Nursing home placement in the donepezil and memantine in moderate to severe Alzheimer's disease (DOMINO) trial: secondary and post-hoc analyses of a randomised trial

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Authors' Competing Interest Statement

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Structured abstract

Background: Observational studies have suggested delay in nursing home placement (NHP) with dementia drug treatment, but an earlier randomised trial in patients with mild to moderate Alzheimer's disease (AD) showed no effect. We investigated the effects of continuing or discontinuing donepezil and starting memantine on subsequent NHP in moderate to severe AD.

Methods: In the DOMINO trial (ISRCTN49545034) 295 community living patients with moderate to severe AD recruited from 15 centres in England and Scotland from February 2008 to March 2010 were randomised with double-blind placebo-control to continue donepezil (73), discontinue donepezil (73), discontinue donepezil and start memantine (76), or continue donepezil and start memantine (73) for 52 weeks. After 52 weeks choice of treatment was left to participants and their physicians. Place of residence was recorded at outcomes assessment points during the first 52 weeks of the trial and subsequently every 26 weeks for a further 3 years. Nursing home placement was an irreversible move from independent accommodation to a residential caring facility and was a secondary trial endpoint. Analyses restricted to the risk of placement in the first year of follow-up were post-hoc.

Findings: 162 patients (55%) underwent NHP within 4 years of randomisation. Numbers of NHPs were similar for all arms (36 in patients who continued donepezil, 42 who discontinued donepezil, 41 who discontinued donepezil and started memantine, and 43 who continued donepezil and started memantine). There was significant (p=0.010) heterogeneity of treatment effect over time with significantly more NHPs in the donepezil discontinuation group during the first year (HR 2.09 (95% CI, 1.29 to 3.39)) and no difference later (HR 0.89 (95% CI, 0.58 to 1.35)). Subsequent analyses focussed on the first year of the trial and on donepezil only were post-hoc. 1-year NHP risk was 17% higher (95% CI 6% to 28%) in patients allocated to discontinue donepezil compared to continuing donepezil. There was no effect of starting memantine compared to no memantine during the first year (HR 0.92 (95% CI 0.58 to 1.45)) or later (HR 1.23 (95% CI 0.81 to 1.87)); difference in 1-year NHP risk 1% (95% CI -12% to 10%).

Interpretation: Withdrawing donepezil in patients with moderate to severe AD increased the risk of NHP during 12 months of trial treatment, but made no difference to NHP over 4 years of follow-up. Decisions to stop or continue drug treatment at this stage should be informed by potential risks of withdrawal, even if the perceived benefits of continued treatment are not clear.

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Introduction

Reasons for nursing home placement (NHP) in Alzheimer's disease (AD) are complex, involving patient and caregiver characteristics as well as the cultural and social environment. White ethnicity, impairments in cognition and activities of daily living, behavioural problems and increased caregiver age and burden all predict nursing home placement in AD.[1] Economic costs in dementia increase markedly with disease severity with NHP contributing substantially to total support costs in severe dementia. Whether cholinesterase inhibitors and memantine can delay the point at which AD patients make the transition to permanent residential care is controversial. AD2000, the only randomised controlled double-blind trial to directly address this question for donepezil was negative.[2] Observational studies, following patients who have participated in double-blind or open trials or received open label treatment with tacrine,[3] donepezil,[4] tacrine, donepezil or rivastigmine,[5,6] galantamine,[7] or memantine combined with a cholinesterase inhibitor[8] have reported positive results. These studies have been criticised as they have not involved randomisation, placebo-control or blinding of treatment allocation.[9-12] The socioeconomic implications of resolving this controversy are clear. Models based on assumptions that the drugs can delay placement indicate large societal and healthcare cost savings.[13]

We have previously shown that continued treatment with donepezil in patients with moderate to severe AD is associated with cognitive and functional benefits over the course of 12 months compared to tapering and discontinuing.[14] It could be argued that modest cognitive and functional treatment benefits in moderate to severe dementia have only limited impact on the lives of patients and caregivers. An important secondary objective of our trial was to investigate whether continuing a drug treatment that improved dementia symptoms would also delay NHP in an AD population who had already reached the severity point at which independent home living was likely to be compromised. Trial participants have completed 4 years of double-blind follow-up and we now report how treatment allocation affected subsequent permanent NHP.

Methods

Study design and participants

The Donepezil and Memantine in Moderate to Severe Alzheimer's Disease (DOMINO) study (ISRCTN49545034) was a multicentre (15 secondary care Memory Services in England and Scotland), double-blind, placebo-controlled, clinical trial with a two-by-two factorial design.[15] Eligible participants met standardized criteria[16] for probable or possible moderate or severe AD, had been prescribed donepezil continuously for at least 3 months with a dose of 10 mg for at least the previous 6 weeks, and had a score between 5 and 13 on the Standardised Mini-Mental State Examination.[17]

Randomisation and masking

The first 80 participants were assigned with the use of a prepared unrestricted randomised list of assignments to ensure allocation concealment.[18] Thereafter, participants were randomly assigned to one of four treatment groups for 12 months: continuation of donepezil 10 mg per day, with placebo memantine; discontinuation of donepezil (following 4 weeks of treatment with 5 mg), with placebo memantine; discontinuation of donepezil and initiation of treatment with memantine 20 mg per day;

or continuation of donepezil 10 mg per day and initiation of memantine 20 mg per day. Treatment assignments were made by the U.K. Medical Research Council Clinical Trials Unit with the use of randomized minimization.[18] Groups were stratified according to centre (among the 15 participating centres), duration of donepezil treatment before entry (3 to 6 months vs. >6 months), baseline SMMSE score (5 to 9 vs. 10 to 13), and age (<60 years, 60 to 74 years, or >74 years). Patients, caregivers, clinicians, outcome assessors, and investigators were blinded to treatment assignments.

