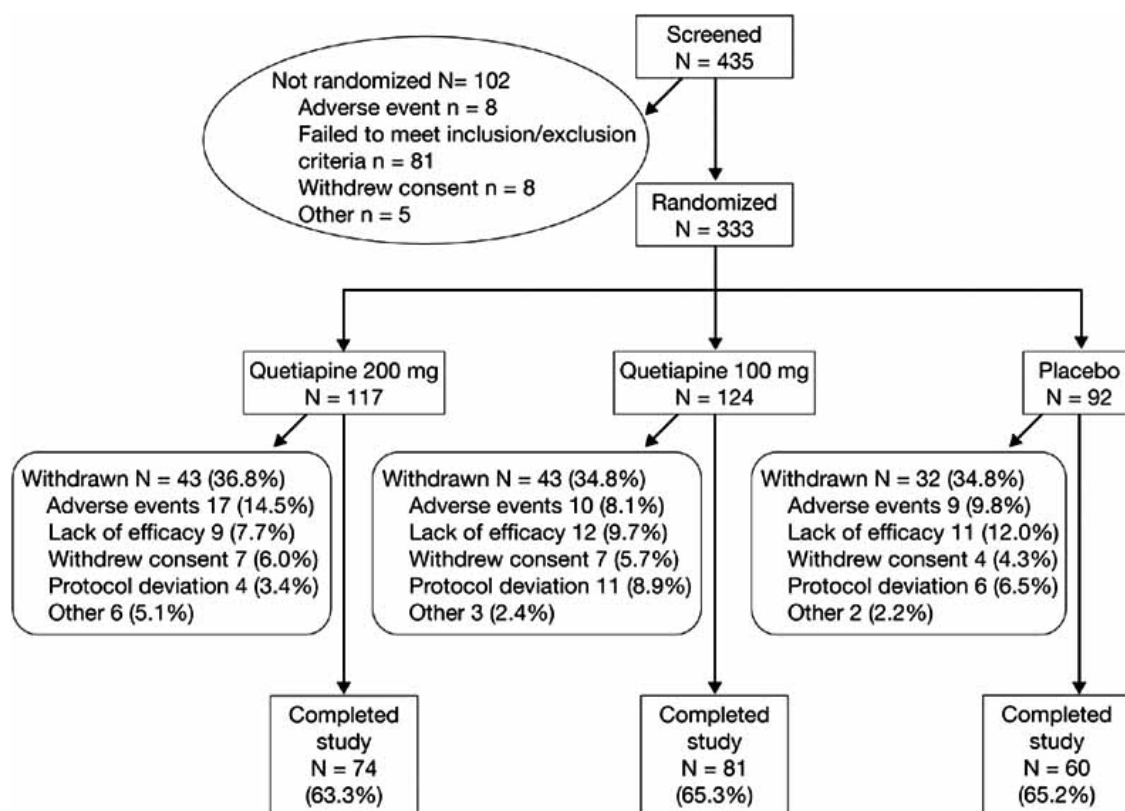


Fig. (1). Participant disposition.

Table 1. Demographic and Baseline Characteristics

Characteristic	Quetiapine 200 mg N=117	Quetiapine 100 mg N=124	Placebo N=92
Sex, N (%)			
Women	92 (78.6)	90 (72.6)	65 (70.7)
Men	25 (21.4)	34 (27.4)	27 (29.3)
Age, (years)			
Mean (SD)	83.5 (8.0)	83.0 (7.2)	83.2 (7.2)
Range	56-97	56-96	58-98
Race, N (%)			
Caucasian	95 (81.2)	107 (86.3)	78 (84.8)
African-American	14 (12.0)	9 (7.3)	4 (4.3)
Hispanic	7 (6.0)	7 (5.6)	8 (8.7)
Asian	1 (0.9)	1 (0.8)	1 (1.1)
Other	0	0	1 (1.1)
Diagnosis, N (%)			
AD	96 (82.1)	94 (75.8)	73 (79.3)
Vascular dementia	13 (11.1)	16 (12.9)	9 (9.8)
Mixed dementia	8 (6.8)	14 (11.3)	10 (10.9)
CGI-S score	N=109	N=115	N=87
Mean (SD)	4.7 (0.9)	4.7 (0.8)	4.8 (0.9)
MMSE Score	N=109	N=118	N=91
Mean (SD)	5.6 (3.6)	4.8 (4.0)	5.5 (4.0)

Table 2. Efficacy Measures: Baseline and Change from Baseline to Endpoint (LOCF/OC)

