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# Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: randomised double blind placebo controlled trial

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## Abstract

**Objectives** To determine the respective efficacy of quetiapine and rivastigmine for agitation in people with dementia in institutional care and to evaluate these treatments with respect to change in cognitive performance.
**Design** Randomised double blind (clinician, patient, outcomes assessor) placebo controlled trial.
**Setting** Care facilities in the north east of England.
**Participants** 93 patients with Alzheimer's disease, dementia, and clinically significant agitation.
**Intervention** Atypical antipsychotic (quetiapine), cholinesterase inhibitor (rivastigmine), or placebo (double dummy).
**Main outcome measures** Agitation (Cohen-Mansfield agitation inventory) and cognition (severe impairment battery) at baseline and at six weeks and 26 weeks. The primary outcome was agitation inventory at six weeks.
**Results** 31 patients were randomised to each group, and 80 (86%) started treatment (25 rivastigmine, 26 quetiapine, 29 placebo), of whom 71 (89%) tolerated the maximum protocol dose (22 rivastigmine, 23 quetiapine, 26 placebo). Compared with placebo, neither group showed significant differences in improvement on the agitation inventory either at six weeks or 26 weeks. Fifty six patients scored >10 on the severe impairment battery at baseline, 46 (82%) of whom were included in the analysis at six week follow up (14 rivastigmine, 14 quetiapine, 18 placebo). For quetiapine the change in severe impairment battery score from baseline was estimated as an average of −14.6 points (95% confidence interval −25.3 to −4.0) lower (that is, worse) than in the placebo group at six weeks (P=0.009) and −15.4 points (−27.0 to −3.8) lower at 26 weeks (P=0.01). The corresponding changes with rivastigmine were −3.5 points (−13.1 to 6.2) lower at six weeks (P=0.5) and −7.5 points (−21.0 to 6.0) lower at 26 weeks (P=0.3).
**Conclusions** Neither quetiapine nor rivastigmine is effective in the treatment of agitation in people with dementia in institutional care. Compared with placebo, quetiapine is associated with significantly greater cognitive decline.

## Introduction

Antipsychotic drugs are commonly prescribed to many people with dementia (up to 45%) in residential or nursing homes,[1] often for prolonged periods. Antipsychotics have modest efficacy[2] but are commonly associated with substantial adverse effects and, more seriously, an increased risk of stroke has been reported with the atypical antipsychotics, risperidone and olanzapine.[3] There are no published randomised controlled trials for other atypical antipsychotics in people with dementia, although a published abstract indicates some benefit of quetiapine in those with agitation,[4] and preliminary evidence indicates that cholinesterase inhibitors may also improve agitation.[5]

One observational study reported a doubling in the rate of cognitive decline in patients with dementia taking typical antipsychotics,[6] although the impact on cognition of newer atypical antipsychotics, was not determined.

We compared quetiapine and rivastigmine with placebo in patients with dementia and agitation in nursing homes in a randomised double blind placebo controlled trial over 26 weeks. Our primary objective was to determine whether either drug was better than placebo for agitation. We also evaluated whether there was a significant difference between the individual

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Summary of change from baseline at six weeks and 26 weeks for main outcomes plus comparative statistics