Outcome measures and trial procedures

The primary outcomes of the trial were scores on the SMMSE and on the caregiver-rated Bristol Activities of Daily Living Scale. Results on these outcomes, along with neuropsychiatric symptoms, participant quality of life and caregiver psychological distress outcomes during completion of the 52 week intervention have been reported in an earlier paper.[14] In addition, the Client Service Receipt Inventory (CSRI)[19] was completed for the 52 weeks of trial treatment. In the CSRI, the following are classified as NHP: care home providing nursing care, care home providing personal care, dual registered home (providing both personal and nursing care), acute psychiatric ward, general medical ward, rehabilitation ward) and the following as non-NHP: owner occupied house/flat, privately rented house/flat, house/flat rented from housing association or local authority, sheltered/warden controlled housing, extra care housing. The CSRI captured the patient's "usual place of residence" since the last assessment, together with the number of days spent living in other locations. When the "usual place of residence" had changed to a NHP from the previous visit, the date of NHP was estimated as the number of days lived outside NHP since the previous assessment date subtracted from the assessment date at which the change was reported. Over the following 3 years, the caregiver was contacted by telephone every 26 weeks and asked whether the participant was still living at home or had moved to live permanently in a residential or nursing home, and if such a move had occurred, the date of transition. The definition of NHP and the date of transition to NHP remained the same throughout the study, despite the change in the method of data collection. The original planned sample size was 800, but was adjusted to 430 due to reduced standard deviations for the primary outcomes from an interim blinded analysis of trial data. The trial was designed with at least 90% power for the primary outcomes, but was not powered to show differences on time to NHP. Trial recruitment was conducted between 11 February 2008 and 5 March 2010 and the last participant completed follow-up in March 2014.

Study oversight

The study was overseen by King's College London and was funded by the U.K. Medical Research Council and the Alzheimer's Society. Full ethical approval was received from the Scotland A Multicentre Research Ethics Committee. Agreement in writing to take part in the study was obtained from participants if they had capacity to give informed consent, and the main caregivers gave written consent for their own involvement and assent for the patients' participation. The corresponding author (RH) vouches for the accuracy and completeness of the data and for the fidelity of the study to the protocol. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. Data sharing: patient level data (without date of birth or recruiting centre) and the full dataset are available with open access from the

corresponding author. Consent was not obtained from participants for data sharing but the presented data are anonymised and risk of identification is low.

Role of the funding source

The UK Medical Research Council and Alzheimer's Society who funded the trial had no role in the study design, the collection, analysis or interpretation of data, the writing of the report or the decision to submit for publication. Pfizer-Eisai and Lundbeck donated drug and placebo supplies but had no involvement in the design or conduct of the study or the analysis or reporting of the data. All authors had full access to all of the study data and Professor Howard had final responsibility for submitting the paper for publication.

Statistical analysis

Following the pre-specified statistical analysis plan, time to NHP was analysed using stratified log-rank (using randomisation minimisation factors as strata) and Cox proportional hazards regression with patients who died or who withdrew from follow-up before NHP censored at date of death or withdrawal. The assumption of proportion hazards was tested using the Shoenfeld residuals with ranking of follow-up time. Since this was a secondary endpoint for the trial, the statistical analysis plan did not include any pre-specified analyses in the event of non-proportional hazards, when the log-rank test has reduced power to detect differences and standard Cox regression is inappropriate. Subsequent analyses were not pre-specified in the analysis plan since the presence of non-proportional hazards was not anticipated. For situations with evidence of non-proportional hazards ($p < 0.05$), follow-up was split into distinct periods with hazards assumed to be proportional within each period (piecewise proportional hazards modelling). Regression models with different time period splits were compared using the Akaike Information Criterion (AIC). Probability of NHP by time after randomisation was calculated from the Kaplan-Meier survivor function with 95% confidence intervals. Differences in centiles of survival time and probability of NHP between groups were calculated with 95% bias-corrected bootstrap confidence intervals using 1000 bootstrap replications. The log-rank statistic was calculated for each strata and tabulated with event rate ratios using methods previously described[20] to explore the effect of stratification.

The protocol and statistical analysis plan pre-specified that death before NHP would be considered as a censoring event in the same way as withdrawal or loss from follow-up. However, NHP may have been more likely in patients who died compared to those who withdrew from follow-up had the patients not died or withdrawn respectively. We therefore conducted two additional sensitivity analyses: 1) considering all deaths as NHP events at the time of death (equivalent to the composite endpoint of death or NHP) and 2) a competing risks analysis[21] modelling the sub-hazard function of NHP in the presence of the competing risk of death.

The following patient baseline covariates were evaluated for association with time to NHP in the regression model: age, gender, prior duration of donepezil treatment, centre, ethnicity, gender of carer, relationship of carer, whether patient lives with carer, sMMSE, BADLS, NPI, DEMQOL-proxy, EQ-5D health state, and NPI subscales of delusions, hallucinations, agitation/aggression and irritability/lability. Covariates were only considered as predictors if the treatment-adjusted effect was significant at the 5% level in separate univariable models.

In addition, parametric models were used to describe how the underlying risk of NHP changes with time. The following standard parametric models were fitted to the data: Weibull, generalized gamma, log-normal, log-logistic and Gompertz. Flexible parametric survival models do not assume an underlying log-linear relationship with time or with hazard and allow a more flexible fully parametric modelling approach.[22] These were compared with standard parametric models, with the best fitting model chosen using the AIC.

Results

Of the 295 patients randomised into the trial, 162 (55%) had NHP within 4 years of randomisation. Table 1 summarises the patient baseline characteristics and Table 2 time to NHP in each of the four treatment groups. Figure 1 shows the patient flowchart.

Primary analysis (pre-specified)

There was evidence of a difference in time to NHP between discontinuing and continuing donepezil (stratified log rank test, p=0.022), although non-significant in the un-stratified analysis (p=0.100). There was no evidence for an interaction (p=0.168 stratified, p=0.446 un-stratified) and no benefit of starting memantine (p=0.719 stratified, p=0.628 un-stratified). Subsequent analyses therefore only consider the effect of discontinuing donepezil. Figure 2A shows the Kaplan-Meier survival curve of cumulative probability of NHP by treatment arm.

The 25th percentile of time to NHP was greater in patients continuing donepezil, 12.7 months (95% CI, 10.4 to 14.0), as compared to 8.9 (95% CI, 5.5 to 10.1) months for patients discontinuing donepezil, a difference of 3.8 months (95% CI, 1.5 to 7.0). There was no difference in median time to NHP: 21.9 months (95% CI, 16.9 to 29.1) and 16.7 months (95% CI, 12.7 to 22.1) respectively.

