Long-term antipsychotic use and cognitive decline in community-dwelling older adults with mild–moderate Alzheimer disease: Data from NILVAD

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Abstract

Introduction: Previous evidence has suggested that antipsychotic use may be associated with accelerated cognitive decline in those living with dementia. However, the cognitive effects of long-term antipsychotic use in community-dwelling older adults with mild–moderate Alzheimer disease (AD) has not been explored to date.

Methods: We assessed the impact of long-term antipsychotic use on the rate of cognitive decline (Alzheimer’s Disease Assessment Scale—Cognitive Subsection) and dementia progression (Clinical Dementia Rating—Sum of Boxes [CDR-Sb]/ Disability Assessment for Dementia [DAD]) over 18 months in older adults with mild–moderate AD.

Results: Of 509 participants with mild–moderate AD, one-tenth (54/509; 10.6%) were prescribed an antipsychotic for the 18-month study duration. Antipsychotic use was significantly associated with accelerated cognitive decline at both 12 (β: 3.53, 0.91–6.17, p = 0.008) and 18 months (β: 3.81, 0.49–7.14, p = 0.024) in addition to greater dementia progression at both 12 (β: 1.85, −0.97–2.73, p < 0.001 for CDR-Sb/β: −3.33, −5.56–1.10, p = 0.003 for DAD) and 18 months (β: 1.41, 0.16–2.67, p = 0.027 for CDR-Sb/β: −3.86, −6.64 to −1.08, p = 0.006 for DAD). APOE ε4 carriers experienced significantly greater cognitive decline with long-term antipsychotic use.

Conclusions: Long-term antipsychotic use was associated with greater cognitive decline and dementia progression in community-dwelling older adults with mild–moderate AD. Our findings are consistent with previous evidence encouraging cautious and careful consideration of risks versus benefits of antipsychotic usage in those with AD.

Keywords: Alzheimer disease, antipsychotic, cognitive decline, dementia
1 | INTRODUCTION

Antipsychotics are commonly used in the management of the Behavioural and Psychological Symptoms of Distress in Dementia (BPSD). Guidelines support only using antipsychotics in dementia once other, non-pharmacological, approaches have been unsuccessful, with treatment response/adverse effects monitored at regular intervals. Further, guidelines advise that antipsychotics only be used in the short-term management of BPSD, as long-term antipsychotic use has been associated with an increased risk of cerebrovascular events, adverse cardio-metabolic outcomes and even increased mortality. Further, there is an emerging body of evidence that antipsychotic use can be associated with accelerated cognitive decline in dementia.

In the Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer’s disease (CATIE-AD) Study, participants with Alzheimer’s disease (AD) and aggression/agitation or psychosis were randomized to either antipsychotic medication or placebo and were followed for 36 weeks. Antipsychotic use was not associated with any significant improvement in BPSD, and in fact the adverse effects of antipsychotic use were found to outweigh the benefits. In analysis of the cognitive data from this trial, antipsychotic use was associated with an accelerated decline on both the Alzheimer’s Disease Assessment Scale—Cognitive Subsection (ADAS-Cog) and the Mini-Mental State Examination (MMSE), consistent with 1 year’s deterioration.

Similarly, in a trial designed to test the potential cognitive benefits of the antipsychotic olanzapine in mild–moderate AD, 268 participants (without psychosis/agitation) were randomized to either olanzapine or placebo. Those randomized to olanzapine experienced an accelerated cognitive decline on both the ADAS-Cog and the MMSE at 26 weeks. Overall, a meta-analysis of randomized controlled trials observed a greater decline in MMSE scores in those prescribed antipsychotic medication versus placebo. A further recent meta-analysis demonstrated strong associations between longer antipsychotic treatment duration and greater cognitive decline in dementia, although the authors advised caution in interpretation of their results. Interestingly, in a study of 206 nursing home residents, treatment with olanzapine was not associated with accelerated rates of cognitive decline on the ADAS-Cog/MMSE.

Studies to date have focused almost exclusively on those with severe dementia, with a strong focus on those in nursing homes and institutional care. Less clear is the effect of antipsychotic usage on community-dwelling older adults living with mild–moderate AD. A previous study which included participants with mild–moderate dementia, demonstrated a significant cognitive decline with antipsychotic use. Further, many trials are limited by short durations (mostly 6–10 weeks). The aforementioned CATIE-AD study is a notable exception, which assessed participants for 36 weeks. Further studies focused on the long-term cognitive side effects of antipsychotic usage are thus warranted.

In the current analysis, we examined the cognitive consequences of antipsychotic use in community-dwelling older adults with mild–moderate AD in a large international cohort of older adults with AD over 18 months.

2 | METHODS

2.1 | Study design

The NILVAD Study (Clinicaltrials.gov, NCT02017340; EudraCT number 2012-002764-27) was an investigator-led randomized controlled trial of the antihypertensive Nilvadipine in mild–moderate AD. NILVAD was negative for the primary end-point (change in the ADAS-Cog).

In order to be included in the NILVAD trial, participants had to have a National Institute of Neurological and Communicative Disorders and Stroke (NINCDS-ADRDA) and a MMSE score between 12 and 26, consistent with mild–moderate AD. Participants were recruited across 23 sites in nine European countries (Ireland, United Kingdom, Italy, the Netherlands, France, Greece, Sweden, Germany and Hungary). The full inclusion/exclusion criteria have been previously published. Of note for the current analysis, exclusion criteria included participants with any other significant neurological disorder or any condition known to interfere with brain function. Similarly, those with any Axis I psychiatric disorder (such as schizophrenia, bipolar disorder or major depression) were excluded as were those with a history of alcohol abuse/dependence in the year before participation. Of note, subjects with any current BPSD symptoms
which would limit participation and completion of 18-month follow-up were also excluded.

Ethical approval was obtained for the NILVAD study from the appropriate National Competent Authorities, Independent Ethics Committees, and Institutional Review Boards for all study Sites. Overall, Trinity College Dublin (Ireland) was responsible for coordination of the trial and the project office was situated in St. James’s Hospital, Dublin.

For the current analysis, we analysed the rate of cognitive decline in those prescribed a long-term antipsychotic in comparison to non-users. As the primary NILVAD analysis was negative for a Nilvadipine treatment effect and participants in the trial demonstrated a clinically significant decline in cognition over the 18 months, we analysed the effect of continuing antipsychotic medication on rates of cognitive decline.

2.2 Assessments of cognitive decline, AD progression and AD severity

The ADAS-Cog was used to assess the severity of cognitive impairment in those with AD at baseline and follow-up. We analysed baseline ADAS-Cog scores in addition to both 12- and 18-month follow-up scores in the current analysis. The ADAS-Cog is scored out of a maximum of 80, with greater scores indicating greater cognitive impairment. In order to assess dementia severity, the Clinical Dementia Rating Scale—Sum of Boxes (CDR-Sb) and Disability Assessment for Dementia (DAD) were used. The CDR-Sb is scored out of a maximal 18, with greater scores indicating a greater dementia severity. The DAD is scored out of 100, with lower scores indicating greater impairment. Both CDR-Sb and DAD scores were analysed at baseline, 12 and 18 months in the current analysis. Finally, the MMSE was performed at baseline only in the current study. The MMSE was used to assess baseline dementia severity (mild vs. moderate), with scores of 20 or greater indicating mild dementia and <20 indicating moderate dementia.