	Quetiapine 200 mg/day				Quetiapine 100mg/day				Placebo		
	n	Baseline Mean (SD)	Change LSM ^a (SE)	Effect size (95% CI) p value ^b	n	Baseline Mean (SD)	Change LSM ^a (SE)	Effect size (95% CI) p value ^b	n	Baseline Mean (SD)	Change LSM (SE)
Primary PANSS-EC total score											
LOCF	114	23.0 (4.3)	-5.7 (0.9)	-1.8 (-3.6 to 0.1) 0.065	120	23.1 (4.9)	-4.9 (0.8)	-1.0 (-2.8 to 0.9) 0.306	92	22.8 (4.3)	-3.9 (0.9)
OC	74	23.0 (4.3)	-7.9 (1.0)	-2.7 (-4.8 to -0.5) 0.014	83	23.1 (4.9)	-6.0 (0.9)	-0.8 (-2.9 to 1.3) 0.457	61	22.8 (4.3)	-5.2 (1.0)
Secondary CGI-C Scores											
LOCF	114	N/A	3.0 (0.2)	-0.5 (-1.0 to -0.1) 0.017	120	N/A	3.2 (0.2)	-0.3 (-0.7 to 0.2) 0.228	92	N/A	3.6 (0.2)
OC	74	N/A	2.4 (0.2)	-0.7 (-1.1 to -0.2) 0.002	83	N/A	3.0 (0.2)	-0.1 (-0.6 to 0.3) 0.561	61	N/A	3.1 (0.2)
NPI-NH total score											
LOCF	114	34.9 (15.8)	-9.7 (2.2)	-1.5 (-6.3 to 3.3) 0.546	120	38.5 (19.4)	-8.9 (2.1)	-0.6 (-5.4 to 4.1) 0.791	92	35.7 (15.9)	-8.2 (2.4)
OC	74	34.9 (15.8)	-14.7 (2.3)	-2.0 (-6.9 to 2.9) 0.416	82	38.5 (19.4)	-11.9 (2.1)	0.8 (-4.1 to 5.6) 0.751	62	35.7 (15.9)	-12.7 (2.4)
NPI-NH agitation score											
LOCF	114	7.4 (3.0)	-1.1 (0.5)	0.2 (-0.9 to 1.2) 0.745	120	7.4 (3.0)	-0.9 (0.5)	0.4 (-0.6 to 1.4) 0.467	92	7.7 (3.1)	-1.2 (0.5)
OC	54	7.4 (3.0)	-1.6 (0.6)	0.4 (-0.9 to 1.7) 0.576	55	7.4 (3.0)	-1.4 (0.5)	0.6 (-0.7 to 1.8) 0.380	46	7.7 (3.1)	-2.0 (0.6)
NPI-NH depression score											
LOCF	114	3.8 (2.5)	-0.4 (0.5)	-1.0 (-2.1 to 0.2) 0.108	120	5.1 (2.9)	-1.1 (0.5)	-1.6 (-2.8 to -0.4) 0.009	92	3.9 (2.4)	0.6 (0.5)
OC	16	3.8 (2.5)	-0.6 (0.9)	-1.8 (-4.1 to 0.5) 0.130	14	5.1 (2.9)	-1.0 (0.7)	-2.2 (-4.5 to 0.1) 0.060	7	3.9 (2.4)	1.2 (1.0)
NPI-NH psychosis score											
LOCF	114	8.6 (4.9)	-2.5 (0.9)	-0.0 (-1.9 to 1.9) 0.985	120	8.6 (5.6)	-1.8 (0.8)	0.7 (-1.2 to 2.5) 0.464	92	8.8 (4.6)	-2.5 (0.9)
OC	25	8.6 (4.9)	-3.8 (1.2)	-1.2 (-3.8 to 1.4) 0.354	31	8.6 (5.6)	-3.3 (0.9)	-0.7 (-3.1 to 1.6) 0.548	19	8.8 (4.6)	-2.6 (1.2)
NPI-NH-occupational disruptiveness scores											
LOCF	114	12.6 (6.9)	-3.6 (0.8)	-0.6 (-2.3 to 1.0) 0.460	120	13.3 (7.5)	-2.8 (0.7)	0.2 (-1.5 to 1.8) 0.839	92	12.4 (0.6)	-3.0 (0.8)
OC	74	12.7 (7.2)	-5.3 (0.8)	-1.1 (-2.8 to 0.6) 0.189	82	13.0 (6.6)	-3.8 (0.7)	0.4 (-1.3 to 2.1) 0.625	62	11.8 (6.0)	-4.2 (0.8)
CMAI total score											
LOCF	114	64.7 (19.1)	-11.0 (2.1)	-2.2 (-6.9 to 2.4) 0.352	120	64.0 (21.4)	-9.2 (2.0)	-0.4 (-5.0 to 4.2) 0.877	92	65.3 (21.23)	-8.8 (2.3)
OC	78	64.7 (19.1)	-13.2 (2.2)	-3.7 (-8.3 to 0.9) 0.119	86	64.0 (21.4)	-11.6 (2.0)	-2.0 (-6.6 to 2.5) 0.384	64	65.3 (21.23)	-9.5 (2.3)

(Table 2) contd....

	Quetiapine 200 mg/day				Quetiapine 100mg/day				Placebo		
	n	Baseline Mean (SD)	Change LSM ^a (SE)	Effect size (95% CI) p value ^b	n	Baseline Mean (SD)	Change LSM ^a (SE)	Effect size (95% CI) p value ^b	n	Baseline Mean (SD)	Change LSM (SE)
CMAI physically aggressive behavior											
LOCF	114	18.4 (8.4)	-3.7 (0.9)	-0.0 (-2.0 to 1.9) 0.976	120	18.3 (8.2)	-3.2 (0.9)	0.3 (-1.7 to 2.2) 0.796	92	19.4 (9.9)	-3.8 (1.0)
OC	78	18.4 (8.4)	-3.8 (0.9)	-0.4 (-2.3 to 1.6) 0.716	86	18.3 (8.2)	-3.9 (0.8)	-0.4 (-2.3 to 1.5) 0.677	64	19.4 (9.9)	-3.5 (1.0)
CMAI non-aggressive physical behavior											
LOCF	114	17.2 (7.7)	-4.0 (0.7)	-1.1 (-2.7 to 0.5) 0.182	120	17.2 (8.2)	-4.1 (0.7)	-1.5 (-3.1 to 0.1) 0.067	92	16.5 (7.2)	-2.9 (0.8)
OC	78	17.2 (7.7)	-2.9 (0.9)	-1.4 (-3.3 to 0.5) 0.146	86	17.2 (8.2)	-3.5 (0.8)	-2.0 (-3.9 to -0.2) 0.033	64	16.5 (7.2)	-1.4 (0.9)
CMAI verbal aggression											
LOCF	114	16.1 (7.4)	-3.4 (0.8)	-1.4 (-3.1 to 0.3) 0.111	120	15.9 (7.5)	-3.1 (0.8)	0.1 (-1.6 to 1.7) 0.942	92	16.1 (8.1)	-3.4 (0.8)
OC	78	16.1 (7.4)	-5.2 (0.9)	-1.7 (-3.2 to 0.3) 0.101	86	15.9 (7.5)	-3.4 (0.9)	0.1 (-1.8 to 2.1) 0.883	64	16.1 (8.1)	-3.6 (1.0)