Figure 3 shows the log rank statistics and event rate ratio for each strata and also by time period of NHP from randomisation, by whether patients were allocated to continue or discontinue donepezil.

There was clear evidence of non-proportional hazards (p=0.01, Figure 2B) indicating that the overall hazard ratio of discontinuing compared to continuing donepezil was not an appropriate summary measure as the effect of discontinuing donepezil changed with time. Kaplan Meier survival curves appeared to separate over the first 12 months and were parallel thereafter. Subsequent results are based on analyses that were not pre-specified in the analysis plan since non-proportional hazards was not anticipated.

Piecewise modelling in the presence of non-proportional hazards

Splitting follow-up time at only 12 months resulted in better model fit, and lower AIC, than splits at any combination of 6, 12 and 24 months (data not shown). Discontinuing donepezil more than doubled the (instantaneous) probability of NHP over the first year (hazard ratio 2.09 (95% CI, 1.29 to 3.39)) compared to continuing donepezil (Table 3). This benefit was maintained after 12 months with curves remaining approximately equidistant (hazard ratio 0.89, (95% CI, 0.58 to 1.35)). This hazard ratio after 12 months should be interpreted with caution due to selection bias;[23] this is estimated from the sub-

group of patients without NHP by 12 months which included more patients that had discontinued than had continued donepezil.

Discontinuing donepezil treatment increased the probability of NHP over the first 6 months from 0.06 to 0.19 (difference 0.13, 95% CI, 0.04 to 0.21) and over the first 12 months from 0.20 to 0.37 (difference 0.17, 95% CI, 0.06 to 0.28), see Table 3. This indicates a number needed to treat of 5.88 patients for 12 months to prevent 1 NHP.

Patients who lived with their carers at baseline had a lower instantaneous risk of NHP throughout follow-up as compared to those that didn't live with their carers (p=0.013, hazard ratio 0.63, 95% CI, 0.44 to 0.89). This effect did not differ by treatment arm (p=0.48, test for interaction) and no other baseline covariates tested were associated with NHP (data not shown).

Sensitivity analyses

66 patients died before NHP with a further 26 deaths reported after NHP. There was no evidence for differences in time to death between arms (p=0.816 stratified, p=0.971 un-stratified). In both the analysis of the composite endpoint of death or NHP and the competing risks analysis, the results were consistent with no evidence of an effect of memantine and evidence of a large benefit with donepezil over the first 12 months that was maintained after 12 months (data not shown).

Parametric survival models

None of the standard parametric models provided a good fit for the data, unlike the flexible parametric survival model. The preferred model was a PH(1) model with 3 degrees of freedom for the time varying covariate of donepezil (active vs placebo). Figure 4 shows the fitted hazard function (Figure 4A) and survivor function (Figure 4B) from this model showing how the underlying risk of NHP changes with time. The risk of NHP in patients discontinuing donepezil is high in the first months, with a peak around 6 months and steadily declining thereafter. The risk of NHP in patients continuing donepezil is lower over the first 12 months, with the peak not occurring until after 12 months and steadily declining after this. There is clear separation of the curves over the first 6-12 months with the risk of NHP approximately equal for both groups from 12 months onwards.

Discussion

This is the first randomised double-blind study to demonstrate a significant effect of dementia drug treatment on NHP. We found that discontinuing donepezil treatment in patients with moderate to severe AD was associated with a doubling of the instantaneous risk of placement to nursing homes over 12 months. There was no significant difference in the risk of placement at later follow-up points and there was no effect of starting memantine treatment, either singly or when combined with donepezil, at any point in the trial. We acknowledge that the comparison of time to NHP was a secondary objective of the DOMINO trial and that the analysis restricted to the first 12 months was not pre-specified in the statistical analysis plan. These results should therefore be considered exploratory and ideally would need to be confirmed in future studies. It is recommended that

restricted mean survival time may be a more appropriate treatment effect measure than (average) hazard ratio in the presence of non-proportional hazards. However, given the apparent disadvantages of withdrawing cholinesterase inhibitor treatment,[14] data from further double-blind trials are unlikely to become available.

The cholinesterase inhibitors are symptomatic treatments for AD and are not disease-modifying. How might symptom worsening, associated with withdrawal of donepezil, increase risk of nursing home placement? Yaffe and colleagues showed that impairment in activities of daily living (ADLs) was a more important predictor of NHP than cognitive impairment.[1] In their study, Kaplan-Meier rates for NHP over 1 year were 24% for patients with a Mini-Mental State Examination (MMSE)[24] score of 15 to 20, and 26% for MMSE score of <15, but 15% for those who were ADL independent and 25% for patients with one or more ADL dependency.[1] Analysis of data from a long-term clinical trial showed that, although baseline ADL score influenced risk for and time to NHP, it was decline in ADL that most strongly predicted placement.[25] Withdrawal from donepezil treatment in the DOMINO trial was associated with an average 3 point Bristol Activities of Daily Living Scale (BADLS)[26] disadvantage during the 12 month intervention period.[14] Given the established impact of ADL status and loss of ADLs upon the risk of NHP,[1,25] it is most likely that the ADL worsening seen when patients were withdrawn from donepezil in the trial represents the mechanism for earlier NHP.

Since NHP is influenced by social and living circumstances, preferences and values,[1] and that an earlier RCT conducted by some of the authors of the current study reached unambiguously negative conclusions,[2] is it truly plausible that donepezil treatment could significantly affect NHP? There are three important differences between the AD2000[2] and DOMINO[14] trials that might have relevance in consideration of this point. First, DOMINO examined the effects of withdrawing established donepezil treatment[27] while AD2000 investigated the effects of commencing treatment. Second, the mean MMSE score of patients entering AD2000 was 19 points, and for DOMINO 9 points. The participant populations were therefore very different in terms of dementia severity and proximity to the time of greatest risk of NHP. Only 9% of donepezil and 14% of placebo treated AD2000 patients moved to NHP in the first 12 months and it is possible that NHP was too rare an event in AD2000 for a treatment effect to be seen. Third, the magnitude of treatment effects on cognition and ADLs were greater in DOMINO than AD2000. Over 2 years, AD2000 participants who received donepezil were on average 0.8 MMSE points and 1.0 BADLS points better than those on placebo,[2] while the average 12-month drug-placebo differences for donepezil in DOMINO were 1.9 SMMSE points and 3.0 BADLS points.[14] Although they showed no overall effect on NHP, the AD2000 authors did find that BADLS and Neuropsychiatric Inventory[28] scores, and age were strong independent predictors of NHP, and using a multivariate model, predicted that a 2 to 3 point improvement in BADLS with donepezil would have reduced the rate of institutionalisation in their sample by 10% in the first year.