2.3 Medication data

A detailed list of concomitant medication was obtained from each NILVAD participant. Medication lists were updated at all follow-up study visits. Details on current medication was coded using Anatomical Therapeutic Classification codes in duplicate. Antipsychotic usage was identified by any medication with the code ‘N05A’ representing ‘Antipsychotics’. Usage was further divided by study authors into first- and second-generation agents. Long-term antipsychotic usage was coded as those using an antipsychotic medication for the entire duration of the study (≥18 months). We further coded for intermittent shorter-term antipsychotic usage and later re-ran analysis excluding intermittent usage to avoid misclassification of those with intermittent antipsychotic usage.

Finally, we coded for use of definite anticholinergic medication using those listed in the Anticholinergic Cognitive Burden Score. Several of the antipsychotic medications included in the current study (including quetiapine and olanzapine) are known definite anticholinergic medication and we wished to assess if the potential cognitive effects of antipsychotic medications were independent of their anticholinergic effects, which may also influence dementia progression in this vulnerable group.

2.4 Covariates

Routine demographic information such as age, gender, years of education and body mass index (BMI) was obtained in a standardized fashion as detailed in the main study protocol. A history of AD was obtained including diagnosis duration and duration since symptom onset. A detailed medical history was also obtained from NILVAD participants. Medical history was coded using International Classification of Diseases coding and included active medical issues/conditions.

We defined a history of BPSD as (i) a documented history of agitation, aggression, behavioural disorder or BPSD on medical history logs or (ii) prescribed a long-term antipsychotic—presumed to be prescribed for BPSD as per review of medical history (in addition to the fact that those with Axis I psychiatric disorders or other neurological disorders were excluded from NILVAD).

Additionally, a subgroup of participants had data on APOE genotype available. We ran a separate subgroup analysis to assess if for APOE ε4 mediated cognitive decline/dementia progression with antipsychotic versus non-carriers, given previous evidence demonstrating APOE-specific effects of medication on cognition.

2.5 Statistical analysis

All statistical analyses were performed using STATA v15.0 (StatCorp). Statistical significance was considered as \( p < 0.05 \). We reported descriptive statistics as means and medians with standard deviations and interquartile ranges as appropriate. In order to compare those with antipsychotic usage to those without, univariate statistics consisted of t-tests, chi-square tests and Wilcoxon rank-sum tests as appropriate. Multivariate Logistic Regression was used in order to model predictors of antipsychotic prescription in those with mild–moderate AD.

ADAS-Cog, CDR-Sb and DAD assessments were performed at baseline, 12 and 18 months. In order to predict the change on the three assessments over time, we used mixed-effects linear regression with country as a random effect and change in ADAS-Cog/CDR-Sb/DAD as the dependent variable. In the first instance, we tested associations unadjusted. Then, we adjusted for important factors known to influence cognitive trajectories such as age, sex, BMI, years of formal education, duration since AD diagnosis and baseline score (on ADAS-Cog/CDR-Sb/DAD) in addition to study group (Nilvadipine...
vs. placebo) and cholinesterase inhibitor usage (model 1). In further models, we also adjusted for total medication burden (excluding long-term antipsychotics) and total number of medical comorbidities (model 2). Finally, we adjusted for use of definite anticholinergic medication (in order to explore if potential effects were independent of anticholinergic effects) in addition to the presence of BPSD, in order to control for confounding by indication (model 3). In those with genotype data available, we assessed whether the effects of long-term antipsychotics were mediated by APOE ε4 carrier status. We used an additive model, with individuals coded as carrying 0, 1 or 2 APOE ε4 alleles. This was done using the same mixed-effects models as above, with the introduction of an APOE ε4 status × antipsychotic interaction term.

Finally, in order to exclude the effects of intermittent antipsychotic usage, we reran all analysis excluding those with intermittent usage to assess if this had any significant effect on observed results.

3 | RESULTS

3.1 | Baseline characteristics

Just over 500 \( (n = 509; \text{aged: } 72.9 \pm 8.3, 61.9\% \text{ female}) \) community-dwelling participants with mild–moderate AD were included in the current analysis. At baseline, a small majority of participants had mild AD \((52.5\%, n = 267/509)\) as defined by MMSE score, with the remainder having moderate AD \((47.5\%, n = 242/509)\). Mean BMI of included participants was 25.5 \((\pm 4.3)\). Mean duration since AD diagnosis was 4.2 \((\pm 2.6)\) years. Mean years of formal education was 16.5 \((\pm 4.2)\). Median number of medical comorbidities was 4 \((2–5)\) and the median number of co-prescribed medications was 5 \((3–7)\). The majority \((450/509, 88.4\%)\) were prescribed a cholinesterase inhibitor.

In terms of cognitive function at baseline, the mean baseline score on the ADAS-Cog was 34.5 \((\pm 10.6)\). In assessment of disease severity, the mean CDR-Sb at baseline was 5.3 \((\pm 2.8)\). Just under one-fifth \((18.5\%, 94/509)\) had a history of BPSD as per the above criteria. Just over half \((54/94; 57.5\%)\) of those with BPSD were using a long-term antipsychotic.

3.2 | Antipsychotic use in mild–moderate Alzheimer disease

Overall, just over one-tenth \((54/509, 10.6\%)\) of participants were prescribed a regular antipsychotic medication for the duration of the trial. Nearly half of those prescribed an antipsychotic were prescribed quetiapine \((44.4\%, 24/54)\). Other common antipsychotics prescribed included risperidone \((13.0\%, 6/54)\), amisulpride \((11.1\%, 6/54)\) and haloperidol \((7.4\%, 4/54)\). One-fifth of those on an antipsychotic medication, 20.4\% \((11/54)\), were prescribed a first-generation antipsychotic with the remainder prescribed a second-generation agent. Antipsychotic usage significantly differed by country \((\chi^2 = 22.88, p = 0.004)\) with the highest usage seen in Italy \((11/55, 20\%)\) and Ireland \((17/110, 15.5\%)\), with lowest rates of usage seen in the United Kingdom \((1/65, 1.5\%)\) and France \((1/57, 1.8\%)\) (see Table 1).

