Nursing home placement in the Donepezil and Memantine in Moderate to Severe Alzheimer's Disease (DOMINO-AD) trial: secondary and post-hoc analyses

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Summary

Background **Findings from observational studies have suggested a delay in nursing home placement with dementia drug treatment, but findings from a previous randomised trial of patients with mild-to-moderate Alzheimer's disease showed no effect. We investigated the effects of continuation or discontinuation of donepezil and starting of memantine on subsequent nursing home placement in patients with moderate-to-severe Alzheimer's disease.**

Methods **In the randomised, double-blind, placebo-controlled Donepezil and Memantine in Moderate to Severe Alzheimer's Disease (DOMINO-AD) trial, community-living patients with moderate-to-severe Alzheimer's disease (who had been prescribed donepezil continuously for at least 3 months at a dose of 10 mg for at least the previous 6 weeks and had a score of between 5 and 13 on the Standardised Mini-Mental State Examination) were recruited from 15 secondary care memory centres in England and Scotland and randomly allocated to continue donepezil 10 mg per day without memantine, discontinue donepezil without memantine, discontinue donepezil and start memantine 20 mg per day, or continue donepezil 10 mg per day and start memantine 20 mg per day, for 52 weeks. After 52 weeks, choice of treatment was left to participants and their physicians. Place of residence was recorded during the first 52 weeks of the trial and then every 26 weeks for a further 3 years. A secondary outcome of the trial, reported in this study, was nursing home placement: an irreversible move from independent accommodation to a residential caring facility. Analyses restricted to risk of placement in the first year of follow-up after the patients had completed the double-blind phase of the trial were post-hoc. The DOMINO-AD trial is registered with the ISRCTN Registry, number ISRCTN49545035.**

Findings **Between Feb 11, 2008, and March 5, 2010, 73 (25%) patients were randomly assigned to continue donepezil without memantine, 73 (25%) to discontinue donepezil without memantine, 76 (26%) to discontinue donepezil and start memantine, and 73 (25%) to continue donepezil and start memantine. 162 (55%) patients underwent nursing home placement within 4 years of randomisation, with similar numbers for all groups (36 [49%] in patients who continued donepezil without memantine, 42 [58%] who discontinued donepezil without memantine, 41 [54%] who discontinued donepezil and started memantine, and 43 [59%] who continued donepezil and started memantine). We noted significant (p=0·010) heterogeneity of treatment effect over time, with significantly more nursing home placements in the combined donepezil discontinuation groups during the first year (hazard ratio 2·09 [95% CI 1·29–3·39]) than in the combined donepezil continuation groups, and no difference during the next 3 years (0·89 [0·58–1·35]). We noted no effect of patients starting memantine compared with not starting memantine during the first year (0·92 [0·58–1·45]) or the next 3 years (1·23 [0·81–1·87]).**

Interpretation **Withdrawal of donepezil in patients with moderate-to-severe Alzheimer's disease increased the risk of nursing home placement during 12 months of treatment, but made no difference during the following 3 years of follow-up. Decisions to stop or continue donepezil treatment 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 are complex, involving patient and caregiver characteristics, and the cultural and social environment. White ethnic origin, impairments in cognition and activities of daily living (ADL), behavioural problems, and increased age of and burden on caregivers all predict nursing home placement in Alzheimer's disease.[1] Economic costs of dementia increase markedly with disease severity, with nursing home placement contributing substantially to total support costs of severe dementia. Whether cholinesterase inhibitors and memantine can delay the point at which patients with Alzheimer's disease make the transition to permanent residential care is controversial. AD2000,[2] the only randomised, controlled, double-blind trial to directly address this question for donepezil, was negative. Investigators of observational studies following up patients who have participated in

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Research in context

Evidence before this study

We searched PubMed up to June 25, 2015, for studies of the effects of dementia drug treatments on nursing home placement using the following terms: ("Alzheimer's treatment" AND "nursing home placement") OR ("Alzheimer's treatment" AND "care home placement") OR ("cholinesterase inhibitor" AND "placement"). We identified a single double-blind, randomised, controlled trial, findings from which showed no effect of donepezil treatment on nursing home placement in mild-to-moderate Alzheimer's disease, and 11 open-treatment or retrospective analyses, investigators of which reported apparent delayed nursing home placement in patients taking cholinesterase inhibitor treatment.