A limitation of our data is that we did not collect information about dementia drug use after the 52 weeks of double-blind trial treatment was completed. Participants were not routinely unblinded following completion of the trial drug treatment and decisions about their subsequent treatment were made by their responsible clinician. A second limitation relates to our examination of follow-up periods. In the pre-specified primary analysis, as described in the Protocol, considering the whole follow-up period (using a stratified log rank test), there was a statistically significant effect for continuing donepezil as compared to withdrawing and substituting placebo ($p = 0.022$). The piecewise modelling, however, considering time to NHP in the first 12 months that we carried out thereafter was

not a pre-specified analysis and this should be borne in mind in interpretation of the results. Further, withdrawal from study drug was significantly more common among participants assigned to discontinue donepezil than those assigned to continue[14] and this should be borne in mind in consideration of the results. A strength of our data was that DOMINO was designed as a pragmatic study, to answer questions about the treatment of typical AD patients within 15 different public health services for people with dementia across England and Scotland, and the inclusion and exclusion criteria were relatively unselective, both to facilitate participant recruitment and to ensure study generalisability.

The economic benefits of preventing or delaying NHP in AD are large and clear,[13,29] as in the UK this reduces costs to the public purse, even if it increases the imputed costs of unpaid care, but there would also be important positive effects upon patient quality of life. A survey of caregivers indicated that they regarded NHP as a major negative determinant of quality of life, with more than two-thirds rating delaying NHP as “extremely important” or “very important” in maintaining quality of life.[30] The decrease in the quality of life for people with dementia associated with NHP, along with societal costs of such placements have driven national policy in England to maintain people with dementia within their own households for as long as is possible. Our data suggest that withdrawing cholinesterase inhibitor treatment in moderate to severe AD brings forward the timing of NHP during the following 52 weeks, but that this effect did not operate at later points during 4-year follow-up. This would be consistent with the effects of modest symptomatic improvement in cognition and function associated with these drugs.

Contributions of authors

All authors contributed to the design and conduct of the trial and to the drafting of the study report. Robert Howard was the Chief Investigator for DOMINO, prepared the first draft of the study report and submitted it for publication. Patrick Phillips was the Trial Statistician and conducted the statistical analyses.

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Figure 1. Patient flowchart.

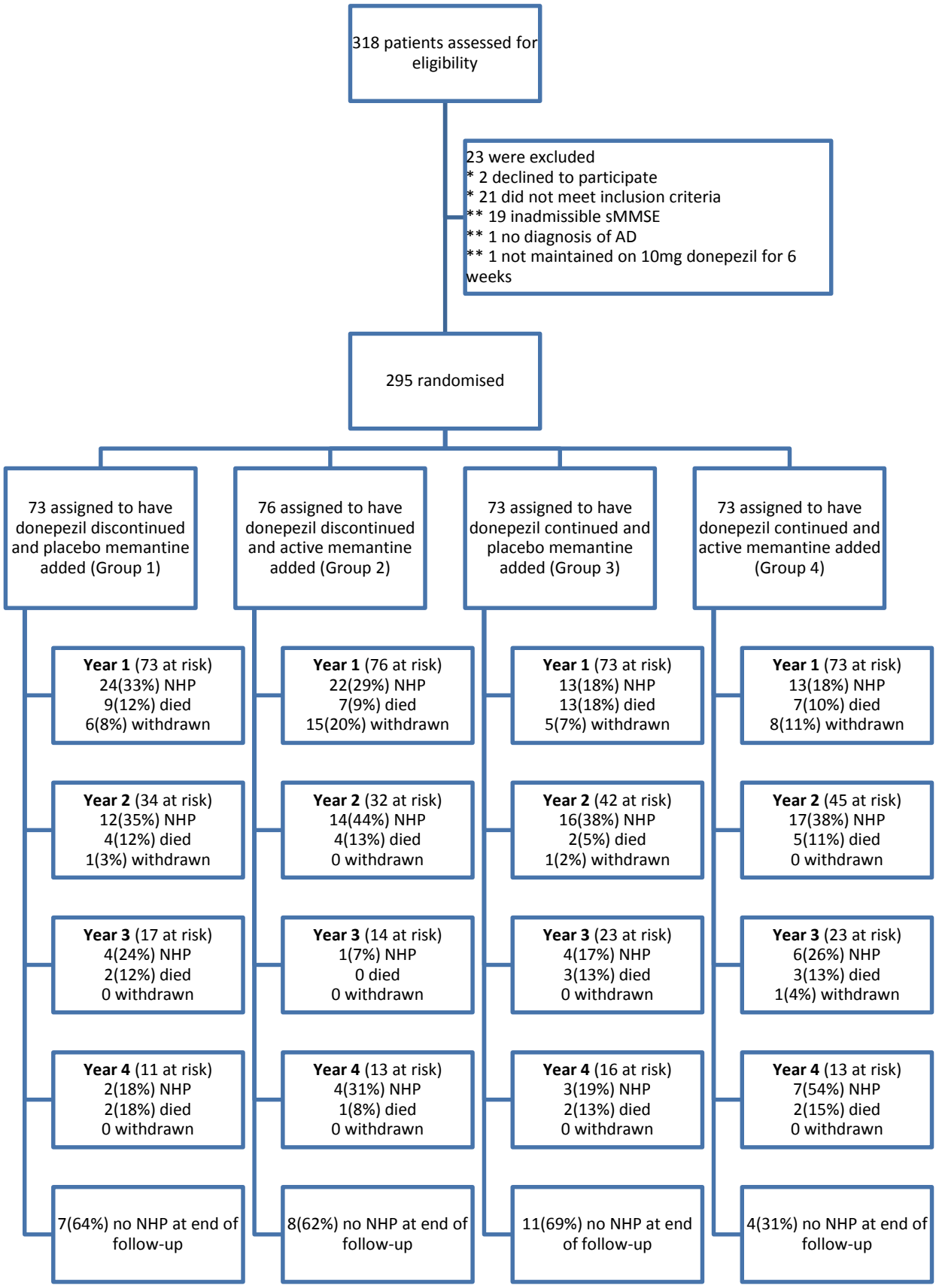
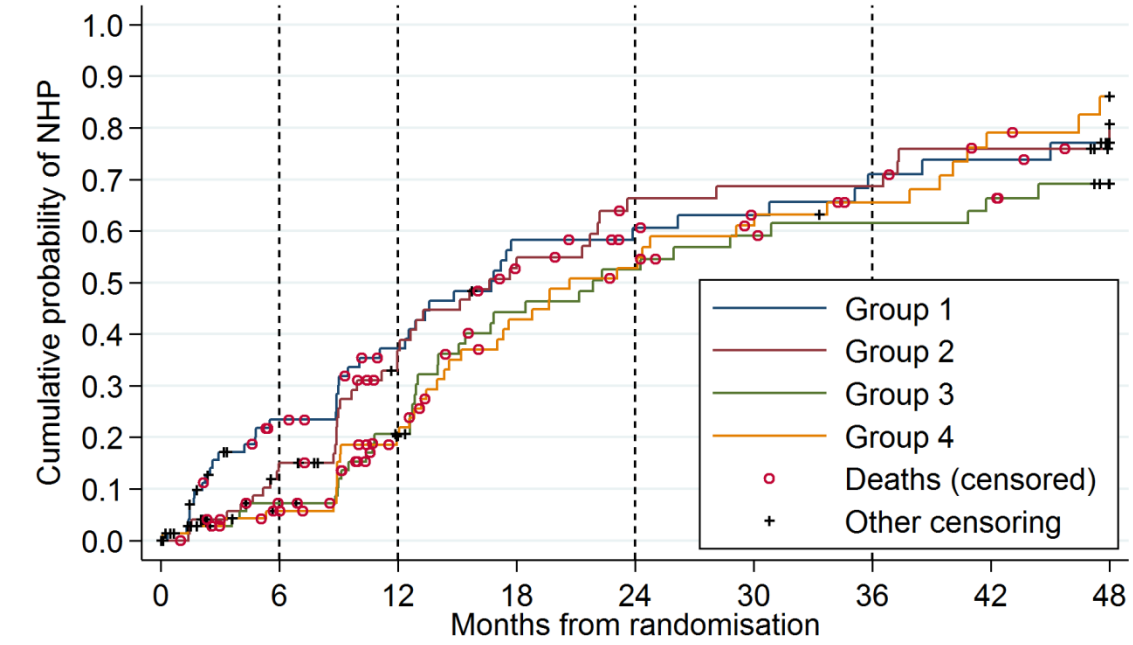