Those prescribed an antipsychotic had greater AD severity at baseline, fewer years of formal education and a greater burden of polypharmacy in comparison to those who were not \((p < 0.05)\). A greater number of those in the antipsychotic group had a history of BPSD, the main indication for treatment with an antipsychotic in AD.

| Characteristic | Long-term antipsychotic \((N = 54)\) | No long-term antipsychotic \((N = 455)\) | Statistical test |
|---------------|---------------------------------|---------------------------------|----------------|
| Age, years \((SD)\) | 74.28 \((\pm 6.91)\) | 71.94 \((\pm 8.39)\) | \(t = -1.33, p = 0.09\) |
| Gender, % female \((N)\) | 57.41\% (31) | 62.42\% (284) | \(\chi^2 = 0.5137, p = 0.47\) |
| Group, % Nilvadipine \((N)\) | 42.59\% (23) | 51.43\% (234) | \(\chi^2 = 1.51, p = 0.22\) |
| AD severity, % mild \((N)\) | 26.42\% (14) | 55.40\% (253) | \(\chi^2 = 16.22, p < 0.001\) |
| AD duration, years \((SD)\) | 1.82 \((\pm 1.48)\) | 1.64 \((\pm 1.76)\) | \(t = -0.73, p = 0.77\) |
| Symptom onset, years \((SD)\) | 4.67 \((\pm 2.65)\) | 4.67 \((\pm 2.53)\) | \(t = -1.29, p = 0.10\) |
| Education, years \((SD)\) | 15.21 \((\pm 3.70)\) | 16.59 \((\pm 4.18)\) | \(t = 2.31, p = 0.01\) |
| BMI, kg/m\(^2\) \((SD)\) | 25.41 \((\pm 4.31)\) | 25.85 \((\pm 3.93)\) | \(t = 0.72, p = 0.76\) |
| No. of medications \((IQR)\) | 7 \((5–10)\) | 5 \((3–7)\) | \(z = -4.95, p < 0.001\) |
| No. of comorbidities \((IQR)\) | 4 \((2–5)\) | 4 \((2–5)\) | \(z = -0.45, p = 0.66\) |
| Baseline ADAS-Cog \((SD)\) | 40.11 \((\pm 10.55)\) | 33.83 \((\pm 10.42)\) | \(t = 4.19, p < 0.001\) |
| Baseline CDR-Sb \((SD)\) | 6.64 \((\pm 2.82)\) | 5.10 \((\pm 2.70)\) | \(t = -3.94, p < 0.001\) |

Abbreviations: AD, Alzheimer disease; ADAS-Cog, Alzheimer’s Disease Assessment Scale—Cognitive Subsection; BMI, body mass index; CDR-Sb, Clinical Dementia Rating, Sum of Boxes; N, number; SD, standard deviation.
TABLE 2 Multivariate logistic regression of likelihood of antipsychotic prescription

| Characteristic          | Odds ratio (95% CI) | p-value |
|-------------------------|---------------------|---------|
| Age (years)             | 1.03 (0.99–1.07)    | 0.21    |
| Gender (female)         | 0.66 (0.35–1.26)    | 0.21    |
| Group (Nilvadipine)     | 0.69 (0.37–1.28)    | 0.24    |
| AD severity (moderate)  | 2.26 (0.99–5.13)    | 0.05    |
| AD duration (years)     | 0.98 (0.79–1.21)    | 0.84    |
| Symptom onset (years)   | 1.02 (0.89–1.17)    | 0.75    |
| Education (years)       | 0.97 (0.89–1.05)    | 0.43    |
| BMI (kg/m²)             | 1.00 (0.94–1.08)    | 0.91    |
| Number of medications   | 1.17 (1.04–1.32)    | 0.01    |
| Number of comorbidities | 0.93 (0.80–1.08)    | 0.35    |
| Baseline ADAS-Cog       | 1.03 (0.99–1.07)    | 0.19    |
| Baseline CDR-Sb         | 1.04 (0.90–1.21)    | 0.60    |

Abbreviations: AD, Alzheimer disease; ADAS-Cog, Alzheimer’s Disease Assessment Scale—Cognitive Subsection; BMI, body mass index; CDR-Sb, Clinical Dementia Rating, Sum of Boxes; N, number; SD, standard deviation.

On multivariate logistic regression, the only significant predictor of increased likelihood of long-term antipsychotic prescription was an increasing number of non-antipsychotic medications (OR = 1.17, 1.04–1.32, p = 0.01) (see Table 2 for full results of the multivariate analysis).

3.3 Long-term antipsychotic use, cognitive decline and dementia progression in mild-moderate Alzheimer disease

From the baseline cohort of 509 participants, 439 (86.24%) had ADAS-Cog assessment at 12 months and 419 (82.3%) had ADAS-Cog assessed at 18 months. Following withdrawals, 452 (88.8%) participants had an ADAS-Cog assessment completed at either 12 or 18 months. Those without assessment did not differ from the overall cohort in terms of ongoing antipsychotic usage (14.3% [8/56] antipsychotic users in those without follow-up assessment than non-carriers at both 12 (β coef: 3.96, 0.74–7.18, p = 0.016) and 18 months (β coef: 4.96, 0.61–9.30, p = 0.025). A similar interaction was seen for effects on the CDR at 18 months (β coef: 1.73, 0.14–3.33, p = 0.033) but not 12 months (β coef: 0.90, −0.09 to 1.88, p = 0.074). Finally, this was also seen on the DAD at 12 (β coef: −3.46, −6.29 to −0.64, p = 0.016) and 18 months (β coef: −4.11, −7.49 to −0.72, p = 0.017). These results persisted under all three adjusted models (as above). The results of this analysis for the fully adjusted models at 12 and 18 months are presented in Table 3. Excluding those with intermittent antipsychotic usage did not significantly alter results.