Added value of this study

We showed that patients with moderate-to-severe Alzheimer's disease who continued donepezil treatment were at reduced risk of nursing home placement during 12 months of a randomised, double-blind, placebo-controlled trial. Benefits were not maintained after 12 months, at which point the patients' treating physicians chose their treatment. Although our results should be deemed exploratory because nursing home placement was a secondary outcome and analysis restricted to the first 12 months of follow-up was not prespecified in the analysis plan, they show that, along with cognitive and functional benefits, continuation of cholinesterase inhibitor treatment is associated with potential advantages in maintenance of independent home living.

Implications of all the available evidence

Because the symptomatic benefits associated with cholinesterase inhibitor treatment in Alzheimer's disease are slight, physicians might consider stopping treatment because of perceived absence of effectiveness 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 than without withdrawal. Decisions to continue or stop treatment in patients with moderate and severe Alzheimer's disease should be made after consideration of these risks.

double-blind or open trials, or who received open-label treatment (with tacrine,[3] with donepezil,[4] with tacrine, donepezil, or rivastigmine,[5,6] with galantamine,[7] or with memantine combined with a cholinesterase inhibitor),[8] have reported positive results. These studies have been criticised because they have not used randomisation, placebo control, or blinding of treatment allocation.[9–12] The socioeconomic implications of resolution of this controversy are clear. Models based on assumptions that the drugs can delay placement show large societal and health-care cost savings.[13]

Previously in the Donepezil and Memantine in Moderate to Severe Alzheimer's Disease (DOMINO-AD) study,[14] we have shown that continued treatment with donepezil in patients with moderate-to-severe Alzheimer's disease is associated with cognitive and functional benefits during 12 months compared with tapering and discontinuing. Slight cognitive and functional treatment benefits in moderate-to-severe dementia could be argued to have only a small effect on the lives of patients and caregivers. Therefore, an important secondary objective of our trial was to investigate whether continuation of a drug treatment that improved dementia symptoms would also delay nursing home placement in patients with Alzheimer's disease 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, in this report, we explore how treatment allocation (to continuation or discontinuation of donepezil and to start or not start memantine) affected subsequent permanent nursing home placement.

Methods

Study design and participants

The DOMINO-AD study was a multicentre (15 secondary care memory services in England and Scotland), randomised, double-blind, placebo-controlled trial, with a two-by-two factorial design.[15] Eligible participants met standardised criteria[16] for probable or possible moderate or severe Alzheimer's disease, had been prescribed donepezil continuously for at least 3 months at a dose of 10 mg for at least the previous 6 weeks, and had a score of between 5 and 13 on the Standardised Mini-Mental State Examination (SMMSE).[17] Each patient's prescribing clinician was also considering a change in drug treatment. Patients were excluded if they had severe or unstable medical disorders, were receiving memantine, or were deemed unlikely to adhere to the study regimens.

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 their patient's participation. The trial protocol has been published previously.[15]

Randomisation and masking

The first 80 participants were assigned with use of a computer-generated unrestricted randomised list of assignments prepared by PPJP to maintain allocation concealment by introduction of random imbalance before the minimisation algorithm commenced. Thereafter, participants were randomly assigned to one

	Discontinue donepezil		Continue donepezil		Total
	Add memantine placebo	Add memantine	Add memantine placebo	Add memantine	
Randomly allocated patients	73	76	73	73	295
Age at baseline (years)	77·7 (8·0)	76·2 (8·9)	77·2 (7·5)	77·5 (9·0)	77·1 (8·4)
Male sex	26 (36%)	30 (39%)	22 (30%)	24 (33%)	102 (35%)
Ethnic origin					
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 treatment before randomisation (months)					
3 to <6	3 (4%)	4 (5%)	3 (4%)	4 (5%)	14 (5%)
6 to <12	8 (11%)	4 (5%)	9 (12%)	3 (4%)	24 (8%)
≥12	62 (85%)	68 (89%)	61 (84%)	66 (90%)	257 (87%)
Male carer	36 (49%)	31 (41%)	36 (49%)	34 (47%)	137 (46%)
Carer lives with patient	65 (89%)	58 (76%)	58 (79%)	53 (73%)	234 (79%)
Relationship of carer					
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%)
SMMSE*	9·1 (2·4)	9·2 (2·5)	9·0 (2·8)	9·1 (2·6)	9·1 (2·6)
BADLS†	28·6 (8·9)	27·1 (9·0)	28·2 (9·0)	26·9 (9·8)	27·7 (9·2)
NPI‡	22·9 (17·0)	23·1 (16·2)	22·3 (16·7)	20·3 (14·4)	22·2 (16·1)

