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A randomized controlled trial of quetiapine versus placebo in the treatment of delirium☆

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Abstract

Background: Delirium is a commonly occurring complex neuropsychiatric disorder. Evidence for its treatment based on randomized controlled trials (RCTs) is poor. **Aims:** To determine the efficacy and acceptability of quetiapine in the treatment of delirium. **Method:** A double-blind, RCT was conducted. A total of 42 patients were randomized to quetiapine or a placebo group. The primary outcome measure was the Delirium Rating Scale Revised 98. Other scales used were the Brief Psychiatric Rating Scale, Mini-Mental State Examination and Clinical Global Improvement. In order to account for missing data, a nonlinear mixed-effects model was used to estimate the difference between the two groups. **Results:** The quetiapine group improved more rapidly than the placebo group. Specifically, the quetiapine group recovered 82.7% faster (S.E. 37.1%, P=.026) than the placebo group in terms of DRS-R-98 severity score. In terms of the DRS-R-98 noncognitive subscale, the quetiapine group improved 57.7% faster (S.E. 29.2%, P=.048) than the placebo group. **Conclusions:** Quetiapine has the potential to more quickly reduce the severity of noncognitive aspects of delirium. This study was underpowered for treatment comparisons at specific points in time but nonetheless detected significant differences when analyzing the whole study period. While it is not possible to draw definitive conclusions, further larger studies exploring the use of quetiapine in other delirium populations seem justified. Larger increments in the dose of quetiapine may yield even stronger results.

Keywords: Delirium; RCT; Randomized Control Trial; Quetiapine; Acute Confusion; Dementia and delirium; Atypical antipsychotics; Non-linear mixed-effects model; DRS-R-98

Introduction

Delirium is a common disorder that occurs in 11–42% of general medical inpatients [1] and up to 50% of the hospitalized elderly [2]. It is a complex neuropsychiatric syndrome that includes a broad range of cognitive and noncognitive symptoms. Historically, treatment has focused on underlying causes. It is also increasingly appreciated that delirium can be persistent with an independent impact on functional capacity, morbidity, and mortality. Delirium

☆ Declaration of interest: This is an investigator initiated study. In terms of the Clinical Trials Directive, AstraZeneca UK has legally sponsored and provided funding for recruitment of a research assistant and trial medication.

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remains understudied, especially in relation to pathophysiology and treatment.

With detection and correction of the underlying cause, the standard management of delirium includes nonpharmacological and pharmacological treatment [3], but when and what drugs to use remains uncertain, reflecting a lack of well-designed efficacy studies. A small open label study suggests that haloperidol and olanzapine may be effective in the treatment of delirium [4]. In two RCTs, olanzapine was recommended as a safe alternative to haloperidol in intensive care for managing delirium [5,6]. In a case series of 12 patients, quetiapine was found to be beneficial with improvement shown on Delirium Rating Scale scores along with improvement in scores of the Mini-Mental State Examination (MMSE) and Clock Drawing Test [7]. An open-labeled randomized prospective flexible dosing study found similar responses for amisulpride and quetiapine [8]. The mean daily dose for the quetiapine group was 113 mg/day [8]. In a more recent case series of 22 patients, a mean (S.D.) dose of quetiapine was 45.7 (28.7) mg/day [9].

Prophylactic effects of haloperidol [10] and donepezil [11] have been studied in placebo-controlled studies as well. The fluctuating nature of delirium and its potential for spontaneous recovery as medical problems improve make placebo-controlled studies especially important in ascertaining the efficacy of drug-treatments.

We report a double blind randomized, placebo-controlled trial to determine the efficacy and acceptability of quetiapine in the treatment of incident delirium in general hospital inpatients with or without minor pre-existing cognitive deficits.

Methodology

Full ethics committee approval was obtained for this investigator initiated study to include participants without mental capacity subject to relative's assent. The South East Wales Research and Ethics Committee and the Cardiff and Vale National Health Service (NHS) Trust Research and Development department formally approved the trial. AstraZeneca UK sponsored the study and provided funding for a research assistant, trial medication, and the randomization codes.