4 DISCUSSION

In over 500 older adults with mild-moderate AD, we found significantly greater cognitive decline and dementia progression in those with long-term antipsychotic use. We observed significant interactions between APOE genotype and antipsychotic usage on cognitive decline in the NILVAD cohort, which to our knowledge is the first report of this association. Our study adds to the mounting evidence against the use of antipsychotics in those with a diagnosis of dementia, especially given the modest clinical benefit gained from their use.3
|                          | Model 1                      | p-value | Model 2                      | p-value | Model 3                      | p-value |
|--------------------------|-----------------------------|---------|-----------------------------|---------|-----------------------------|---------|
|                          | β coef. (95% CI)             |         | β coef. (95% CI)             |         | β coef. (95% CI)             |         |
| ADAS-Cog change: 12 months |                             |         |                             |         |                             |         |
| Long-term antipsychotic use | 3.46 (1.04, 5.89)           | 0.005*  | 3.12 (0.64, 5.59)           | 0.014*  | 3.53 (0.91, 6.17)           | 0.008*  |
| Age                      | −0.18 (−0.27, −0.09)        | <0.001* | −0.19 (−0.28, −0.10)        | <0.001* | −0.18 (−0.27, 0.09)         | <0.001* |
| Gender (female)           | −0.43 (−1.95, 1.08)         | 0.574   | −0.46 (−1.95, 1.04)         | 0.547   | −0.55 (−2.04, 0.95)         | 0.474   |
| BMI                      | −0.20 (−0.37, −0.03)        | 0.020*  | −0.21 (−0.38, −0.04)        | 0.014*  | −0.19 (−0.36, −0.02)        | 0.031*  |
| Education (years)         | 0.08 (−0.11, 0.28)          | 0.407   | 0.09 (−0.10, 0.28)          | 0.347   | 0.07 (−0.12, 0.27)          | 0.460   |
| Baseline ADAS-Cog         | 0.07 (−0.01, 0.15)          | 0.050   | 0.08 (0.01, 0.15)           | 0.038*  | 0.09 (0.02, 0.16)           | 0.018*  |
| Diagnosis duration        | −0.19 (−0.61, 0.23)         | 0.374   | −0.22 (−0.64, 0.20)         | 0.307   | −0.31 (−0.74, 0.12)         | 0.153   |
| Study group (Nilvadipine) | 0.67 (−0.79, 2.12)          | 0.361   | 0.70 (−0.73, 2.13)          | 0.337   | 0.72 (−0.70, 2.15)          | 0.322   |
| Cholinesterase inhibitor  | −0.29 (−2.60, 2.03)         | 0.808   | −0.43 (−2.72, 1.87)         | 0.716   | −0.35 (−2.63, 1.94)         | 0.764   |
| Total medications         | 0.16 (−0.14, 0.45)          | 0.304   | 0.16 (−0.14, 0.46)          | 0.285   |                             |         |
| Total comorbidities       | −0.01 (−0.36, 0.33)         | 0.935   | −0.16 (0.36, 0.32)          | 0.928   | −0.55 (−2.92, 1.82)         | 0.650   |
| 'Definite' anticholinergic use |                             |         |                             |         |                             |         |
| BPSD                      | −2.40 (−5.03, 0.28)         | 0.075   |                             |         |                             |         |
| ADAS-Cog change: 18 months |                             |         |                             |         |                             |         |
| Long-term antipsychotic use | 4.01 (−0.93, 7.09)          | 0.011*  | 3.95 (0.81, 7.10)           | 0.014*  | 3.81 (0.49, 7.14)           | 0.024*  |
| Age                      | −0.24 (−0.34, −0.13)        | <0.001* | −0.25 (−0.36, −0.14)        | <0.001* | −0.25 (−0.36, −0.14)        | <0.001* |
| Gender (female)           | −0.43 (−2.18, 1.33)         | 0.635   | −0.48 (−2.25, 1.28)         | 0.591   | −0.53 (−2.29, 1.23)         | 0.555   |
| BMI                      | −0.30 (−0.49, −0.10)        | 0.003*  | −0.30 (−0.50, −0.11)        | 0.002*  | −0.30 (−0.49, 0.10)         | 0.003*  |
| Education (years)         | 0.10 (−0.12, 0.28)          | 0.370   | 0.11 (−0.12, 0.33)          | 0.350   | 0.10 (0.13, 0.32)           | 0.387   |
| Baseline ADAS-Cog         | 0.19 (−0.10, 0.28)          | <0.001* | 0.19 (0.10, 0.28)           | <0.001* | 0.20 (0.11, 0.29)           | <0.001* |
| Diagnosis duration        | −0.48 (−0.99, 0.02)         | 0.059   | −0.49 (−1.00, 0.01)         | 0.055   | −0.55 (−1.07, −0.03)        | 0.038*  |
| Study group (Nilvadipine) | −0.15 (−1.82, 1.51)         | 0.860   | −0.14 (−1.81, 1.53)         | 0.870   | −0.08 (−1.75, 1.59)         | 0.921   |
| Cholinesterase inhibitor  | 0.43 (−2.21, 3.06)          | 0.751   | 0.36 (−2.30, 3.01)          | 0.793   | 0.36 (−2.29, 3.02)          | 0.789   |
| Total medications         | 0.01 (−0.33, 0.36)          | 0.935   | 0.00 (−0.35, 0.35)          | 0.995   | 0.14 (−0.26, 0.54)          | 0.486   |
| Total comorbidities       | 0.14 (−0.26, 0.53)          | 0.494   | 0.90 (−1.86, 3.66)          | 0.533   | −1.32 (−4.35, 1.70)         | 0.391   |
| 'Definite' anticholinergic use |                             |         |                             |         |                             |         |
| BPSD                      | −2.40 (−5.03, 0.28)         | 0.075   | −0.55 (−2.92, 1.82)         | 0.650   | −0.55 (−2.92, 1.82)         | 0.650   |
| (Continues)               |                             |         |                             |         |                             |         |
|                                | Model 1 β coef. (95% CI) | p-value | Model 2 β coef. (95% CI) | p-value | Model 3 β coef. (95% CI) | p-value |
|--------------------------------|--------------------------|---------|--------------------------|---------|--------------------------|---------|
| **CDR-Sb change: 12 months**   |                          |         |                          |         |                          |         |
| Long-term antipsychotic use    | 1.98 (1.18, 2.77)        | <0.001* | 1.96 (1.15, 2.77)        | <0.001* | 1.85 (0.97, 2.73)        | <0.001* |
| Age                            | -0.03 (-0.06, 0.00)      | 0.093   | -0.03 (-0.06, 0.01)      | 0.104   | -0.03 (-0.06, 0.00)      | 0.087   |
| Gender (female)                | -0.01 (-0.51, 0.50)      | 0.978   | -0.01 (-0.51, 0.50)      | 0.984   | 0.01 (-0.49, 0.51)       | 0.973   |
| BMI                            | -0.03 (-0.08, 0.03)      | 0.380   | -0.03 (-0.08, 0.03)      | 0.383   | -0.03 (-0.09, 0.03)      | 0.306   |
| Education (years)              | -0.04 (-0.19, 0.11)      | 0.211   | -0.04 (-0.11, 0.02)      | 0.217   | -0.04 (-0.10, 0.03)      | 0.286   |
| Baseline CDR-Sb                | 0.08 (-0.01, 0.18)       | 0.079   | 0.09 (-0.01, 0.18)       | 0.080   | 0.08 (-0.02, 0.18)       | 0.105   |
| Diagnosis duration             | -0.04 (-0.19, 0.11)      | 0.577   | -0.04 (-0.19, 0.10)      | 0.569   | -0.02 (-0.17, 0.13)      | 0.770   |
| Study group (Nilvadipine)      | 0.24 (-0.24, 0.73)       | 0.328   | 0.24 (-0.24, 0.72)       | 0.325   | 0.24 (-0.24, 0.72)       | 0.333   |
| Cholinesterase inhibitor       | -0.08 (-0.84, 0.69)      | 0.846   | -0.08 (-0.85, 0.69)      | 0.838   | -0.10 (-0.87, 0.67)      | 0.797   |
| Total medications              | 0.01 (-0.09, 0.11)       | 0.836   | 0.01 (-0.09, 0.11)       | 0.849   | 0.01 (-0.09, 0.11)       | 0.849   |
| Total comorbidities            | -0.01 (-0.13, 0.11)      | 0.858   | -0.01 (-0.13, 0.11)      | 0.864   | -0.01 (-0.13, 0.11)      | 0.864   |
| 'Definite' anticholinergic use  |                          |         |                          |         |                          |         |
| BPSD                           |                          |         |                          |         |                          |         |
| **CDR-Sb change: 18 months**   |                          |         |                          |         |                          |         |
| Long-term antipsychotic use    | 1.62 (0.49, 2.75)        | 0.005*  | 1.50 (0.34, 2.65)        | 0.011*  | 1.41 (0.16, 2.67)        | 0.027*  |
| Age                            | -0.07 (-0.11, -0.03)     | 0.001*  | -0.08 (-0.12, -0.03)     | <0.001* | -0.08 (-0.12, -0.03)     | <0.001* |
| Gender (female)                | -0.28 (-0.99, 0.42)      | 0.430   | -0.31 (-1.01, 0.40)      | 0.394   | -0.29 (-0.99, 0.41)      | 0.414   |
| BMI                            | -0.02 (-0.09, 0.07)      | 0.733   | -0.02 (-0.10, 0.06)      | 0.674   | -0.02 (-0.10, 0.06)      | 0.610   |
| Education (years)              | -0.02 (-0.11, 0.08)      | 0.693   | -0.02 (-0.09, 0.06)      | 0.726   | -0.01 (-0.10, 0.08)      | 0.808   |
| Baseline CDR-Sb                | 0.25 (0.11, 0.38)        | <0.001* | 0.25 (0.12, 0.39)        | <0.001* | 0.25 (0.11, 0.38)        | <0.001* |
| Diagnosis duration             | 0.13 (-0.35, 0.09)       | 0.248   | -0.13 (-0.35, 0.09)      | 0.233   | -0.11 (-0.34, 0.11)      | 0.330   |
| Study group (Nilvadipine)      | 0.08 (-0.59, 0.75)       | 0.815   | 0.08 (-0.59, 0.75)       | 0.810   | 0.07 (-0.60, 0.75)       | 0.831   |
| Cholinesterase inhibitor       | -0.24 (-1.29, 0.81)      | 0.655   | -0.29 (-1.34, 0.76)      | 0.591   | -0.31 (-1.36, 0.75)      | 0.567   |
| Total medications              | 0.05 (-0.09, 0.18)       | 0.515   | 0.05 (-0.12, 0.20)       | 0.511   | 0.05 (-0.12, 0.20)       | 0.511   |
| Total comorbidities            | 0.05 (-0.12, 0.21)       | 0.591   | 0.05 (-0.12, 0.21)       | 0.572   | 0.05 (-0.12, 0.21)       | 0.572   |
| 'Definite' anticholinergic use  |                          |         |                          |         |                          |         |
| BPSD                           |                          |         |                          |         |                          |         |
### TABLE 3 (Continued)