^aLeast square mean (LSM) change; ^bversus placebo; LOCF, last observation carried forward; OC, observed cases; SD, standard deviation; SE, standard error; CI, confidence interval.

Table 3. Tolerability Measures: Change from Baseline to Final Visit

Measures	Quetiapine 200 mg N=117		Quetiapine 100 mg N=124		Placebo N=92	
	Mean Baseline (SD)	Mean Change (SD)	Mean Baseline (SD)	Mean Change (SD)	Mean Baseline (SD)	Mean Change (SD)
MMSE total score	5.6 (3.6)	0 (2.5)	4.8 (4.0)	0 (2.8)	5.5 (4.0)	0 (2.0)
AIMS	2.1 (4.6)	0.4 (3.95)	2.2 (4.8)	-0.3 (3.26)	1.4 (3.1)	-0.1 (1.90)
SAS	4.1 (4.8)	-0.2 (3.45)	4.5 (5.4)	-0.7 (3.09)	4.0 (5.5)	0.1 (2.44)
Fasting glucose, mg/dL	96.7 (31.5)	2.0 (31.7)	95.7 (28.7)	-1.8 (29.0)	93.2 (20.6)	1.0 (26.3)
Body weight, kg	63.4 (14.8)	0 (3.0)	62.1 (13.1)	0.4 (3.3)	62.5 (12.3)	-0.8 (2.7)
Body mass index, kg/m ²	24.5 (4.4)	0 (1.1)	23.9 (4.5)	0.2 (1.3)	23.3 (3.4)	-0.3 (1.1)

PANSS-EC scores was not significant for quetiapine 100 mg/day versus placebo with either analytic approach. The post hoc MMRM analysis demonstrated that quetiapine 200 mg/day was statistically superior to placebo in reducing the PANSS-EC score at the end of treatment (p=0.005), and

reconfirmed that quetiapine 100 mg/day did not differentiate from placebo.

Secondary: Participants treated with quetiapine 200 mg/day showed significantly greater improvement on the CGI-C score from baseline to endpoint than those in the