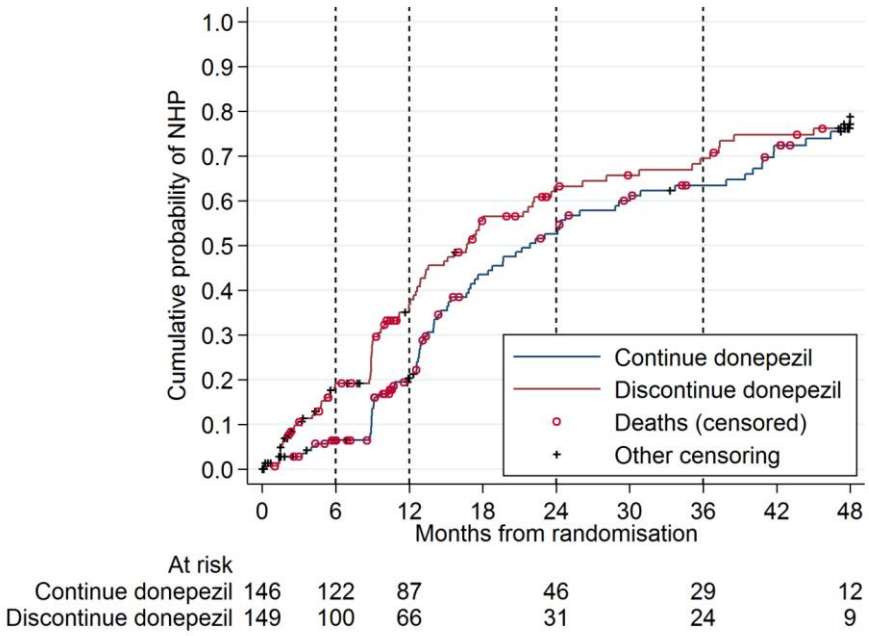
Figure 2: Kaplan-Meier curve of cumulative probability of NHP (A) by treatment group, (B) by discontinue vs continue donepezil and (C) by adding memantine. Patients were allocated to discontinue donepezil (group 1), discontinue donepezil and start memantine, continue donepezil (group 3), or continue donepezil and start memantine (group 4) for 52 weeks.

A



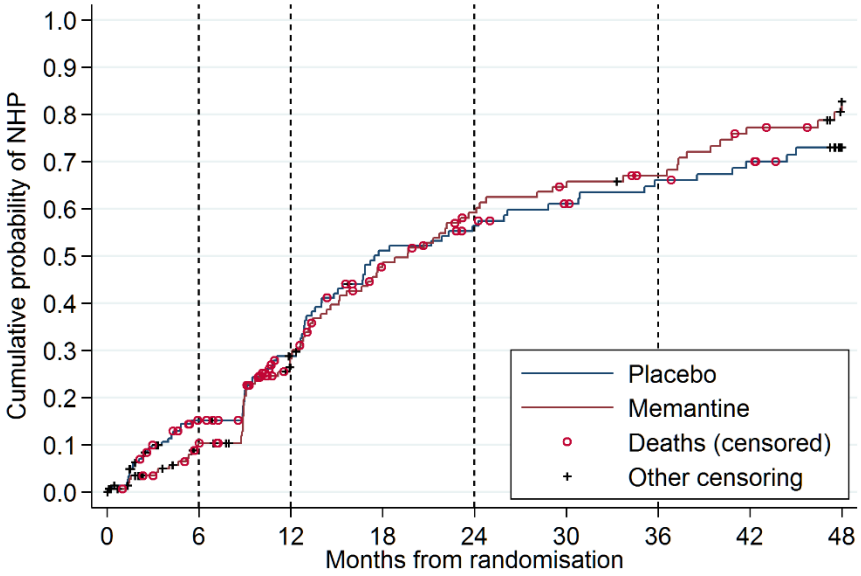
At risk						
Group 1	73	47	34	17	11	4
Group 2	76	53	32	14	13	5
Group 3	73	61	42	23	16	8
Group 4	73	61	45	23	13	4