|                          | Model 1 | p-value  | Model 2 | p-value  | Model 3 | p-value  |
|--------------------------|---------|----------|---------|----------|---------|----------|
|                          | β coef. (95% CI) |         | β coef. (95% CI) |         | β coef. (95% CI) |         |
| DAD change: 12 months    |         |         |         |         |         |         |
| Long-term antipsychotic use | -3.73 (-5.75, -1.72) | <0.001* | -3.87 (-5.93, 1.81) | <0.001* | -3.33 (-5.56, -1.10) | 0.003* |
| Age                      | 0.12 (0.05, 0.20) | 0.002* | 0.12 (0.04, 0.20) | 0.004* | 0.12 (0.04, 0.20) | 0.003* |
| Gender (female)          | -0.17 (-1.45, 1.11) | 0.795 | -0.19 (-1.48, 1.09) | 0.769 | -0.20 (-1.49, 1.08) | 0.758 |
| BMI                      | 0.01 (-0.15, 0.14) | 0.937 | -0.01 (-0.16, 0.13) | 0.865 | -0.01 (-0.15, 0.14) | 0.927 |
| Education (years)        | 0.14 (-0.03, 0.29) | 0.102 | 0.14 (-0.02, 0.30) | 0.093 | 0.13 (-0.04, 0.29) | 0.130 |
| Baseline DAD             | -0.05 (0.13, 0.03) | 0.232 | -0.05 (-0.13, 0.03) | 0.249 | -0.05 (-0.14, 0.03) | 0.219 |
| Diagnosis duration       | -0.18 (-0.54, 0.18) | 0.328 | -0.19 (-0.56, 0.17) | 0.301 | -0.21 (-0.59, 0.16) | 0.265 |
| Study group (Nilvadipine) | 0.06 (-1.17, 1.29) | 0.922 | 0.07 (-1.16, 1.30) | 0.909 | 0.05 (-1.18, 1.28) | 0.933 |
| Cholinesterase inhibitor | 0.18 (-1.77, 2.13) | 0.856 | 0.10 (-1.86, 2.06) | 0.922 | 0.19 (-1.76, 1.28) | 0.848 |
| Total medications        | 0.04 (-0.26, 0.33) | 0.794 | 0.05 (-0.25, 0.34) | 0.753 | 0.05 (-0.25, 0.34) | 0.753 |
| Total comorbidities      |         |         |         |         |         |         |
| ‘Definite’ anticholinergic use |         |         |         |         |         |         |
| BPSD                     | 0.85 (-3.16, 1.46) | 0.472 |         |         |         |         |
| DAD change: 18 months    | -4.65 (-7.14, -2.14) | <0.001* | -4.74 (-7.29, -2.18) | <0.001* | -3.86 (-6.64, -1.08) | 0.006* |
| Age                      | 0.17 (0.08, 0.26) | <0.001* | 0.16 (-0.07, 0.26) | 0.001* | 0.17 (0.07, 0.27) | 0.001* |
| Gender (female)          | -0.65 (-2.19, 0.90) | 0.414 | -0.67 (-2.22, 0.88) | 0.398 | -0.67 (-2.22, 0.87) | 0.391 |
| BMI                      | -0.04 (-0.22, 0.13) | 0.619 | -0.05 (-0.22, 0.13) | 0.573 | -0.05 (-0.22, 0.13) | 0.609 |
| Education (years)        | 0.05 (-0.15, 0.25) | 0.650 | 0.05 (-0.15, 0.25) | 0.627 | 0.04 (-0.13, 0.07) | 0.717 |
| Baseline DAD             | -0.03 (-0.13, 0.07) | 0.567 | -0.03 (-0.13, 0.07) | 0.585 | -0.03 (-0.13, 0.07) | 0.549 |
| Diagnosis duration       | -0.16 (-0.63, 0.32) | 0.516 | -0.16 (-0.63, 0.32) | 0.521 | -0.17 (-0.66, 0.31) | 0.485 |
| Study group (Nilvadipine) | 0.62 (-0.86, 2.10) | 0.412 | 0.63 (-0.85, 2.10) | 0.405 | 0.62 (-0.85, 2.10) | 0.406 |
| Cholinesterase inhibitor | 0.62 (-1.69, 2.93) | 0.598 | 0.57 (-1.75, 2.89) | 0.633 | 0.69 (-1.63, 3.01) | 0.561 |
| Total medications        | 0.05 (-0.26, 0.35) | 0.766 | 0.07 (-0.24, 0.37) | 0.665 | 0.07 (-0.24, 0.37) | 0.665 |
| Total comorbidities      | 0.06 (-0.30, 0.42) | 0.741 | 0.07 (-0.29, 0.43) | 0.710 | 0.07 (-0.29, 0.43) | 0.710 |
| ‘Definite’ anticholinergic use |         |         |         |         |         |         |
| BPSD                     | -1.87 (-4.33, 0.59) | 0.136 |         |         |         |         |
| Abbreviations: AD, Alzheimer disease; ADAS-Cog, Alzheimer’s Disease Assessment Scale—Cognitive Subsection; BMI, body mass index; BPSD, Behavioural and Psychological Symptoms of Dementia; CDR-Sb, Clinical Dementia Rating, Sum of Boxes; DAD, Disability Assessment for Dementia.