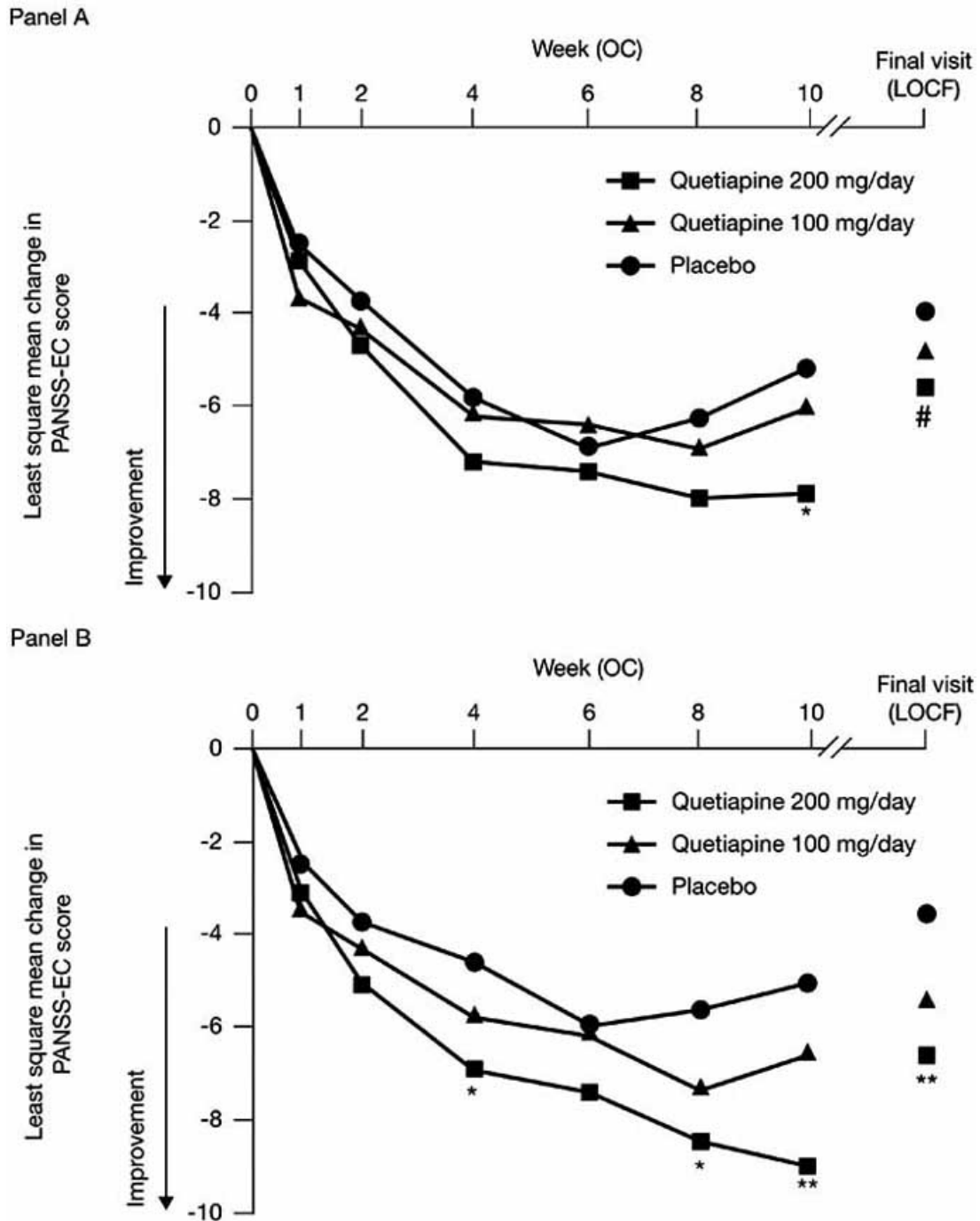


Fig. (2). PANSS-EC score: (Panel A) mean change from baseline in all participant populations $*p = 0.014$; $\#p = 0.065$ vs placebo and (Panel B) in participants with Alzheimer's disease $*p < 0.05$; $**p = 0.01$ vs placebo. PANSS-EC, Positive and Negative Symptom Scale – Excitement Component; LOCF, last observation carried forward. All participant population: quetiapine 200 mg/day (n=114, LOCF; n=74, OC), quetiapine 100 mg/day (n=120, LOCF; n=83, OC), placebo (n=92, LOCF; n=61, OC). Alzheimer's disease population: quetiapine 200 mg/day (n=93, LOCF; n=64, OC), quetiapine 100 mg/day (n=89, LOCF; n=63, OC), placebo (n=73, LOCF; n=47, OC).

placebo group in both LOCF ($p=0.017$) and OC ($p=0.002$) analyses (Table 2, Fig. (3)). Time-dependent analyses showed that this effect was significant at Weeks 2, 8, and 10 Fig. (3). CGI-C scores for those treated with quetiapine

100 mg/day were inconsistent and did not differentiate from placebo at endpoint in either analysis, although there were significant differences at earlier timepoints (Table 2, Fig. (3)).