| | | | | Mean difference (95% CI), P value | | |
|---|---|---|---|---|---|---|
| | Rivastigmine | Quetiapine | Placebo | Rivastigmine *v* placebo | Quetiapine *v* placebo | Rivastigmine *v* quetiapine |
| Mean (SD) change in CMAI from baseline: | | | | | | |
| To week 6 | –5.1 (16.3) (n=24) | –4.0 (15.4) (n=27) | –6.2 (17.6) (n=29) | 4.1 (–4.2 to 12.3), P=0.3 | 3.5 (–3.7 to 10.8), P=0.3 | 0.29 (–8.0 to 8.6), P=0.9 |
| To week 26 | –10.8 (19.9) (n=24) | –8.1 (12.7) (n=27) | –9.0 (16.5) (n=30) | 2.2 (–5.3 to 9.7), P=0.6 | 2.0 (–4.2 to 8.3); P=0.5 | –0.52 (–8.0 to 6.9), P=0.9 |
| Mean (SD) change in SIB from baseline: | | | | | | |
| To week 6 | 1.8 (14.7) (n=14) | –10.5 (14.8) (n=14) | 3.2 (15.1) (n=18) | –3.5 (–13.1 to 6.2), P=0.5 | –14.6 (–25.3 to –4.0), P=0.009 | 12.0 (0.76 to 23.2), P=0.04 |
| To week 26 | –3.1 (20.6) (n=15) | –11.3 (15.6) (n=15) | 3.3 (17.4) (n=19) | –7.5 (–21.0 to 6.0), P=0.3 | –15.4 (–27.0 to –3.8), P=0.01 | 8.3 (–5.6 to 22.3), P=0.2 |

CMAI=Cohen-Mansfield agitation inventory; SIB=severe impairment battery.

active treatments and placebo with respect to cognitive change.

## Method

Participants were all people with dementia living in care facilities. Our inclusion criteria were a diagnosis of probable or possible Alzheimer's disease; age >60; clinically significant agitation for at least six weeks using the Cohen-Mansfield agitation inventory,[7] and the irritability or aberrant motor behaviour scales of the neuropsychiatric inventory; and no use of antipsychotics or cholinesterase inhibitors for four weeks before entry into the study. We excluded patients known to be sensitive to cholinesterase inhibitors or antipsychotics and those with advanced, severe, progressive, or unstable disease or disability that might prevent them from completing study procedures (see bmj.com).

### Evaluations

We assessed all patients before the start of the pharmacological intervention (baseline) and after six and 26 weeks. At 12 weeks participants underwent an additional severe impairment battery[8] because people with behavioural problems commonly refuse cognitive assessment at least once. Assessors were blind to treatment allocation.

### Outcomes

Our primary outcome measure was a validated standardised evaluation of agitation at six weeks.[7] We used the severe impairment battery for cognitive assessment.[8] General assessments included electrocardiography, full blood count, and evaluation of severity of dementia (functional assessment staging) at baseline.

### Randomisation

We randomly assigned patients in equal numbers to active quetiapine plus placebo rivastigmine; placebo quetiapine plus active rivastigmine; or placebo rivastigmine plus placebo quetiapine (double dummy).

We aimed to attain doses of 25-50 mg quetiapine twice a day and 3-6 mg rivastigmine twice a day by week 12, and doses of 50 mg quetiapine twice a day or ≥9 mg rivastigmine daily between week 12 and week 26.

### Sample size and analysis

We calculated that we needed a sample size of 23 in each group, assuming similar efficacy of active treatments. Allowing for a dropout rate of 25%, we needed 31 patients per treatment group. (See bmj.com for details of participant flow.)

We summarised demographic factors and clinical characteristics. We restricted comparative analysis to those patients who had at least one assessment after randomisation; a modified intention to treat analysis. For the agitation inventory score, for everyone who completed the six week evaluation but dropped out thereafter we carried forward the last total score. For the severe impairment battery, we carried forward the last total score from either the six week or supplementary three month assessment.

For the primary analysis, we summarised the change in the agitation inventory score from baseline to six weeks using the mean (SD). To establish the magnitude and direction of the treatment effect, we used analysis of covariance to compare pairs of treatment groups, giving the mean difference (in change in agitation inventory from baseline to six weeks) between groups (plus 95% confidence intervals) with adjustment for baseline value.

We made no formal adjustment for multiple significance testing. We report our main objective of active treatment versus placebo but also active treatment group comparisons for completeness given the dearth of published data. We also report results at the 26 week follow up to show whether the effects are temporary or sustained. See bmj.com for full details.