Data are n, mean (SD), or n (%). SMMSE=Standardised Mini-Mental State Examination. BALDS=Bristol Activities of Daily Living Scale. NPI=Neuropsychiatric Inventory. *Range 0–30, with higher scores showing better cognitive function. †Range 0–60, with higher scores showing greater functional impairment. ‡Range 0–144, with higher scores showing increased behavioural and psychological symptoms. Reproduced from Howard and colleagues[14] by permission of the Massachusetts Medical Society.

***Table 1*: Baseline characteristics**

of four treatment groups using randomised minimisation:[18] continuation of donepezil, with initiation of memantine placebo; discontinuation of donepezil, with initiation of memantine placebo; discontinuation of donepezil and initiation of memantine; or continuation of donepezil and initiation of memantine. Treatment assignments were done by the Medical Research Council Clinical Trials Unit. Groups were stratified according to centre, duration of donepezil treatment before entry (3–6 months *vs* longer than 6 months), baseline SMMSE score (5–9 *vs* 10–13), and age (younger than 60 years, 60–74 years, or older than 74 years). Patients, caregivers, clinicians, outcome assessors, and investigators were all masked to treatment assignment.

Procedures

Depending on treatment allocation, donepezil was continued at 10 mg per day or discontinued after 4 weeks of treatment with 5 mg donepezil, and memantine was initiated at 20 mg per day. In the Client Service Receipt Inventory (CSRI),[19] the following are classified as nursing home placement: a care home providing nursing care, a care home providing personal care, a dual-registered home (providing both personal and nursing care), an acute psychiatric ward, a general medical ward, and a rehabilitation ward. The following are classified as non-nursing home placement: an owner-occupied house or flat, a privately rented house or flat, a house or flat rented from a housing association or local authority, sheltered or warden-controlled housing, or extra care housing. The CSRI captures the patient's usual place of residence since the last assessment together with the number of days spent living in other locations. If the usual place of residence had changed to a nursing home from the previous visit, the date of nursing home placement was estimated as the number of days lived outside of a nursing home since the previous assessment date subtracted from the assessment date at which the change was reported. After use of the CSRI in the first year, for 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, what the date of transition was. The definition of nursing home placement and the date of transition to nursing home placement remained the same throughout the study, despite the change in the method of data collection.

	Discontinue donepezil		Continue donepezil	
	Add memantine placebo (n=73)	Add memantine (n=76)	Add memantine placebo (n=73)	Add memantine (n=73)
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%)
NHP rate per 10 person-years	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 (months)				
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%	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 (months; Kaplan-Meier estimates)				
6	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	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	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	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	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 after NHP	4 (5%)	7 (9%)	7 (10%)	8 (11%)

NHP=nursing home placement.

Table 2: **Time to NHP and deaths**

Outcomes

The primary outcomes of the DOMINO-AD trial were scores on the SMMSE and caregiver-rated Bristol Activities of Daily Living Scale (BADLS).[20] Results of these outcomes, along with the secondary outcomes of neuropsychiatric symptoms, participant quality of life, and caregiver psychological distress outcomes during completion of the 52 week intervention, have been reported previously.[14] In this study, nursing home placement is reported with use of the CSRI for the 52 weeks of trial treatment and telephone calls to the patients' caregivers for the following 3 years.

Statistical analysis

The original planned sample size was 800, but this size was adjusted to 430 because of reduced SDs for the primary outcomes from an interim masked analysis of trial data. The trial was designed with an at least 90% power for the primary outcomes, but was not powered to show differences for time to nursing home placement.