B



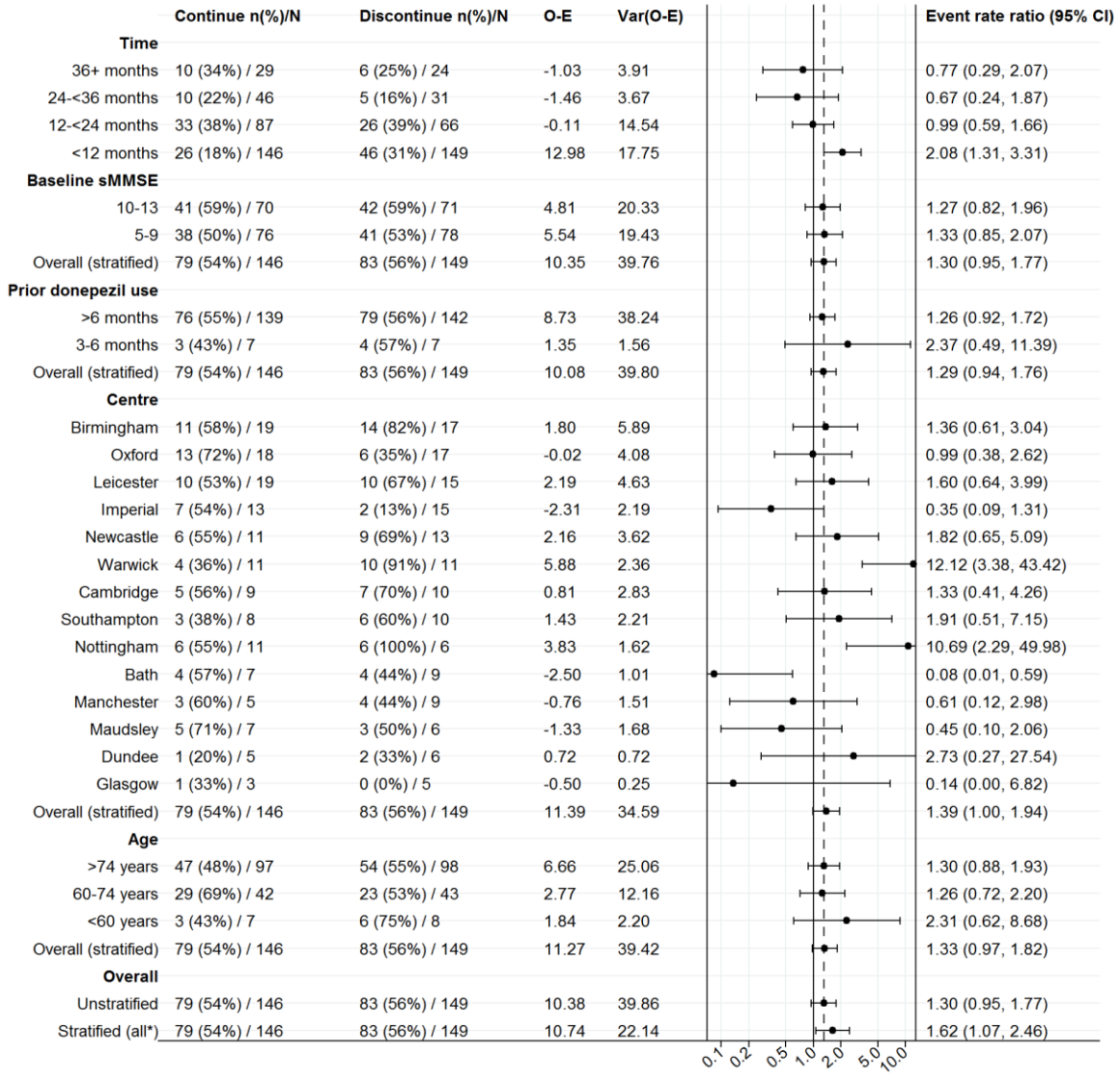
At risk						
Continue donepezil	146	122	87	46	29	12
Discontinue donepezil	149	100	66	31	24	9

C.



At risk						
Placebo	146	108	76	40	27	12
Memantine	149	114	77	37	26	9

Figure 3. Comparison of the effect of discontinuing with continuing donepezil on risk of NHP in each category of randomisation minimisation strata and time period from randomisation. O-E refers to the difference between the Observed and Expected events within each strata and is the log-rank statistic. The comparison of the effect of memantine is not shown since there was no overall difference on event rate, stratified or un-stratified.



*All excluding time from randomisation.

Figure 4: Graphs of fitted hazard (A) and cumulative probability of NHP (B) for flexible parametric survival model (dashed lines) with regions showing 95% confidence regions. Solid lines show fitted estimates and dashed line in B shows Kaplan-Meier (KM) non-parametric estimates. This was a post-hoc analysis to describe how the hazard (instantaneous risk) of NHP changes over time.