Sample size calculations indicated that 34 patients in each treatment group were required to have a 95% power to detect a mean five-point difference on the Delirium Rating Scale Revised 98 (DRS-R-98) [12] between the two groups at the 0.05 confidence level assuming a standard deviation of 5.6 at a specific time point.

Screening for delirium was conducted by daily contact with medical, surgical and orthopedic wards at the University Hospital of Wales by a research assistant. An attempt was made to recruit those who met the *DSM-IV* criteria for delirium on the same day if they had a DRS-R-98 total score of 15 or more. Individuals with major pre-existing cognitive deficits, alcohol withdrawal, pre-existing psychosis, substance dependence, inability to comply with the constraints of the trial, or who were on medication that interacted with quetiapine were excluded from the study. The nature and degree of any pre-existing cognitive deficits were determined by reviewing clinical notes and by obtaining information from a reliable informant. Informed consent was obtained from participants with mental capacity.

The DRS-R-98 total mean score was the primary outcome measure. This score was used to evaluate improvement at each contact. Secondary outcome measures included the MMSE, the Brief Psychiatric Rating Scale (BPRS) and the Clinical Global Improvement (CGI). Tolerability was assessed by using the Abnormal Involuntary Movements Scale (AIMS) and clinical examination. The participants were assessed on Days 1, 2, 3, 4, 7, and 10. A follow-up assessment was also undertaken on Day 30. Physical status and investigations were considered at each time point by reviewing the medical case notes.

After collecting baseline data, participants were blindly randomized to a flexible dosing regime of 25 mg once daily oral quetiapine or a matching placebo tablet with dose titration of 25 mg/day to a maximum daily dose of 175 mg in divided doses. Computer-generated randomization codes were kept in sealed envelopes at the University Hospital of Wales' Pharmacy. In addition, a set of individual treatment codes was kept by the Scottish Poisons Information Bureau, Royal Infirmary Edinburgh, for emergency out-of-hours use only. The dose of quetiapine was only increased if the DRS-R-98 and clinical condition did not show any improvement. In addition to the clinical response and tolerability, information from nursing and medical staff was also considered prior to dose changes. The decision to increase the dose was taken by the clinicians involved in the trial up to a maximum of 10 days after recruitment. If the treatment was successful and symptoms were resolved as shown by improvement in the DRS-R-98 and clinical condition, the dose was down-titrated in the reverse pattern from initial titration.

To account for the noncompleters, due to various reasons given below, it was important to take into account missing data and the improvement in delirium with or without medication; we used non-linear, mixed-effects model to estimate differences in recovery trajectories between treatment groups. Initially, we considered models that allowed different starting and long-term mean values in the two treatment groups; however, no significant evidence of such differences was found. The final models therefore took the form

$$\mathrm{outcome_i}(t) = (f_0+f_i) + (\mathrm{s_0+s_i})-(\mathrm{f_0+f_i})\ \exp{-\mathrm{r}(1+\mathrm{a}\ \mathrm{x_i})\mathrm{t}+e_i(t)}$$

where s_0 is the overall mean starting value; s_i is a subject-specific deviation from this starting value for the ith individual; f_0 and f_i are the equivalent parameters describing the overall mean and subject-specific deviation from the long-term prognosis; t represents the elapsed (calendar) time from the Day 1 of inclusion in the trial; r describes the rate at which the placebo group progresses from starting value to long-term prognosis; x_i indicates the treatment group of