Following the prespecified statistical analysis plan, we analysed time to nursing home placement using stratified log-rank (using randomisation minimisation factors as strata) and Cox proportional hazards regression, with patients who died or withdrew from follow-up before nursing home placement censored at date of death or withdrawal. We tested the assumption of proportional hazards using Shoenfeld residuals, with ranking of follow-up time. Because we were analysing a secondary outcome of the trial, the statistical analysis plan did not include any prespecified 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 prespecified in the analysis plan because the presence of non-proportional hazards was not expected. For situations with evidence of non-proportional hazards ($p<0·05$), we split follow-up into distinct periods, with hazards assumed to be proportional within each period (piecewise proportional hazards modelling). We compared regression models with different time period splits using the Akaike Information Criterion (AIC). We calculated probability of nursing home placement by time after randomisation from the Kaplan-Meier survivor function, with 95% CIs. We calculated differences in centiles of survival time and probability of nursing home placement between groups with 95% bias-corrected bootstrap CIs using 1000 bootstrap replications. We calculated the log-rank statistic for each stratum and tabulated it with event rate ratios using methods previously described[21] to explore the effect of stratification.

The protocol and statistical analysis plan prespecified that death before nursing home placement would be deemed a censoring event in the same way as withdrawal or loss from follow-up. However, nursing home placement might have been more likely in patients who died than in those who withdrew from follow-up had the patients not died or withdrawn. We therefore did two additional sensitivity analyses: first, deeming all deaths as nursing home placement events at the time of death (equivalent to the composite endpoint of death or nursing home placement), and second, a competing-risks analysis[22] modelling the subhazard function of nursing home placement in the presence of the competing risk of death.

We assessed the following patient baseline covariates for association with time to nursing home placement in the regression model: age; sex; previous duration of donepezil treatment; centre; ethnic origin; sex of carer; relationship of carer; whether the patient lives with their

carer; SMMSE, BADLS, Neuropsychiatric Inventory (NPI),[23] and DEMQOL-proxy scores;[24] EuroQol-5D health state; and NPI subscales of delusions, hallucinations, agitation and aggression, and irritability and lability. We deemed covariates to be predictors only if the treatment-adjusted effect was significant at the 5% level in separate univariable models.

Additionally, we used parametric models to describe how the underlying risk of nursing home placement changes with time. We fitted the following standard parametric models to the data: Weibull, generalised γ, log-normal, log-logistic, and Gompertz. Flexible parametric survival models do not assume an underlying log-linear relation with time or hazard and allow a flexible fully parametric modelling approach.[25] We compared these models with standard parametric models, choosing the best fitting model using the AIC.

The DOMINO-AD trial is registered with the International Standard Randomised Controlled Trial Number Registry, number ISRCTN49545035.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or