*p < 0.05.
|                      | Model 1 | Model 2 | Model 3 |
|----------------------|---------|---------|---------|
|                      | β coef. (95% CI) | p-value | β coef. (95% CI) | p-value | β coef. (95% CI) | p-value |
| **ADAS-Cog change: 12 months** |         |         |         |
| Long-term antipsychotic use x APOE ε4 allele | 4.12 (−0.97, 7.37) | 0.010* | 4.07 (0.91, 7.23) | 0.012* | 3.91 (−0.67, 7.15) | 0.018* |
| Age                  | −0.15 (−0.26, −0.04) | 0.008* | −0.17 (−0.28, −0.06) | 0.003* | −0.18 (−0.29, −0.07) | 0.001* |
| Gender (female)      | 0.20 (−1.60, 2.01) | 0.825 | 0.20 (−1.61, 2.00) | 0.829 | 0.21 (−1.29, 2.02) | 0.820 |
| BMI                  | −0.13 (−0.35, 0.09) | 0.238 | −0.15 (−0.36, 0.07) | 0.180 | −0.14 (−0.35, 0.08) | 0.208 |
| Education (years)    | 0.04 (−0.20, 0.28) | 0.750 | 0.06 (−0.18, 0.30) | 0.620 | 0.07 (−0.17, 0.31) | 0.570 |
| Baseline ADAS-Cog    | 0.02 (−0.07, 0.12) | 0.625 | 0.03 (−0.07, 0.12) | 0.566 | 0.03 (−0.06, 0.12) | 0.540 |
| Diagnosis duration   | −0.14 (−0.69, 0.42) | 0.623 | −0.18 (−0.74, 0.38) | 0.530 | −0.19 (−0.75, 0.37) | 0.516 |
| Study group (Nilvadipine) | −0.30 (−2.03, 1.43) | 0.735 | −0.34 (−2.07, 1.39) | 0.702 | −0.27 (−2.01, 1.59) | 0.757 |
| Cholinesterase inhibitor | −1.17 (−4.01, 1.66) | 0.419 | −1.39 (−4.24, 1.46) | 0.340 | −1.26 (−4.11, 1.15) | 0.387 |
| Total medications    | 0.21 (−0.17, 0.58) | 0.278 | 0.23 (0.15, 0.60) | 0.236 |                  |        |
| Total comorbidities  | 0.10 (−0.30, 0.50) | 0.621 | 0.11 (−0.28, 0.50) | 0.578 |                  |        |
| 'Definite' anticholinergic use |                  |        |                  |        |                  |        |
| BPSD                 | −2.25 (−5.11, 0.61) | 0.123 |                  |        |                  |        |