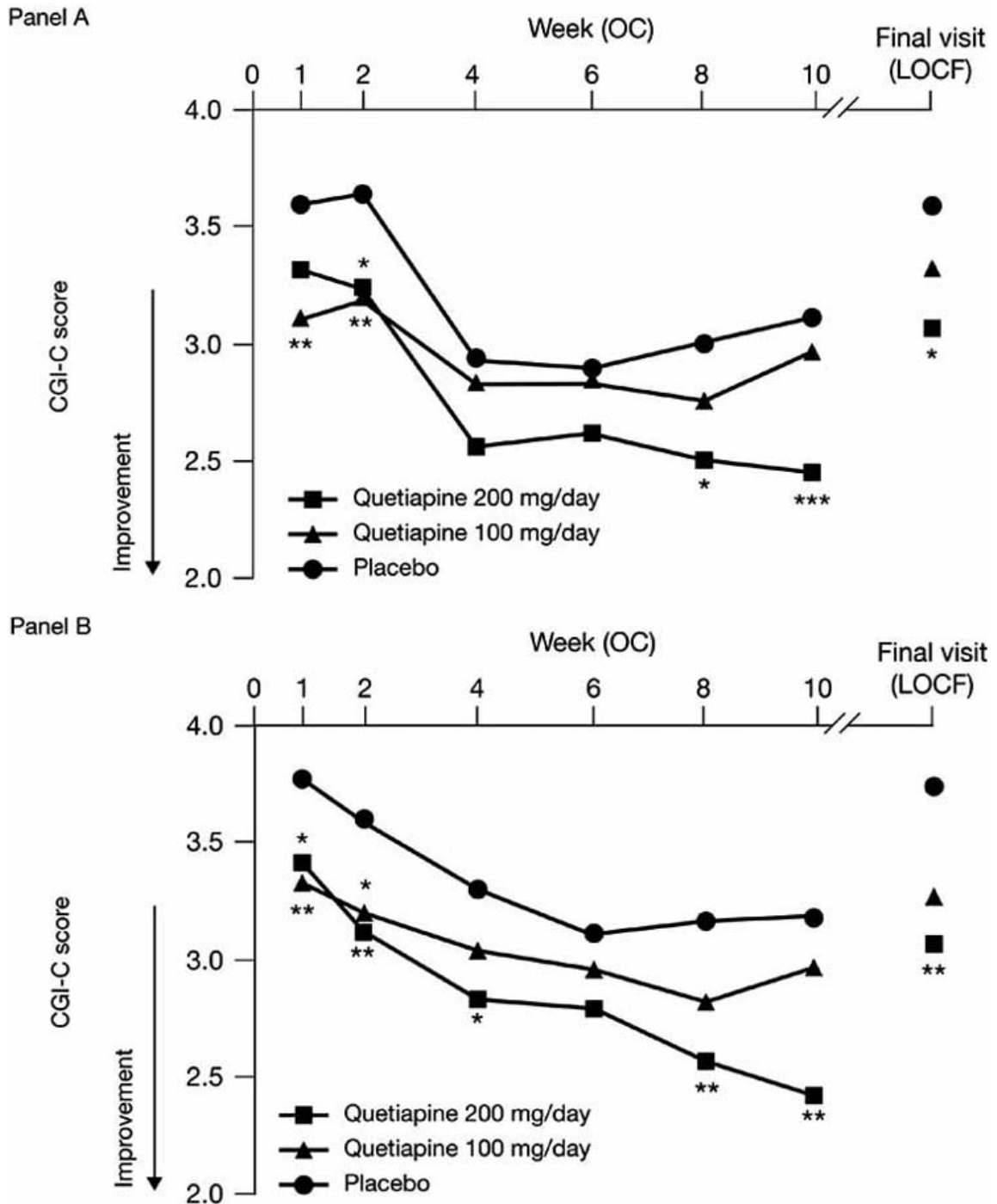


Fig. (3). CGI-C score: mean score at Week 10 (OC) or study withdrawal (LOCF) in all participant populations $p < 0.05$; $p = 0.01$ vs placebo (Panel A) and in participants with Alzheimer's disease (Panel B) $p < 0.05$; $p < 0.01$ vs placebo. CGI-C, Clinical Global Impressions of Change. All participant population: quetiapine 200 mg/day (n=114, LOCF; n=74, OC), quetiapine 100 mg/day (n=120, LOCF; n=83, OC), placebo (n=92, LOCF; n=61, OC). Alzheimer's disease population: quetiapine 200 mg/day (n=93, LOCF; n=64, OC), quetiapine 100 mg/day (n=89, LOCF; n=63, OC), placebo (n=73, LOCF; n=47, OC).

A significantly greater percentage of participants in the quetiapine 200 mg/day group (52%, 59/114) were rated "moderately" or "markedly" improved at endpoint on the

CGI-C scale (CGI-C <3) compared with placebo (30%, 28/92, $p=0.002$) using the LOCF analysis Fig. (4). This difference from placebo was even greater in the OC analysis

(71%, 53/75 vs 41%, 25/61 with placebo; $p < 0.001$). Quetiapine 100 mg/day was not superior to the placebo group in the percentage of participants with moderate/marked improvement using either LOCF or OC analyses Fig. (4).

There were no significant between-group differences in the proportions of participants with 40% reductions on PANSS-EC from baseline to endpoint. For the LOCF analysis, response rates were 38%, 33%, and 29% for quetiapine 200 mg/day, quetiapine 100 mg/day, and placebo, respectively. The corresponding values for the OC analysis were 49%, 39%, and 38%, respectively. In a predefined exploratory analysis using 30% reduction as the cut-off point, the proportion of participants achieving this response in the LOCF analysis was significantly greater in the quetiapine 200 mg/day group (51%, 58/114) compared with the placebo group (34%, 31/92 $p = 0.014$), but not in the quetiapine 100 mg/day group (44%, 53/120, $p = 0.111$). Similar results were seen with the OC analysis: 69% (52/75) responded in the quetiapine 200 mg/day group compared with 43% (26/61) in the placebo group ($p = 0.002$); 53% (44/83) responded in the quetiapine 100 mg/day group ($p = 0.203$ vs placebo).

Improvements on NPI-NH and CMAI total and subscale scores were observed in all treatment groups with no drug-placebo differences (Table 2).

Efficacy in the AD Subgroup

Treatment with quetiapine 200 mg/day resulted in significantly greater reductions in PANSS-EC scores from baseline to endpoint compared with placebo in both LOCF ($p = 0.005$) and OC analyses ($p = 0.001$) in the 255 participants with AD. When an additional analysis was carried out, replacing the protocol-specified dementia diagnosis with the dichotomized AD and ‘other’ (vascular and mixed dementia) terms in the model, there was no statistical significance; but if the interaction term was placed in the model instead, then

the dementia type by treatment interaction was a statistically significant contributor to the overall variance observed ($p = 0.04$). This interaction indicated that AD patients were responding differently to treatment and a post hoc evaluation of this population was appropriate.

Time-dependent analyses showed that the effect of the 200 mg/day dose on PANSS-EC scores was significant versus placebo at Weeks 4, 8, and 10 Fig. (2). The drug-placebo differences at endpoint were not significant for quetiapine 100 mg/day in either the LOCF ($p = 0.086$) or the OC ($p = 0.248$) analyses.

Improvement in the CGI-C scores from baseline to endpoint was significantly greater for quetiapine 200 mg/day than placebo in both LOCF ($p = 0.006$) and OC analyses ($p = 0.002$), an effect seen at Weeks 1, 2, 4, 8, and 10 Fig. (3). Quetiapine 100 mg/day was not superior to placebo at endpoint in either the LOCF ($p = 0.056$) or OC ($p = 0.366$) analyses.

Significantly higher percentages of participants in both the quetiapine 200 mg/day group and the 100 mg/day group were rated ‘very much improved’ or ‘much improved’ on the CGI-C (< 3) at endpoint compared with placebo in the LOCF analysis ($p < 0.05$). In the OC analysis this difference was significant in the quetiapine 200 mg/day group ($p < 0.05$ vs placebo) but not in the 100 mg/day group ($p = 0.257$).