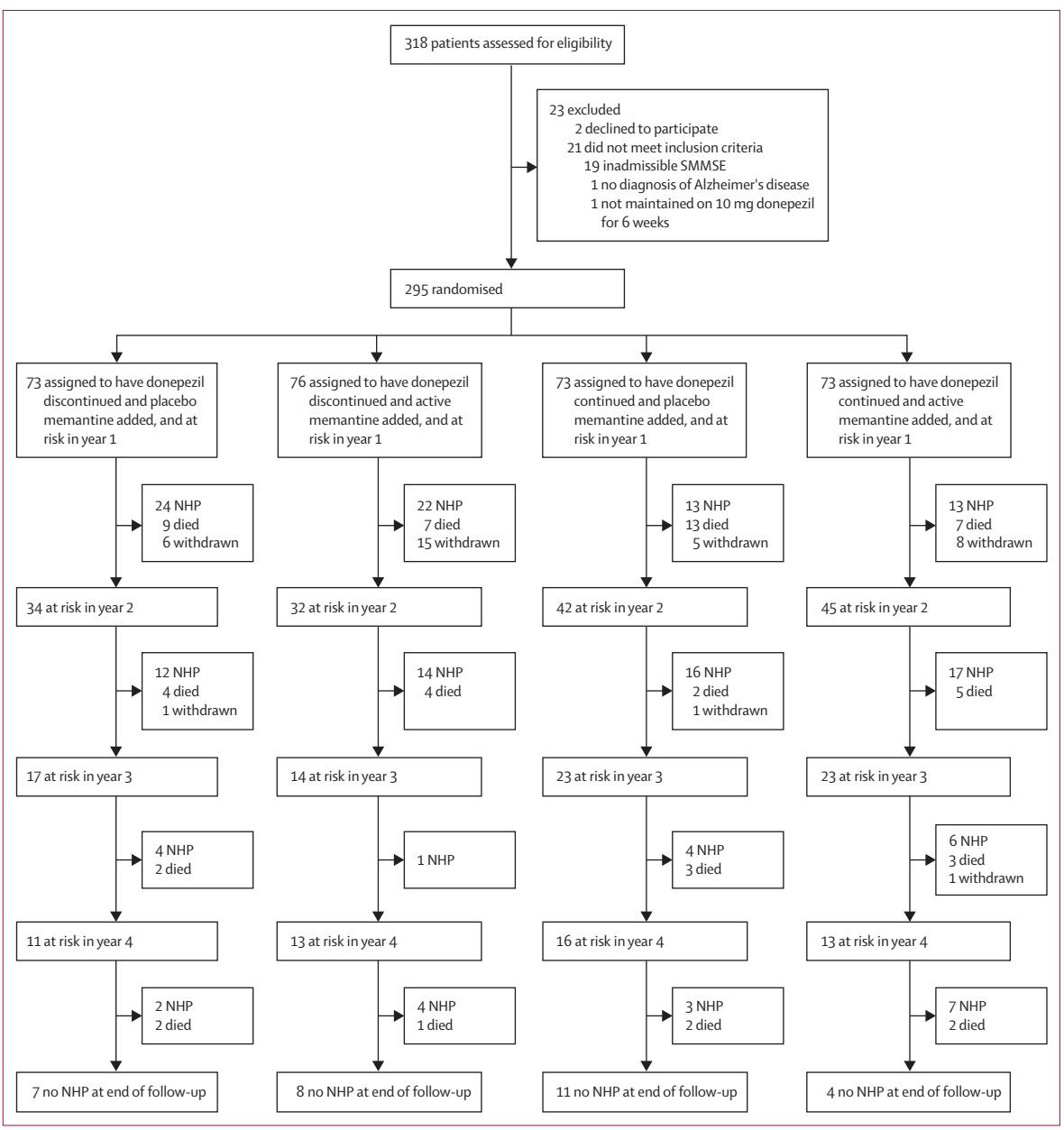
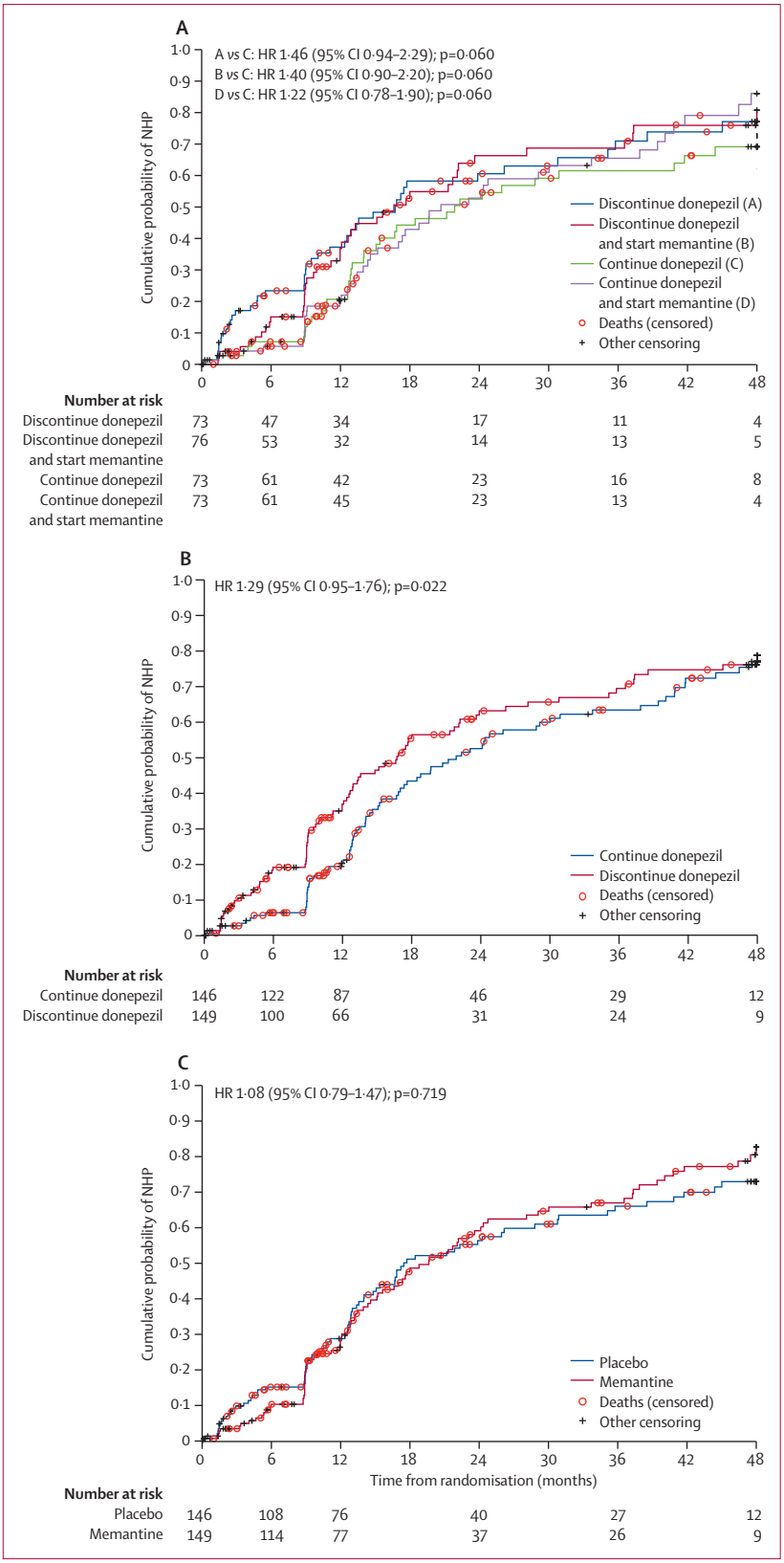