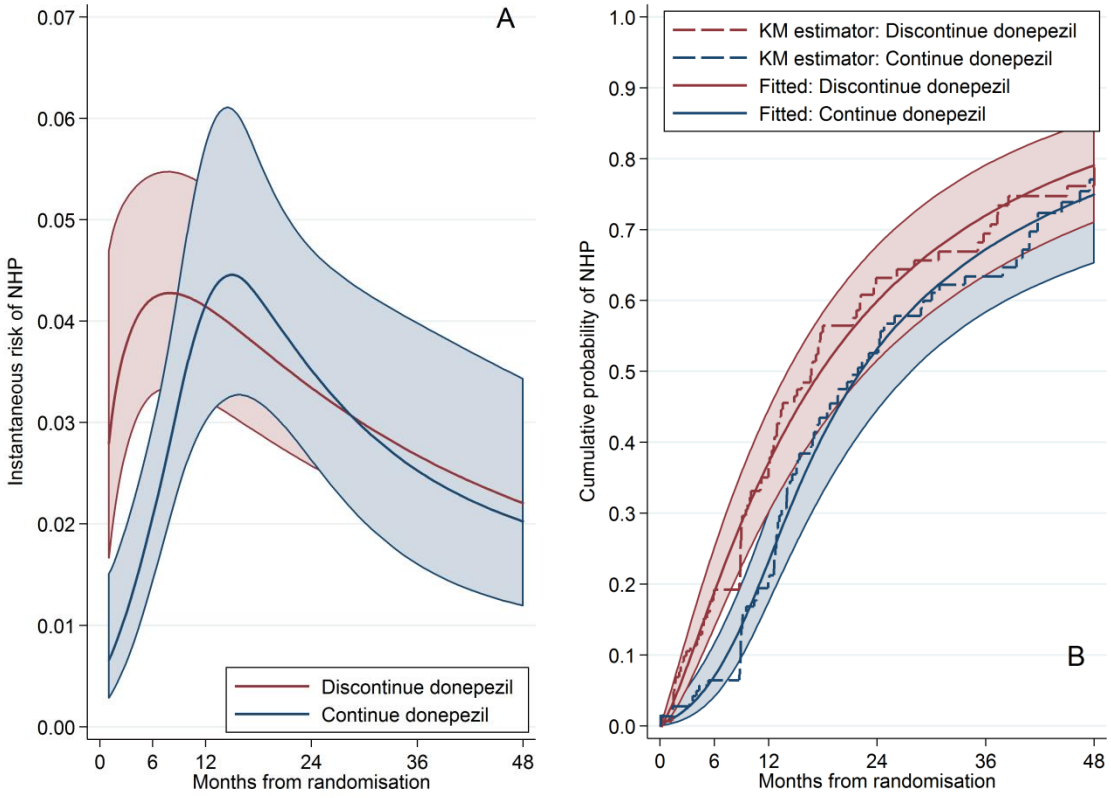


Table 1. Patient baseline characteristics by treatment arm.

		Discontinue donepezil		Continue donepezil		Total
		Add placebo memantine	Add memantine	Add placebo memantine	Add memantine	
Total randomised		**73**	**76**	**73**	**73**	**295**
Age in years at baseline / Mean (SD)		77.7 (8.0)	76.2 (8.9)	77.2 (7.5)	77.5 (9.0)	**77.1 (8.4)**
Male / N (%)		26 (36%)	30 (39%)	22 (30%)	24 (33%)	**102 (35%)**
Ethnicity N (%)	**White**	71 (97%)	73 (96%)	69 (95%)	67 (92%)	**280 (95%)**
	Black	2 (3%)	2 (3%)	1 (1%)	4 (5%)	**9 (3%)**
	Other	0	1 (1%)	3 (4%)	2 (3%)	**6 (2%)**
Donepezil duration prior to randomisation / N (%)	**3-<6Months**	3 (4%)	4 (5%)	3 (4%)	4 (5%)	**14 (5%)**
	6- <12 Months	8 (11%)	4 (5%)	9 (12%)	3 (4%)	**24 (8%)**
	12+ Months	62 (85%)	68 (89%)	61 (84%)	66 (90%)	**257 (87%)**
Male carer / N(%)		36 (49%)	31 (41%)	36 (49%)	34 (47%)	137 (46%)
Carer lives with patient / N(%)		65 (89%)	58 (76%)	58 (79%)	53 (73%)	234 (79%)
Relationship of carer/ N(%)	Spouse or partner	56 (77%)	49 (64%)	41 (56%)	43 (59%)	189 (64%)
	Son or daughter	15 (21%)	18 (24%)	30 (41%)	28 (38%)	91 (31%)
	Other relative	0	7 (9%)	1 (1%)	1 (1%)	9 (3%)
	Friend or neighbour	0	2 (3%)	0	0	2 (1%)
	Paid Carer	2 (3%)	0	1 (1%)	1 (1%)	4 (1%)
Mean (SD) sMMSE at baseline		9.1 (2.4)	9.2 (2.5)	9.0 (2.8)	9.1 (2.6)	**9.1 (2.6)**
Mean (SD) BADLS at baseline		28.6 (8.9)	27.1 (9.0)	28.2 (9.0)	26.9 (9.8)	**27.7 (9.2)**
Mean (SD) NPI at baseline		22.9 (17.0)	23.1 (16.2)	22.3 (16.7)	20.3 (14.4)	**22.2 (16.1)**

Standardised Mini-Mental State Examination (sMMSE, range 0 to 30, higher scores indicate better cognitive function); Bristol Activities of Daily Living Scale (BADLS, range 0 to 60, higher scores indicate greater functional impairment); Neuropsychiatric Inventory (NPI, range 0 to 144, higher scores indicate increased behavioural and psychological symptoms)

Table 2. Summary of time to NHP and deaths by treatment arm.

		Discontinue donepezil		Continue donepezil	
		Add placebo memantine	Add memantine	Add placebo memantine	Add memantine
Total follow-up time at risk (person-years)		97.0	100.7	121.0	117.8
Number of NHP events		42 (58%)	41 (54%)	36 (49%)	43 (59%)
Observed NHP Rate per 10 person-years (95% CI)		4.33 (3.20, 5.86)	4.07 (3.00, 5.53)	2.98 (2.15, 4.13)	3.65 (2.71, 4.92)
Centiles of time to NHP in months (95% CI)	**25%**	8.9 (2.6, 11.1)	9.0 (6.0, 12.0)	12.7 (9.5, 14.0)	12.8 (8.9, 15.2)
	50% (median)	16.7 (11.1, 26.2)	16.6 (12.0, 22.2)	21.9 (14.0, 40.9)	20.7 (15.2, 30.0)
Probability of NHP by time after randomisation (95% CI)	**6 months**	0.23 (0.15, 0.35)	0.15 (0.08, 0.26)	0.07 (0.03, 0.16)	0.06 (0.02, 0.15)
	12 months	0.37 (0.27, 0.50)	0.37 (0.26, 0.51)	0.21 (0.12, 0.33)	0.20 (0.12, 0.32)
	24 months	0.61 (0.48, 0.73)	0.66 (0.53, 0.79)	0.53 (0.40, 0.66)	0.53 (0.40, 0.67)
	36 months	0.71 (0.58, 0.83)	0.69 (0.56, 0.81)	0.62 (0.48, 0.75)	0.65 (0.53, 0.78)
	48 months	0.77 (0.64, 0.88)	0.76 (0.63, 0.87)	0.69 (0.56, 0.2)	0.86 (0.73, 0.95)
Deaths before NHP		17 (23%)	12 (16%)	20 (27%)	17 (23%)
Deaths reported after NHP		4 (5%)	7 (9%)	7 (10%)	8 (11%)