| **ADAS-Cog change: 18 months** |         |         |         |
| Long-term antipsychotic use x APOE ε4 allele | 4.57 (0.35, 8.79) | 0.034* | 4.68 (0.43, 8.92) | 0.031* | 4.81 (−0.50, 9.11) | 0.029* |
| Age                  | −0.23 (−0.37, −0.10) | <0.001* | −0.26 (−0.39, 0.12) | <0.001* | −0.26 (−0.39, −0.12) | <0.001* |
| Gender (female)      | −0.78 (−2.98, 1.42) | 0.487 | −0.82 (−3.02, 1.39) | 0.467 | −0.91 (−3.13, 1.31) | 0.421 |
| BMI                  | −0.14 (−0.40, 0.12) | 0.297 | −0.16 (−0.41, 0.10) | 0.233 | −0.14 (−0.40, 0.12) | 0.277 |
| Education (years)    | 0.11 (−0.18, 0.30) | 0.442 | 0.13 (−0.16, 0.42) | 0.386 | 0.11 (−0.18, 0.40) | 0.441 |
| Baseline ADAS-Cog    | 0.11 (−0.01, 0.22) | 0.069 | 0.11 (−0.00, 0.23) | 0.057 | 0.12 (0.01, 0.24) | 0.043* |
| Diagnosis duration   | −0.29 (−0.94, 0.36) | 0.383 | −0.27 (−0.92, 0.38) | 0.411 | −0.34 (−1.01, 0.34) | 0.327 |
| Study group (Nilvadipine) | −0.34 (−2.44, 1.77) | 0.755 | −0.36 (−2.47, 1.75) | 0.738 | −0.39 (−2.50, 1.72) | 0.717 |
| Cholinesterase inhibitor | −0.50 (−3.98, 2.98) | 0.778 | −0.60 (−4.11, 2.90) | 0.737 | −0.50 (−4.01, 3.02) | 0.783 |
| Total medications    | 0.09 (−0.36, 0.54) | 0.699 | 0.11 (−0.35, 0.57) | 0.642 |                  |        |
| Total comorbidities  | 0.22 (−0.26, 0.70) | 0.375 | 0.22 (−0.26, 0.70) | 0.374 |                  |        |
| 'Definite' anticholinergic use |                  |        |                  |        |                  |        |
| BPSD                 | −1.14 (−4.58, 2.30) | 0.515 |                  |        |                  |        |
|                          | Model 1       |            | Model 2       |            | Model 3       |            |
|--------------------------|--------------|------------|--------------|------------|--------------|------------|
|                          | β  coef. (95% CI) | p-value    | β  coef. (95% CI) | p-value    | β  coef. (95% CI) | p-value    |
| **CDR-Sb change: 12 months** |              |            |              |            |              |            |
| *Long-term antipsychotic use x APOE ε4 allele* |              |            |              |            |              |            |
| Age                      | −0.04 (−0.07, −0.01) | 0.022* | −0.04 (−0.08, −0.01) | 0.022* | −0.04 (−0.08, −0.01) | 0.017* |
| Gender (female)           | 0.17 (−0.39, 0.73) | 0.556      | 0.19 (−0.37, 0.75) | 0.510      | 0.23 (−0.33, 0.79) | 0.420      |
| BMI                       | 0.01 (−0.05, 0.08) | 0.689      | 0.12 (−0.06, 0.08) | 0.721      | 0.00 (−0.06, 0.07) | 0.914      |
| Education (years)         | −0.02 (−0.09, 0.06) | 0.643      | −0.14 (−0.09, 0.06) | 0.711      | −0.00 (−0.08, 0.07) | 0.935      |
| Baseline CDR-Sb           | 0.02 (−0.09, 0.13) | 0.745      | 0.02 (−0.09, 0.13) | 0.712      | −0.01 (−0.10, 0.12) | 0.869      |
| Diagnosis duration        | −0.02 (−0.20, 0.16) | 0.810      | −0.04 (−0.22, 0.14) | 0.675      | 0.01 (−0.18, 0.19) | 0.926      |
| Study group (Nilvadipine) | 0.00 (−0.54, 0.54) | 0.990      | 0.00 (−0.54, 0.54) | 0.987      | −0.01 (−0.54, 0.53) | 0.984      |
| Cholinesterase inhibitor  | −0.18 (−1.05, 0.69) | 0.680      | −0.25 (−1.12, 0.63) | 0.583      | −0.31 (−1.18, 0.57) | 0.491      |
| Total medications         | −0.05 (−0.18, 0.07) | 0.387      | 0.07 (−0.04, 0.19) | 0.211      | 0.07 (−0.05, 0.18) | 0.267      |
| Total comorbidities       |              |            |              |            |              |            |
| 'Definite' anticholinergic use |              |            |              |            |              |            |
| BPSD                      |              |            |              |            |              |            |
| **CDR-Sb change: 18 months** |              |            |              |            |              |            |
| *Long-term antipsychotic use x APOE ε4 allele* |              |            |              |            |              |            |
| Age                      | −0.09 (−0.14, −0.03) | 0.002*     | −0.09 (−0.15, 0.04) | 0.001*     | −0.09 (−0.15, −0.04) | 0.001*     |
| Gender (female)           | −0.29 (−1.17, 0.60) | 0.529      | −0.29 (−1.18, 0.60) | 0.524      | −0.29 (−1.18, 0.60) | 0.520      |
| BMI                       | 0.05 (−0.05, 0.16) | 0.321      | 0.05 (−0.06, 0.15) | 0.369      | 0.05 (−0.06, 0.15) | 0.406      |
| Education (years)         | 0.01 (−0.11, 0.13) | 0.859      | 0.02 (−0.10, 0.13) | 0.797      | 0.02 (−0.10, 0.14) | 0.767      |
| Baseline CDR-Sb           | 0.21 (0.03, 0.39) | 0.022*     | 0.21 (0.03, 0.39) | 0.020*     | 0.20 (−0.02, 0.38) | 0.027*     |
| Diagnosis duration        | −0.03 (−0.32, 0.27) | 0.855      | −0.06 (−0.36, 0.24) | 0.690      | −0.04 (−0.35, 0.27) | 0.806      |
| Study group (Nilvadipine) | 0.29 (−0.56, 1.14) | 0.500      | 0.28 (−0.57, 1.13) | 0.518      | 0.26 (−0.59, 1.11) | 0.548      |
| Cholinesterase inhibitor  | −0.04 (−1.41, 1.32) | 0.950      | −0.16 (−1.53, 1.21) | 0.820      | −0.14 (−1.52, 1.24) | 0.843      |
| Total medications         | −0.11 (−0.08, 0.29) | 0.254      | 0.11 (−0.07, 0.29) | 0.237      |                  |            |
| Total comorbidities       | 0.01 (−0.19, 0.21) | 0.941      | 0.01 (−0.19, 0.21) | 0.924      |                  |            |
| 'Definite' anticholinergic use |              |            |              |            |              |            |
| BPSD                      |              |            |              |            |              |            |

*Continues*
| Table 4 (Continued) | Model 1 | Model 2 | Model 3 |
|---------------------|---------|---------|---------|
|                     | β coef. (95% CI) | p-value | β coef. (95% CI) | p-value | β coef. (95% CI) | p-value |
| DAD change: 12 months |         |         |         |         |         |         |
| Long-term antipsychotic use × APOE ε4 allele | −3.40 (−6.12, −0.67) | 0.015 | −3.34 (−6.08, 0.60) | 0.017 | −3.08 (−5.89, −0.26) | 0.032 |
| Age                 | 0.16 (0.06, 0.25) | 0.001 | 0.16 (0.06, 0.26) | 0.001 | 0.16 (−0.07, 0.26) | 0.001 |
| Gender (female)     | −1.14 (−2.70, 0.42) | 0.153 | −1.16 (−2.72, 0.41) | 0.147 | −1.22 (−2.79, 0.35) | 0.127 |
| BMI                 | −0.07 (−0.25, 0.12) | 0.490 | −0.06 (0.25, 0.12) | 0.514 | −0.05 (−0.24, 0.14) | 0.592 |
| Education (years)   | 0.25 (0.05, 0.45) | 0.015 | 0.25 (−0.04, 0.45) | 0.017 | 0.23 (−0.02, 0.43) | 0.030 |
| Baseline DAD        | −0.12 (−0.23, −0.02) | 0.021 | −0.13 (−0.23, −0.02) | 0.019 | −0.13 (−0.23, −0.02) | 0.013 |
| Diagnosis duration  | −0.45 (−0.23, 0.02) | 0.063 | −0.42 (−0.90, 0.05) | 0.081 | 0.05 (−0.30, 0.39) | 0.748 |
| Study group (Nilvadipine) | 0.27 (−1.23, 1.76) | 0.726 | 0.26 (−1.23, 1.76) | 0.731 | 0.26 (−1.23, 1.76) | 0.732 |
| Cholinesterase inhibitor | 1.39 (−1.03, 3.80) | 0.261 | 1.46 (−0.95, 3.92) | 0.233 | 1.46 (−0.95, 3.92) | 0.194 |
| Total medications   | −0.11 (−0.43, 0.22) | 0.526 | −0.11 (−0.43, 0.22) | 0.598 | −0.11 (−0.43, 0.22) | 0.598 |
| Total comorbidities | 0.05 (−0.30, 0.39) | 0.783 | 0.05 (−0.30, 0.39) | 0.748 | 0.05 (−0.30, 0.39) | 0.748 |
| 'Definite' anticholinergic use | 0.471 |       |         |         |         |         |
| BPSD                | 0.323 |       |         |         |         |         |