Figure 1: **Trial profile**
NHP=nursing home placement. SMMSE=Standardised Mini-Mental State Examination.



writing of the report. Pfizer-Eisai and Lundbeck donated drug and placebo supplies, but had no involvement in design or conduct of the study or analysis or reporting of the data. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

Between Feb 11, 2008, and March 5, 2010, 73 (25%) patients were randomly assigned to continue donepezil without memantine, 73 (25%) to discontinue donepezil without memantine, 76 (26%) to discontinue donepezil and start memantine, and 73 (25%) to continue donepezil and start memantine. The last participant completed follow-up on April 28, 2014. Of the 295 patients, 162 (55%) had nursing home placement within 4 years of randomisation. Table 1 summarises the patient baseline characteristics and table 2 summarises the time to nursing home placement in each of the four treatment groups. Figure 1 shows the trial profile.

In the prespecified analysis, we noted evidence of a difference in time to nursing home placement between those discontinuing and continuing donepezil (stratified log-rank test p=0·022), although this difference was non-significant in the unstratified analysis (p=0·100). We noted no evidence for an interaction (stratified p=0·168; unstratified p=0·446) or a benefit to patients of starting memantine (stratified p=0·719; unstratified p=0·628). Subsequent analyses therefore consider only the effect of discontinuation of donepezil. Figure 2 shows the Kaplan-Meier survival curves of cumulative probability of nursing home placement by treatment group. The 25th percentile of time to nursing home placement was greater in patients continuing (12·7 months [95% CI 10·4–14·0])than in those discontinuing (8·9 months [5·5–10·1]) donepezil, with a difference of 3·8 months (95% CI 1·5–7·0). We noted no difference in median time to nursing home placement: 21·9 months (16·9–29·1) versus 16·7 months (12·7–22·1).

Figure 3 shows the log-rank statistics and event rate ratio for each stratum and by time period of nursing home placement from randomisation, by whether patients were allocated to continue or discontinue donepezil. We noted clear evidence of non-proportional hazards (p=0·01; figure 2), showing that the overall hazard ratio (HR) of discontinuation compared with continuation of donepezil was not an appropriate summary measure because the effect of discontinuation of donepezil changed with time. Kaplan-Meier survival curves seemed to separate during the first 12 months and were parallel thereafter. Subsequent results are based on analyses that were not prespecified in the analysis plan because non-proportional hazards were not expected.

Figure 2: **Kaplan-Meier curves of cumulative probability of nursing home placement by (A) treatment group, (B) continuation versus discontinuation of donepezil, and (C) addition of memantine**
HR=hazard ratio. NHP=nursing home placement.