Table 3: Summary of time to NHP by donepezil group, and separately by memantine group. The analysis separated in 0-12 and 12-48 month periods was not a planned analysis, but is appropriate in the presence of non-proportional hazards.

		Continue donepezil	Discontinue donepezil	Difference between groups	Add placebo memantine	Add memantine	Difference between groups
Total randomised		146	149		149	146	
Overall	Time at risk (years)	238.8	197.8		218.0	218.6	
	Number of NHP events	79	83		78	84	
	NHP Rate (per 10 years)	3.31 (2.65, 4.12)	4.20 (3.38, 5.20)		3.58 (2.87, 4.47)	3.84 (3.10, 4.76)	
	Hazard ratio (95% CI)	Reference	1.29 (0.95, 1.76)		Reference	1.08 (0.79, 1.47)	
	Proportional hazards	p = 0.010			p = 0.068		
0 – 12 months	Time at risk (years)	120.5	104.2		109.8	114.9	
	Number of NHP events	26	46		37	35	
	NHP Rate (per 10 years)	2.16 (1.47, 3.17)	4.42 (3.31, 5.89)		3.37 (2.44, 4.65)	3.05 (2.19, 4.24)	
	Hazard ratio (95% CI)	Reference	2.09 (1.29, 3.39)		Reference	0.92 (0.58, 1.45)	
12 – 48 months	Time at risk (years)	118.3	93.6		108.2	103.7	
	Number of NHP events	53	37		41	49	
	NHP Rate (per 10 years)	4.48 (3.42, 5.86)	3.95 (2.87, 5.46)		3.79 (2.79, 5.15)	4.73 (3.57, 6.25)	
	Hazard ratio (95% CI)	Reference	0.89 (0.58, 1.35)		Reference	1.23 (0.81, 1.87)	
Centiles of time to NHP in months (95% CI)	25th	12.7 (10.4, 14.0)	8.9 (5.5, 10.1)	-3.8 (-7.0, -1.5)	10.1 (8.9, 12.6)	11.2 (8.9, 12.8)	1.1 (-2.7, 4.2)
	Median	21.9 (16.9, 29.1)	16.7 (12.7, 22.1)	-5.1 (-12.7, 2.6)	17.5 (14.0, 26.2)	19.6 (15.1, 24.1)	2.2 (-5.5, 9.3)
Probability of NHP by time after randomisation, Kaplan-Meier estimates (95% CI)	6 months	0.06 (0.03, 0.12)	0.19 (0.13, 0.27)	0.13 (0.04, 0.21)	0.15 (0.10, 0.22)	0.10 (0.06, 0.17)	-0.05 (-0.12, 0.03)
	12 months	0.20 (0.14, 0.28)	0.37 (0.29, 0.46)	0.17 (0.06, 0.28)	0.29 (0.22, 0.38)	0.28 (0.21, 0.37)	-0.01 (-0.12, 0.10)
	24 months	0.53 (0.43, 0.62)	0.63 (0.54, 0.72)	0.11 (-0.02, 0.23)	0.56 (0.47, 0.66)	0.59 (0.50, 0.69)	0.03 (-0.10, 0.16)
	36 months	0.63 (0.54, 0.73)	0.69 (0.60, 0.78)	0.06 (-0.06, 0.21)	0.66 (0.57, 0.75)	0.67 (0.58, 0.76)	0.01 (-0.13, 0.15)
	48 months	0.77 (0.68, 0.85)	0.76 (0.67, 0.84)	-0.01 (-0.14, 0.13)	0.73 (0.63, 0.82)	0.81 (0.71, 0.88)	0.08 (-0.06, 0.20)

Panel: Research in context

Evidence before this study We searched PubMed on 25/6/2015 for articles on studies of the effects of dementia drug treatments on nursing home placement using the following terms: “Alzheimer’s treatment” AND “Nursing home placement” and “Alzheimer’s treatment” AND “Care home placement” and “Cholinesterase inhibitor” AND “Placement”. We identified a single double-blind randomised controlled trial that demonstrated no effect of donepezil treatment on nursing home placement in mild to moderate Alzheimer’s disease and 11 open treatment or retrospective analyses that reported apparent delayed nursing home placement in patients taking cholinesterase inhibitor treatment.

Added value of this study

We showed that moderately-to-severely affected Alzheimer’s disease patients who continued donepezil treatment were at reduced risk of nursing home placement during the 12-months of a randomised double-blind controlled trial. Benefits were not maintained after 12 months at which point the patients’ treating physicians chose their treatment. Although our results should be considered exploratory as nursing home placement was a secondary outcome and analysis restricted to the first 12 months of follow-up was not pre-specified in the analysis plan, they indicate that along with cognitive and functional benefits, continuing cholinesterase inhibitor treatment is associated with advantages in maintaining independent home living.

Implications of all the available evidence

Because the symptomatic benefits associated with cholinesterase inhibitor treatment in Alzheimer’s disease are modest, it is difficult for physicians to evaluate whether their patients are deriving benefit from treatment and they may consider stopping treatment because of perceived lack of efficacy once patients have become moderately to severely affected. The evidence suggests that withdrawal of cholinesterase inhibitor treatment is associated with worse cognitive and functional outcomes and, from this study, earlier transfer to a nursing home. Decisions to continue or stop treatment in patients with moderate and severe Alzheimer’s disease should be made after consideration of these risks.