DAD change: 18 months

| Long-term antipsychotic use × APOE ε4 allele | 4.26 (−7.53, −0.99) | 0.011 | −4.20 (−7.48, 0.90) | 0.013 | −4.19 (−7.56, −0.81) | 0.015 |
| Age                 | 0.22 (0.11, 0.33) | <0.001 | 0.22 (−0.10, 0.34) | <0.001 | 0.22 (−0.10, 0.34) | <0.001 |
| Gender (female)     | −1.38 (−3.25, 0.48) | 0.145 | −1.41 (−3.28, 0.46) | 0.139 | −1.41 (−3.29, 0.46) | 0.139 |
| BMI                 | −0.16 (−0.38, 0.06) | 0.143 | −0.16 (−0.38, 0.06) | 0.142 | −0.16 (−0.38, 0.06) | 0.146 |
| Education (years)   | −0.04 (−0.21, 0.29) | 0.751 | −0.04 (−0.21, 0.28) | 0.765 | −0.04 (−0.21, 0.29) | 0.774 |
| Baseline DAD        | −0.12 (−0.25, 0.01) | 0.074 | −0.12 (−0.25, 0.01) | 0.074 | −0.12 (−0.25, 0.01) | 0.075 |
| Diagnosis duration  | −0.42 (−1.04, 0.19) | 0.181 | −0.41 (−1.03, 0.22) | 0.203 | −0.41 (−1.05, 0.23) | 0.207 |
| Study group (Nilvadipine) | −0.11 (−1.66, 1.88) | 0.905 | 0.10 (−1.67, 1.87) | 0.913 | 0.10 (−1.67, 1.88) | 0.910 |
| Cholinesterase inhibitor | 0.91 (−1.95, 3.78) | 0.532 | 0.96 (−1.92, 3.84) | 0.515 | 0.96 (−1.93, 3.86) | 0.515 |
| Total medications   | −0.06 (−0.44, 0.33) | 0.770 | −0.06 (−0.44, 0.33) | 0.773 | −0.06 (−0.44, 0.33) | 0.773 |
| Total comorbidities | −0.08 (−0.35, 0.50) | 0.719 | −0.08 (−0.35, 0.50) | 0.718 | −0.08 (−0.35, 0.50) | 0.718 |
| 'Definite' anticholinergic use | −0.01 (−3.34, 3.32) | 0.995 |         |         |         |         |
| BPSD                | −0.14 (−3.31, 3.04) | 0.933 |         |         |         |         |

Abbreviations: AD, Alzheimer disease; ADAS-Cog, Alzheimer’s Disease Assessment Scale—Cognitive Subsection; BMI, body mass index; BPSD, Behavioural and Psychological Symptoms of Dementia, CDR-Sb, Clinical Dementia Rating, Sum of Boxes; DAD, Disability Assessment for Dementia.

*p < 0.05.
Those individuals in our study continuously using an antipsychotic medication experienced greater cognitive decline and dementia severity at both 12 and 18 months. These findings persisted on controlling for baseline dementia severity, duration since the diagnosis of dementia was made and other factors known to have an important effect on cognition. Fully adjusted models additionally controlled for the presence of BPSD to mitigate effects of confounding-by-indication in addition to the effects of using definite anticholinergics, which itself may act as a risk for later cognitive decline. Our results are largely consistent with previous reports in the literature, particularly the results from the CATIE-AD study in addition to the study by Kennedy and colleagues, the only previous study to examine the impact of antipsychotics in mild‐moderate AD.

Participants in this study were living in their own homes, and well enough to participate in a clinical trial. As the first study to address this question in community-dwelling people with mild–moderate AD, this is significant in the context that any intervention which could accelerate cognitive decline and dementia severity at this clinical stage, could influence peoples escalating care needs for additional home supports or transition to long-term care. This has significant implications for quality of life for both the individual living with dementia and their carers. It may also influence the cost of care for those living with dementia.

The 18-month duration in this study represents the longest follow-up of cognitive trajectories in those with mild–moderate AD examining the impact of antipsychotic usage. In the first instance, antipsychotics are only recommended for short durations in AD, with tapering or withdrawal advised after a duration of 4 months. A recent Cochrane review has concluded that there is no effect on the severity of BPSD following withdrawal of antipsychotics, consistent with the fact that most behavioural complications of dementia are intermittent and rarely persist for more than 3 months. Thus, our evidence supports previous reports calling for the discontinuation of antipsychotic usage after a period of 3–4 months in order to prevent later harm such as cognitive decline and adverse events in older adults with mild–moderate AD.

Our study is also the first study to analyse the potential APOE genotype-dependent effects of antipsychotic use on cognition in those with dementia. Of note, previous evidence suggests that those carrying the APOE ε4 allele are at greater risk of psychotic symptoms in AD. APOE ε4 carriers have an earlier age of dementia onset and studies have demonstrated accelerated accumulation of amyloid deposition, neurofibrillary tangle formation and even clinical progression. Our current results suggest that APOE ε4 carriers may experience accelerated cognitive decline in comparison to non-carriers with antipsychotic use.

Our study has several notable strengths. First, our inclusion, both 12- and 18-month follow-up timepoints, is a notable strength. As already discussed, our study represents the longest duration of follow-up in studies examining the adverse cognitive consequences of antipsychotic usage in dementia. Further, by the detailed ADAS-Cog, we were able to detect clinically meaningful cognitive decline, which may not have been detected on the MMSE, used by most studies on antipsychotic use in the literature. We were also able to control for baseline cognitive severity as well as a number of other important factors that may affect cognitive trajectories.

However, our study has several notable limitations. The principal limitation of the current study is that the presence of BPSD was recorded as a binary variable, with no specific data on the severity of neuropsychiatric symptoms or treatment response to antipsychotics preceding trial enrolment. However, in this medication trial recruited into by senior clinicians, those with significant BPSD were excluded from participation in the first instance. In our study, those continuously using an antipsychotic (only half of those coded as actually having BPSD) may represent those with particularly severe BPSD which may explain the deterioration in cognitive function over time. In this light, we may not be fully able to exclude confounding by indication; however, we have been able to minimize it.

In conclusion, we demonstrated a significant impact of long-term antipsychotic use on accelerated cognitive decline and dementia progression in mild–moderate AD. Our results also highlight the fact that those with APOE risk alleles may be particularly vulnerable to cognitive decline with long-term antipsychotic use. Our findings have important implications for those considering the use of antipsychotics in dementia and advocate for their withdrawal, where possible, in those with mild–moderate AD.

ACKNOWLEDGEMENTS
NILVAD Study Group

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The funding for the NILVAD study was from the European Commission Framework 7 Programme Health Theme Collaborative Project (grant 279093; PI: Brian Lawlor).

CONFLICT OF INTEREST
Authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT
Data available from authors on reasonable request.

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How to cite this article: Dyer AH, Murphy C, Lawlor B, Kennelly SP, for the NILVAD Study Group. Long-term antipsychotic use and cognitive decline in community-dwelling older adults with mild–moderate Alzheimer disease: data from NILVAD. *Int J Geriatr Psychiatry*. 2021;36(11):1708-1721. doi:10.1002/gps.5591