The proportion showing 40% reduction in PANSS-EC total scores was significantly greater for quetiapine 200 mg/day (40%, 37/93) than for placebo (23%, 17/73, $p = 0.025$); the difference between quetiapine 100 mg/day (34%, 30/89) and placebo was not significant ($p = 0.147$; LOCF analysis). Similarly, with the OC analysis, 52% (33/64) responded in the quetiapine 200 mg/day group compared with 34% (16/47) in the placebo group ($p = 0.067$) and the response in the quetiapine 100 mg/day group was not

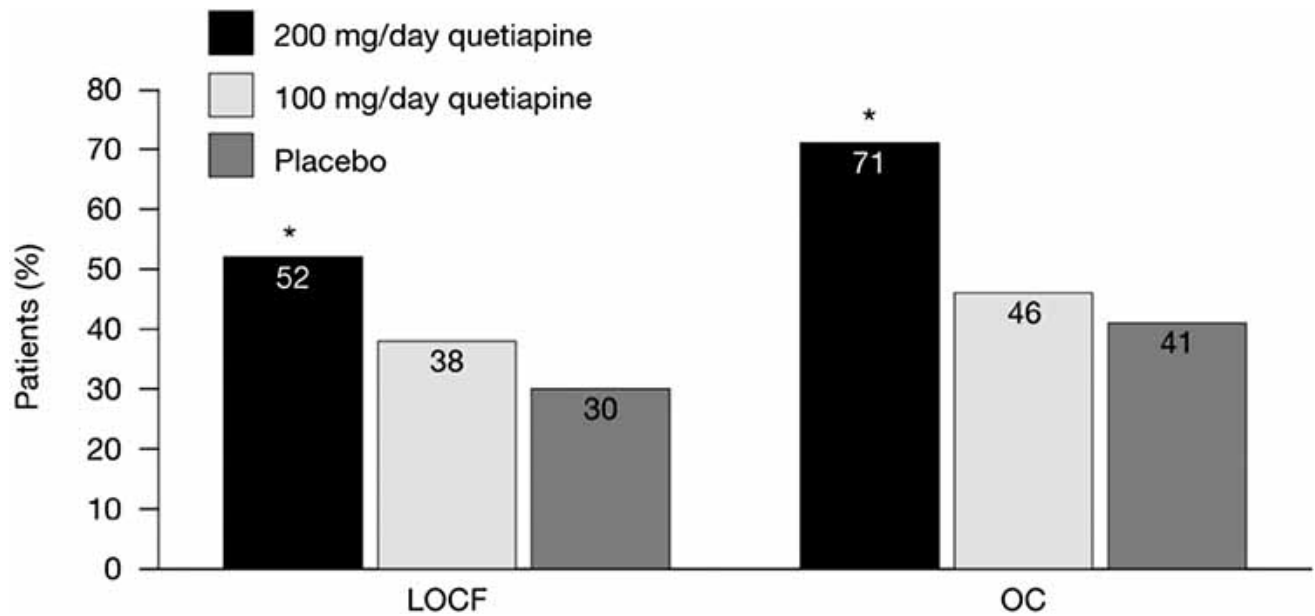


Fig. (4). Clinical Global Impressions of Change (CGI-C) response rate: percentage of participants rated ‘much improved’ or ‘very much improved’ in all participant populations * $p < 0.05$ vs placebo.

significantly different to placebo (40%, 25/63; $p=0.547$). Using 30% reduction as alternative cut-off criteria, in the LOCF analysis both quetiapine 100 mg/day (47%, 42/89) and 200 mg/day (56%, 52/93) produced significantly higher response rates compared with placebo (27%, 20/73, $p<0.05$). While in the OC analysis response was significantly higher in the quetiapine 200 mg/day group (75%, 48/64 vs 38%, 18/74 with placebo; $p<0.001$) but not in the quetiapine 100 mg/day group (56%, 35/63; $p=0.074$ vs placebo).

There were no drug-placebo differences in NPI-NH and CMAI total scores for either dose of quetiapine with either the LOCF or OC analysis.

Tolerability and Safety

The overall rates of AEs were similar among three treatment groups (Table 4). The percentage of participants withdrawing from the study due to AEs did not differ significantly across the three groups Fig. (1). The rates of serious AEs were 6.8% (quetiapine 200 mg/day), 11.3% (quetiapine 100 mg/day), and 9.8% (placebo). AEs occurring in >5% of participants are reported in Table 4. Somnolence, sedation, constipation, vomiting and abnormal gait were reported by more patients in the quetiapine groups, and rash, decreased

weight, back pain, chest pain, dyspepsia and pneumonia were reported by more patients in the placebo group. Because of special concern about the consequences of falls, supplemental information was obtained using the Modified Hendrich Fall Scale. [27] The rates of visible injuries sustained as a result of falls were 26.4% for quetiapine 200 mg/day, 40% for 100 mg/day, and 37.5% for placebo; the rates for head injuries were 3.8%, 10.9%, and 10%, respectively. More participants in the quetiapine groups experienced somnolence and sedation than those in the placebo group; most of these episodes (94%) were rated mild or moderate in intensity and four receiving quetiapine were withdrawn from the study because of either somnolence or sedation, compared with no participants in the placebo group. Gait abnormalities were reported only in the quetiapine groups. In all cases, these were described as “unsteady gait” or “worsening of unsteady gait”; 75% of these events were rated as “mild” and one resulted in study withdrawal. Vomiting was reported more frequently in the quetiapine groups compared with the placebo group. Intensity was mild for the majority of participants in both the quetiapine (72%) and placebo (67%) groups; no participant withdrew as a result of this.