## Results

Ninety three patients (31 per arm), most with severe dementia were randomised between September 2001 and April 2003, of whom 80 (86%) started treatment (25 rivastigmine, 26 quetiapine, 29 placebo). Seventy one (89%) tolerated the maximum protocol dose (22 rivastigmine, 23 quetiapine, 26 placebo). Eighty seven (94%) completed the agitation inventory assessment at baseline and 80 (86%) did so at six weeks (24 rivastigmine, 27 quetiapine, 29 placebo). Wherever possible we assessed outcomes irrespective of whether a patient commenced treatment.

Demographic characteristics and stage of dementia were similar across the three groups, but there was a slight imbalance on severe impairment battery at baseline (10 point difference in favour of patients in the placebo group) (see bmj.com).

### Agitation inventory

There were no significant differences between treatments in the change in agitation inventory scores

between baseline and six weeks and baseline and 26 weeks (table).

**Severe impairment battery**

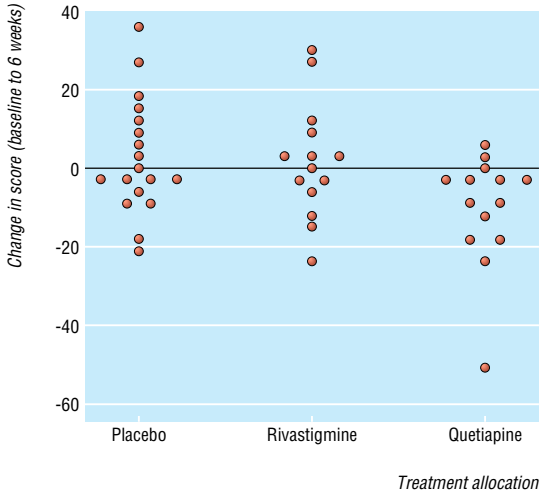
Fifty six of the 93 (60%) participants scored >10 on the severe impairment battery at baseline (20 rivastigmine, 17 quetiapine, 19 placebo). Forty six (82%) of these patients also completed it at six weeks. For these 46 patients, the mean (SD) scores at baseline were 71.6 (24.6) placebo; 66.6 (21.3) quetiapine and 65.1 (22.6) rivastigmine (2.6, 7.2, and 6.3 points higher, respectively, than the scores at six weeks). This was not explained by those with a poorer cognitive function being more likely to drop out and baseline figures were almost identical for participants who did or did not complete the agitation inventory at six weeks.

Patients who received quetiapine experienced, on average, an estimated mean difference in change in severe impairment battery score from baseline of −14.6 points (95% confidence interval −25.3 to −4.0) compared with the placebo treated group at six weeks; indicating a significantly greater deterioration in the quetiapine group (table and figure). A similar magnitude of difference was evident at 26 weeks. In contrast, the corresponding comparison of change in score from baseline for rivastigmine with placebo was an average of −3.5 points lower at six weeks and −7.5 points lower at 26 weeks.

## Discussion

Compared with placebo, the atypical antipsychotic drug quetiapine does not result in significant improvement in agitation in patients with dementia and is associated with a greater decline in cognitive function. This result is consistent with data from previous observational and preliminary clinical trials.[6] It is unlikely that the differences we found can be explained by any potential confounding factors.

Even though quetiapine has a relatively more favourable pharmacological profile than other antipsychotic agents, it was still associated with a detrimental impact on cognition. One postulated mechanism is suppression of brain derived neurotrophic factor (BDNF), accelerating the accumulation of the core pathological substrates of Alzheimer's disease.[9] Another possible mechanism involves antimuscarinic properties.[10] Preliminary reports indicate potential cognitive benefits of quetiapine in people with schizophrenia,[11] although the mechanisms of cognitive impairment in the two conditions are completely different.