Table 1
Demographic characteristics

Demographic characteristic		Quetiapine (*n*=21)	Placebo (*n*=21)	Total (*n*=42)
Sex: *n* (%) of patients	Male	6 (28.6)	6 (28.6)	12 (28.6)
	Female	15 (71.4)	15 (71.4)	30 (71.4)
Age	Mean (S.D.)	84.1 (9.45)	84.3 (7.16)	84.2 (8.28)
	Range	58 to 95	71 to 98	58 to 98
DRS-R-98 <15 *n* (%) on Day 7		18 (85.7%)	17 (80.9%)	
Maximum mean dose of quetiapine (Day 4)		40 mg		
No. of patients prescribed Lorazepam		4		

subject *i*; and *a* describes the difference in recovery rate in the quetiapine group. If $a>0$, the quetiapine group recovers more quickly; if $a=0$, there is no difference in recovery trajectories, and if $a<0$ the quetiapine group recovers more slowly. For instance, if $a=1$, then the quetiapine group would recover twice as quickly as the placebo group.

We reiterate that, following nonsignificant tests of inequality, the quetiapine and placebo groups were assumed to have the same mean response at baseline in all nonlinear models. Note, however, that as the BPRS and CGI measurements were only made at three time points, they were not suitable for analysis using non-linear models. For BPRS and CGI, therefore, the treatment groups were compared on the three available measurements occasions.

Statistical Package R and SPSS (Version 16) were used for the analyses.

Results

Between June 2003 and April 2005, 372 patients were screened to recruit 42 (21 in each group) patients for this study. Reasons for exclusion were a score less than 15 on the DRS-R-98, inability to obtain relative's assent, physical illness of a severity preventing recruitment into the study, and impairment of mental capacity. Only one patient was able to consent.

Nineteen of the recruited sample had undergone a surgical operation. Others had a medical cause for admission. Of the 19 who had surgery, 14 had undergone an orthopedic

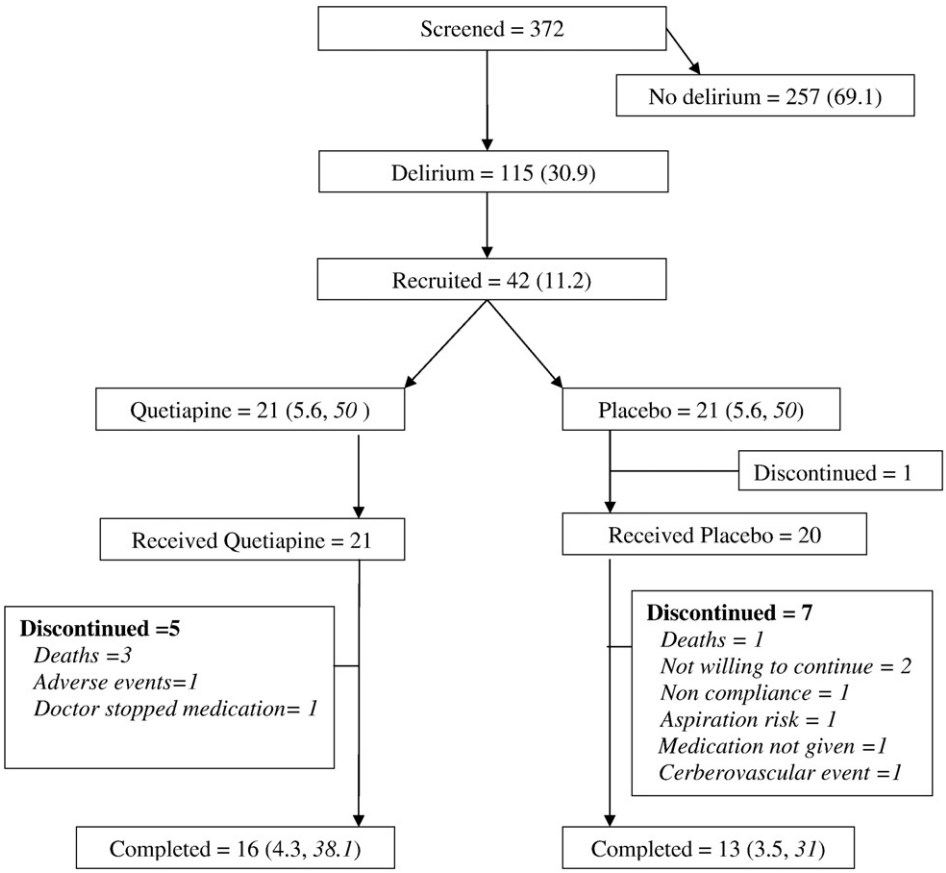

Fig. 1. The CONSORT diagram showing patient disposition n (% of total; % of recruited sample).