Table 4. Adverse Events Occurring in 5% of Participants

Adverse event (%) ^a	Quetiapine 200 mg N=117	Quetiapine 100 mg N=124	Placebo N=92
Any adverse events	84.6	80.6	80.4
Fall ^b	26.5	25.8	26.1
Lethargy	11.1	6.5	3.3
Skin laceration	11.1	15.3	14.1
Somnolence	9.4	8.1	2.2
Vomiting	9.4	5.6	3.3
Sedation	7.7	3.2	3.3
Urinary tract infection	7.7	16.1	7.6
EPS ^c	6.8	4.8	5.4
Decreased appetite	6.0	1.6	3.3
Constipation	6.0	5.6	1.1
Peripheral edema	5.1	7.3	6.5
Upper respiratory tract infection	5.1	4.8	4.3
Cardiovascular ^d	5.1	1.6	4.3
Gait abnormalities	5.1	4.8	0
Nausea	4.3	5.6	2.2
Headache	3.4	5.6	3.3
Weight decreased	3.4	4.0	5.4

^aDenominators used are the safety population for each group; ^bFalls were recorded separately to other AEs; ^cCombined incidence of: tremor, restlessness, muscle rigidity, akathisia, akinesia, dyskinesia, cogwheel rigidity, extrapyramidal disorder and tardive dyskinesia; ^dCombined incidence of complete atrioventricular block, bradycardia, left bundle branch block, congestive cardiac failure, coronary artery disease, mitral valve incompetence, myocardial infarction and pericardial effusion.

Table 5. Description of CVAEs and Participants' Clinical History

Treatment group	Description of CVAE	Clinical history
Quetiapine 200 mg/day	Subdural hematoma	Hypertension, subdural hematoma, venous insufficiency, hypercholesterolemia, hypothyroidism, depression
Quetiapine 100 mg/day	Cerebrovascular accident with left hemiparesis, subsequent cerebral infarction 2 weeks later and died.	Hypertension, atherosclerotic cardiovascular disease, prior MI, peripheral vascular disease, type II diabetes mellitus, anemia, gastritis, glaucoma, bilateral below-the-knee amputations
Placebo	Transient ischemic attack (cerebral ischemia)	Transient ischemic attacks, falls, fractures, atrial fibrillation, edema, chronic obstructive pulmonary disease

The numbers of participants with orthostatic hypotension as an AE were: three (2.6%) in the quetiapine 200 mg/day group (one withdrew after reaching 100 mg/day on Day 5), one (0.8%) in the quetiapine 100 mg/day group, and one (1.1%) in the placebo group. These events occurred only during the titration period. The incidence of CVAEs was similar among the three treatment groups: 0.9% (1/117) for quetiapine 200 mg/day, 0.8% (1/124) for quetiapine 100 mg/day, and 1.1% (1/92) for placebo. All affected had risk factors including a prior history of cardiovascular disease. Details of these participants' clinical history and a description of the CVAEs are summarized in Table 5.

Changes on other safety and tolerability measures are presented in Table 4. There were no between-group differences in the change from baseline on MMSE, AIMS, or SAS scores. Changes in fasting glucose, weight, and body mass index were minimal and similar for all groups. In addition, there were no significant between-group differences in hematology, clinical chemistry, or ECG parameters. There were no reports of QTc interval prolongation (>450 msec) in any group.

There were 19 deaths in the study; 9 occurred during the double-blind treatment period, and 10 occurred during the 30-day follow-up period. None were considered by the investigators to be related to treatment; 2 participants in the quetiapine group were residents of hospice care. The mortality rates were 5.1% (quetiapine 200 mg/day), 7.3% (quetiapine 100 mg/day), and 3.3% (placebo). The relative risk for death on quetiapine versus placebo was 2.08 (95% CI: 0.61-7.16); the difference was not statistically significant (exposure was 36.4 [quetiapine] and 14.1 [placebo] participant years). Cardiac-related deaths occurred at similar rates for quetiapine (1.6%) and placebo (1.1%); 4 participants in the quetiapine groups (1.6%) and none in the placebo group died as the result of infection. No specific organ system was consistently implicated in the cause of death.

The safety and tolerability profile of participants in the AD subgroup were similar to that in the overall participant population presented above.

DISCUSSION

The primary objective of this study was to evaluate the efficacy of two fixed doses of quetiapine compared with placebo in treating agitation in patients with dementia. The effect size for quetiapine 200 mg/day for the primary end-

point, PANSS-EC, was 1.8 units; this is of a similar magnitude to the improvement seen with intramuscular olanzapine in studies of elderly patients with acute agitation [19]. Although the change in PANSS-EC in the 200 mg group missed significance in the LOCF population, it was significant in the OC analysis. More importantly, there was a statistically significant improvement in the CGI-C score, a measure of actual clinical improvement, in the quetiapine 200 mg/day group for both analyses. The anti-agitation effect was evident on some measures by Week 1 of treatment. In the AD subgroup in particular, a more robust response was observed compared with the overall population that included participants with vascular and mixed dementia. The smaller number of participants with non-AD dementias reduced the power to discern a treatment effect in this subgroup. Differences in the pathological processes that underlie these dementias may have also contributed to differences in treatment response. The efficacy of quetiapine 200 mg/day, however, was not seen consistently across all secondary measures of agitation such as the NPI-NH and CMAI. The basis for these discrepancies is unclear but may be related to the fact that the latter two are caregiver rating scales with different sensitivities. Treatment with quetiapine 100 mg/day did not result in a significant reduction in agitation.