Change in score on severe impairment battery (baseline to six weeks) by treatment group

### What is already known on this topic

Antipsychotic drugs are widely used for the control of behavioural manifestations in dementia, of which agitation is the most common

Central cholinesterase inhibitors are increasingly used to treat the behavioural manifestations of dementia

Observational data have suggested that (typical) antipsychotics might accelerate cognitive decline in dementia

### What this study adds

Central cholinesterase inhibitors and atypical antipsychotics are not effective for the treatment of agitation in people with dementia

Quetiapine (an atypical antipsychotic) is associated with accelerated cognitive decline

Patients in the rivastigmine group did not experience any significant improvement in agitation nor did they seem to experience a significant decline in cognitive function compared with patients in the placebo group.

**Strengths and limitations**

The improvements seen in the placebo group are consistent with most previous reports[2] and are probably explained by a Hawthorne effect—residents in an unstimulating environment respond positively to the increased interaction as part of the study procedures. Though our study is limited because of the modest sample size, multiple evaluations, and the substantial proportion of patients who were unable to complete the severe impairment battery, the possible impact of quetiapine on cognition is clinically important.

We did not adjust for multiple significance testing because we considered the six week results would be the most important because of the anticipated dropout rate; comparison of treatment versus placebo was of primary importance, hence the interpretation of the significant result; and comparison of active treatments was always going to be of secondary importance, hence the caution with the six week result for rivastigmine versus quetiapine. When interpreting the cognitive function result for quetiapine compared with placebo, it can be argued that, in the light of a lack of evidence of efficacy, even a suggestion of a decline in what was a secondary outcome is noteworthy. As one could argue that it is not necessary to show significant evidence of harm under these particular circumstances, a formal adjustment was not deemed necessary.

**Conclusion**
Quetiapine and rivastigmine seemed of no benefit in patients with dementia and agitation in institutional care, and quetiapine was associated with greater cognitive decline than placebo. Our results suggest that quetiapine should not be used in people with dementia and highlight concerns regarding the long term use of antipsychotics in these patients.

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Competing interests: C Ballard has received honorariums and research donations to support his general research programme from Astra Zeneca and Novartis.

Ethical approval: The study was approved by a properly constituted local research ethics committee.

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# A feasibility study of signed consent for the collection of patient identifiable information for a national paediatric clinical audit database

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## Abstract

**Objectives** To investigate the feasibility of obtaining signed consent for submission of patient identifiable data to a national clinical audit database and to identify factors influencing the consent process and its success.
**Design** Feasibility study.
**Setting** Seven paediatric intensive care units in England.
**Participants** Parents/guardians of patients, or patients aged 12-16 years old, approached consecutively over three months for signed consent for submission of patient identifiable data to the national clinical audit database the Paediatric Intensive Care Audit Network (PICANet).
**Main outcome measures** The numbers and proportions of admissions for which signed consent was given, refused, or not obtained (form not returned or form partially completed but not signed), by age, sex, level of deprivation, ethnicity (South Asian or not), paediatric index of mortality score, length of hospital stay (days in paediatric intensive care).
**Results** One unit did not start and one did not fully implement the protocol, so analysis excluded these two units. Consent was obtained for 182 of 422 admissions (43%) (range by unit 9% to 84%). Most (101/182; 55%) consents were taken by staff nurses. One refusal (0.2%) was received. Consent rates were significantly better for children who were more severely ill on admission and for hospital stays of six days or more, and significantly poorer for children aged 10-14 years. Long hospital stays and children aged 10-14 years remained significant in a stepwise regression model of the factors that were significant in the univariate model.
**Conclusion** Systematically obtaining individual signed consent for sharing patient identifiable information with an externally located clinical audit database is difficult. Obtaining such consent is unlikely to be successful unless additional resources are specifically allocated to training, staff time, and administrative support.

## Introduction

The paediatric intensive care audit network (PICANet) was established in 2001 in collaboration with the Paediatric Intensive Care Society. This prospective clinical audit database of all admissions to paediatric intensive care units in England and Wales aims to identify evidence based best practice, facilitate resource planning, and study the epidemiology of paediatric critical illness (see www.picanet.org.uk). The Data Protection Act requires that patients give their consent

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