Table 2
Mean scores for DRS-R-98 and MMSE for days 1,3 and 10 for quetiapine and placebo groups with mean difference

	Variable	Mean quetiapine (S.E.)	Mean placebo (S.E.)	Mean difference
Day 1	DRS-R-98 Severity	19.070 (2.921)	19.070 (2.921)	0
	DRS-R-98 total	22.736 (3.098)	22.736 (3.098)	0
	DRS-R-98 Cognitive	8.881 (0.995)	8.881 (0.995)	0
	DRS-R-98 Non-cognitive	10.283 (1.262)	10.283 (1.262)	0
	MMSE	11.829 (4.080)	11.829 (4.080)	0
Day 3	DRS-R-98 Severity	9.673 (2.647)	12.255 (2.204)	−2.582
	DRS-R-98 Total	11.983 (3.115)	14.308 (2.634)	−2.325
	DRS-R-98 Cognitive	5.796 (0.933)	6.419 (0.850)	−0.623
	DRS-R-98 Non-cognitive	3.961 (0.735)	5.228 (0.698)	−1.267
	MMSE	16.773 (3.838)	16.317 (3.689)	−0.456
Day 10	DRS-R-98 severity	7.132 (3.347)	7.387 (3.264)	−0.256
	DRS-R-98 Total	8.192 (4.223)	8.456 (4.133)	−0.265
	DRS-R-98 Cognitive	4.994 (1.120)	5.033 (1.109)	−0.04
	DRS-R-98 Non-Cognitive	2.391 (0.915)	2.465 (0.899)	−0.074
	MMSE	18.534 (4.757)	18.504 (4.739)	−0.03

procedure; 11, a hip replacement. Many recruited patients had a number of medical comorbidities, the commonest being urinary tract infection (5), diabetes (3), atrial fibrillation (3), and chest infection (2).

The mean (S.D.) age was 84.2 (8.28) years (range 58–98). All participants were over the age of 65 except for one 58-year old. Both groups included 15 females. Sixteen patients from the quetiapine group and 13 from the placebo group completed the study (Table 1 and Fig. 1).

The highest mean dose of quetiapine was 40 mg on day 4 (day 1=25 mg, day 10=37.50 mg).

Efficacy of quetiapine

The two groups were not dissimilar in their baseline scores for DRS-R-98 (Table 2). The mean (S.E.) baseline total DRS-R-98 scores was 22.736 (3.098) at the start of the study. Although the total mean DRS-R-98 score tended to decrease more rapidly for the quetiapine group, no differences at individual time points reached statistical significance. On Day 3, mean (S.E.) DRS-R-98 total score for the quetiapine group was 11.983 (3.115) compared to 14.308 (2.634) for the placebo group. The mean difference for MMSE scores for Days 3 and 10 were −0.456 and −0.03 between the quetiapine and the placebo groups (Table 2).

Table 3
The difference in rate of improvement between quetiapine and placebo groups for the period of trial

	Rate difference between quetiapine and placebo (S.E., *P* value)
DRS-R-98 Severity	0.827 (0.371, *P*=.026)
DRS-R-98 Total	0.55 (0.285, *P*=.054)
DRS-R-98 Cognitive	0.572 (0.443, *P*=.197)
DRS-R-98 Non-cognitive	0.577 (0.292, *P*=.048)

Rate of improvement

The differences in rate of improvement (S.E., *P* value) between the two groups for DRS-R-98 total and severity scores were 0.55 (0.285, *P*=.54) and 0.827 (0.37, *P*=.026), respectively. This suggests that the quetiapine group's severity scores improved significantly (82%) more quickly than the placebo group's (Table 3 and Fig. 2).