Rapid titration to 200 mg/day by Day 8 with no subsequent dose adjustment was generally well tolerated. Despite the use of forced titration and fixed doses, the overall safety and tolerability profile of the present study was similar to the earlier study that used a slower titration and flexible doses [15]. Withdrawals due to AEs (7.8% vs 10.5%) and rates of falls (28% in each study) were similar in the current and previous study.

Somnolence and sedation were reported more often in the quetiapine groups compared with the placebo group, which is consistent with previous findings [15]. These effects usually occurred early in treatment, were generally mild in intensity, and the majority of participants became tolerant to this side effect. Somnolence and sedation alone seldom led to study withdrawal and may be beneficial in the treatment of some agitated patients. Other adverse events that were reported more frequently in the quetiapine groups (constipation and vomiting) are consistent with the known side-effect profile of quetiapine, and were most often mild in severity and did not usually lead to withdrawal. Gait abnormalities were also reported more frequently with quetiapine; however, this side effect led to withdrawal in only one patient,

and there was no difference between treatment groups in the incidence of falls.

Interestingly, the rate of postural hypotension was lower (1.6 %) in this study compared with the previous study (7%). The reason for this is unclear, but may be related to the stricter regimen of titration imposed in the current study. The similar safety and tolerability profiles of the fast and slow titration trials suggest that the occurrence of these AEs was not likely a consequence of titration. In addition, the comparable rates between the quetiapine 100 mg/day and 200 mg/day dose groups in the current study on rates of falls, hypotension, sedation, EPS, CVAEs, and cardiovascular AEs suggest an absence of dose-dependency for tolerability and safety.

Quetiapine did not worsen cognition in this population in this study or in our previous multicenter, placebo-controlled trial [15] contrary to the results from a smaller, more recent study [28]. Rates of EPS were similar for quetiapine and placebo in the present study. This observation suggests that quetiapine may have a relative tolerability advantage in this vulnerable patient population, which is at a higher risk of developing EPS than those without dementia [29].

Recently, the use of atypical antipsychotics has been found to be associated with an increased risk of CVAEs compared with treatment with placebo in this population (unpublished data^{iv}) [30-36]. Recent analyses of data from studies of risperidone, olanzapine and aripiprazole showed that, compared with placebo, all three were associated with an increased risk of CVAEs in elderly patients with dementia (unpublished dataⁱⁱⁱ). The incidence of CVAEs in the present quetiapine study was comparable among the three treatment groups, and findings of a combined analysis of the present study with the previous placebo-controlled study did not discern a significantly increased risk of CVAE with quetiapine [37].

The FDA recently performed an analysis of 17 placebo-controlled trials with atypical antipsychotics (risperidone, olanzapine, quetiapine, and aripiprazole) in elderly patients with dementia and behavioral problems. They concluded that these agents are associated with an increase in mortality and directed that their labeling be changed to reflect this [13]. The incidence of mortality in patients treated with quetiapine in the current study was numerically, but not statistically higher than in the placebo group; similar results were obtained in a pooled analysis of the current study and the previous placebo-controlled study (n=568) [15]. However, larger studies are required to allow more definitive conclusions to be reached and in the meantime, all atypical antipsychotics should be used with caution in elderly patients with dementia.

In terms of age, sex and disease severity, the population of participants used in the current study is generally representative of patients with dementia and agitation. Patients with unstable medical conditions were excluded from the study; consequently, the results cannot be extrapolated to all

patients seen in long-term care facilities in general clinical practice. In addition, there are no data available beyond 10 weeks of treatment with quetiapine.

In conclusion, this randomized, double-blind, placebo-controlled, fixed-dose study suggested that quetiapine 200 mg/day was an effective treatment for agitation associated with dementia in patients residing in long-term care facilities; those with AD appeared to be particularly responsive to treatment with quetiapine. Participants tolerated rapid titration and the AEs were not dose dependent. However, caution should be exercised given the concerns regarding increased mortality with atypical antipsychotics in this vulnerable patient population.

ACKNOWLEDGEMENT

AstraZeneca Pharmaceuticals supported this study (5077US/0046).

ABBREVIATIONS

AD	=	Alzheimer's disease
ADCS-CGI-C	=	Alzheimer's Disease Cooperative Study Clinical Global Impression of Change
AE	=	Adverse event
AIMS	=	Abnormal Involuntary Movement Scale
ANCOVA	=	Analysis of covariance
ANOVA	=	Analysis of variance
CI	=	Confidence interval
CMAI	=	Cohen-Mansfield Agitation Inventory
CVAE	=	Cerebrovascular adverse event
DSM-IV	=	Diagnostic and Statistical Manual of Mental Disorders-fourth edition
ECG	=	Electrocardiogram
EPS	=	Extrapyramidal symptoms
FDA	=	Food and Drug Administration
ITT	=	Intention-to-treat
LOCF	=	Last observation carried forward
LSM	=	Least square mean
MMRM	=	Mixed Model Repeat Measure
MMSE	=	Mini-Mental State Examination
NINCDS/ADRDA	=	National Institute of Neurological and Communicative Disorders and Stroke/the Alzheimer's Disease and Related Disorders Association
OC	=	Observed case
PANSS	=	Positive and Negative Syndrome Scale
SAS	=	Simpson-Angus Scale

^{iv} Racoosin JA. Evaluating a safety signal in the postmarketing period: cerebrovascular adverse events associated with risperidone and olanzapine. Oral presentation at the 17th Annual Meeting of the American Association for Geriatric Psychiatry, Baltimore, MD, 21-25, February 2004.

SD = Standard deviation

SE = Standard error

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