We further explored the data by dividing DRS-R-98 into noncognitive (Items 1–8) and cognitive (Items 9–13) subscales. For the trial period, the mean rate difference (S.E., *P* value) for improvement for the quetiapine group in comparison to the placebo group was 0.577 (0.292, *P*=.048) and 0.572 (0.443, *P*=.197) on the noncognitive and cognitive subscales, respectively. Thus, the quetiapine group improved significantly (57%) faster than the placebo group for noncognitive scores (Table 3 and Fig. 2). There were no significant differences found between treatment groups for MMSE, BPRS, or CGI Global scores.

Tolerability of quetiapine

Seven patients died within 30 days of entering the study (four in the quetiapine group and three in the placebo group). One patient was withdrawn from quetiapine due to complaints of sedation. No other patients were unable to tolerate the trial medication. There were low rates of abnormal involuntary movements in both groups throughout the 10 days (quetiapine 4.8%; placebo 14.3%).

Dropouts

Apart from seven deaths, other reasons for dropout from the trial included doctors stopping medication without consultation with the trial team, patient being nil by mouth for operation, sedation, patient refusal to comply with medication, and medication not given by the nursing staff. On review of clinical information, the deaths were considered to be related to

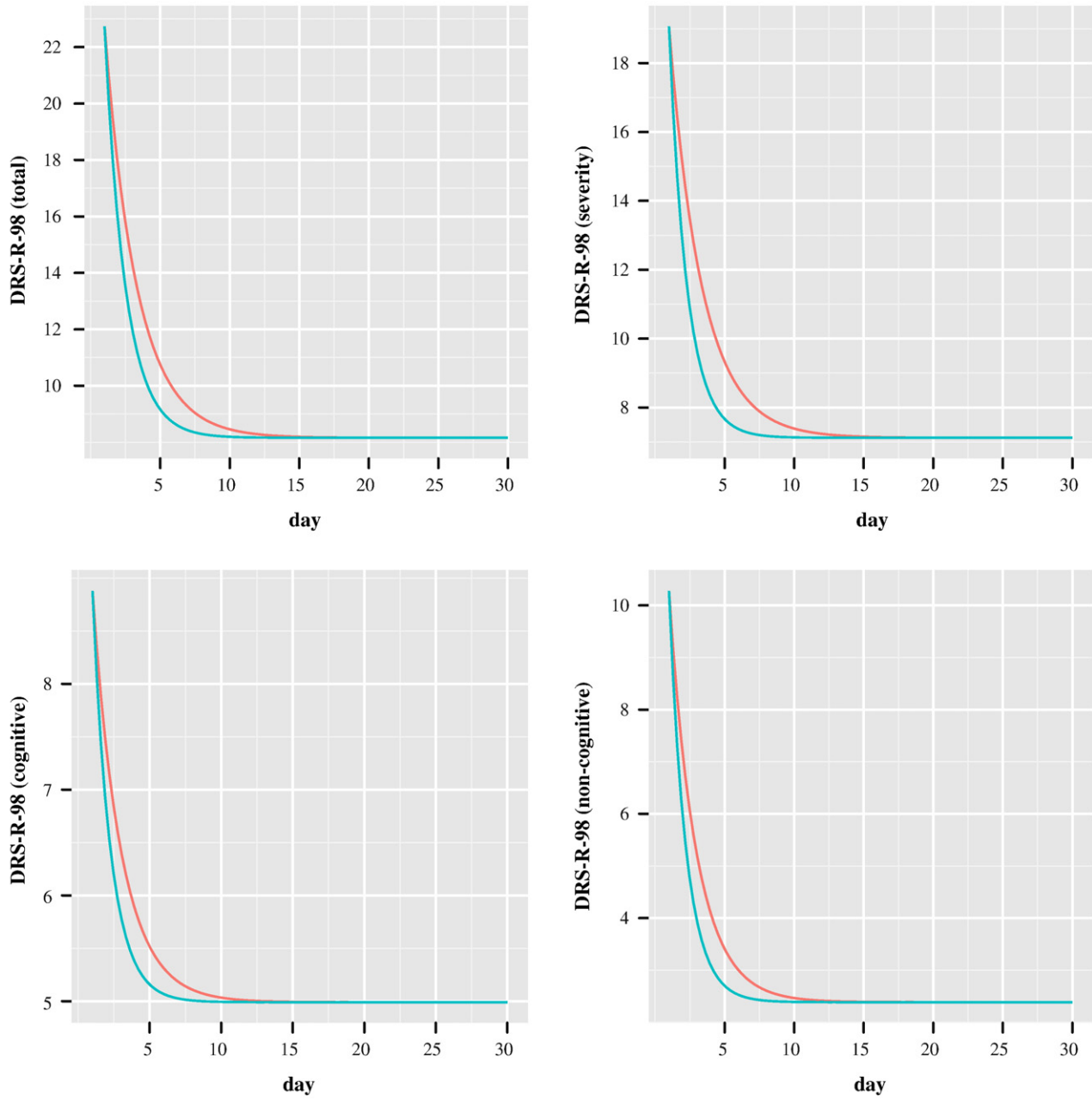

Fig. 2. Response to treatment for quetiapine and placebo groups using the non linear mixed effects model.

underlying serious medical conditions including cardiovascular events rather than the trial medication.

Discussion

This is the first placebo-controlled RCT of quetiapine in delirium. The trial was stopped early at the request of the manufacturer due to the Food and Drug Administration's concerns on the use of antipsychotic medication in the elderly. Even though the study was underpowered and can be considered a failed study due to the small sample size, a significantly faster response for quetiapine was shown on DRS-R-98 severity score. In addition, a statistically significant improvement in noncognitive items including restlessness, agitation, thought disorder, and perceptual impairment on the DRS-R-98 was found on Day 3 with a mean dose of quetiapine lower than previously documented, possibly contributed to by the high mean age of 84 years.

The small sample size is the main limitation of the study which should be regarded as a pilot study. Strict inclusion criteria, a high baseline score on the validated primary outcome measure, use of other validated measures, information from the case notes to supplement the patient and nursing staff interviews, homogeneity of subjects, use

of a flexible dosing regimen, and frequent follow-up to 30 days are strengths in the methodology of this study. Indeed, a similar methodology has been recommended for designing clinical trials in this field [13].

Difficulty in recruiting delirium sufferers to treatment trials is not a new phenomenon. This study had a larger sample size than any of the RCTs in delirium reviewed by Boettger and Breitbart [14]. Even with a low dose, these results are consistent with the findings of previous RCTs of atypical antipsychotic medication [5,6,8] for delirium and non-RCT work with quetiapine [7,9]. The results of previous studies also suggest that low-dose antipsychotic medication effects improvement in the initial phase of treatment [14-16]. This is important as improvement of delirium is likely to reduce the distress for patients and their carers and to potentially reduce inpatient stays.

Despite the inclusion of patients who had pre existing minor cognitive deficits, quetiapine appeared to be a well-tolerated treatment with no evidence of significant adverse effects such as extra pyramidal side effects, sedation (except one patient), or cerebrovascular problems.

As delirium can also improve irrespective of treatment given, the statistical approaches for delirium trials should take this into account. Instead of comparing group means at a particular end point, trial reporting should summarize the whole mean recovery trajectory. Our approach used nonlinear models to find a trajectory for the recovery rate. Such nonlinear models with different recovery rates can be a method to set up an analysis that allows the hypothesis of equal areas under the mean trajectories to be statistically tested.

Further studies are now needed with larger samples, exploration of response predictors, and relationship with resolution of underlying medical disorder to clarify the role and safety of antipsychotics in the management of delirium.

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