Splitting of follow-up time at only 12 months resulted in better model fit and lower AIC than splits at any combination of 6 months, 12 months, and 24 months (data not shown). Discontinuation of donepezil more than doubled the instantaneous risk of nursing home placement during the first year (HR 2·09 [95% CI [1·29–3·39]) compared with continuation of donepezil (table 3). This benefit was maintained after 12 months because curves remained roughly equidistant (0·89 [0·58–1·35]). This HR after 12 months should be interpreted with caution because of selection bias:[26] it is estimated from the subgroup of patients without nursing

	Continue donepezil	Discontinue donepezil	Observed–expected*	Var (observed–expected)	Event rate ratio
Time					
≥36 months	10 (34%)/29	6 (25%)/24	−1·03	3·91	0·77 (0·29–2·07)
24 to <36 months	10 (22%)/46	5 (16%)/31	−1·46	3·67	0·67 (0·24–1·87)
12 to <24 months	33 (38%)/87	26 (39%)/66	−0·11	14·54	0·99 (0·59–1·66)
<12 months	26 (18%)/146	46 (31%)/149	12·98	17·75	2·08 (1·31–3·31)
Baseline SMMSE					
10–13	41 (59%)/70	42 (59%)/71	4·81	20·33	1·27 (0·82–1·96)
5–9	38 (50%)/76	41 (53%)/78	5·54	19·43	1·33 (0·85–2·07)
Overall (stratified)	79 (54%)/146	83 (56%)/149	10·35	39·76	1·30 (0·95–1·77)
Previous donepezil use					
>6 months	76 (55%)/139	79 (56%)/142	8·73	38·24	1·26 (0·92–1·72)
3–6 months	3 (43%)/7	4 (57%)/7	1·35	1·56	2·37 (0·49–11·39)
Overall (stratified)	79 (54%)/146	83 (56%)/149	10·08	39·80	1·29 (0·94–1·76)
Centre					
Birmingham	11 (58%)/19	14 (82%)/17	1·80	5·89	1·36 (0·61–3·04)
Oxford	13 (72%)/18	6 (35%)/17	−0·02	4·08	0·99 (0·38–2·62)
Leicester	10 (53%)/19	10 (67%)/15	2·19	4·63	1·60 (0·64–3·99)
London	7 (54%)/13	2 (13%)/15	−2·31	2·19	0·35 (0·09–1·31)
Newcastle	6 (55%)/11	9 (69%)/13	2·16	3·62	1·82 (0·65–5·09)
Warwick	4 (36%)/11	10 (91%)/11	5·88	2·36	12·12 (3·38–43·42)
Cambridge	5 (56%)/9	7 (70%)/10	0·81	2·83	1·33 (0·41–4·26)
Southampton	3 (38%)/8	6 (60%)/10	1·43	2·21	1·91 (0·51–7·15)
Nottingham	6 (55%)/11	6 (100%)/6	3·83	1·62	10·69 (2·29–49·98)
Bath	4 (57%)/7	4 (44%)/9	−2·50	1·01	0·08 (0·01–0·59)
Manchester	3 (60%)/5	4 (44%)/9	−0·76	1·51	0·61 (0·12–2·98)
Maudsley	5 (71%)/7	3 (50%)/6	−1·33	1·68	0·45 (0·10–2·06)
Dundee	1 (20%)/5	2 (33%)/6	0·72	0·72	2·73 (0·27–27·54)
Glasgow	1 (33%)/3	0 (0%)/5	−0·50	0·25	0·14 (0·00–6·82)
Overall (stratified)	79 (54%)/146	83 (56%)/149	11·39	34·59	1·39 (1·00–1·94)
Age					
>74 years	47 (48%)/97	54 (55%)/98	6·66	25·06	1·30 (0·88–1·93)
60–74 years	29 (69%)/42	23 (53%)/43	2·77	12·16	1·26 (0·72–2·20)
<60 years	3 (43%)/7	6 (75%)/8	1·84	2·20	2·31 (0·62–8·68)
Overall (stratified)	79 (54%)/146	83 (56%)/149	11·27	39·42	1·33 (0·97–1·82)
Overall					
Unstratified	79 (54%)/146	83 (56%)/149	10·38	39·86	1·30 (0·95–1·77)
Stratified (all†)	79 (54%)/146	83 (56%)/149	10·74	22·14	1·62 (1·07–2·46)

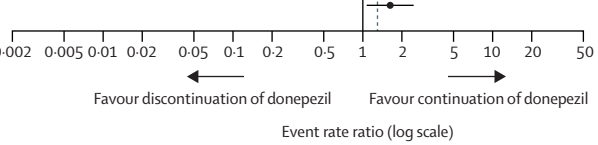


Figure 3: **Comparison of the effect of discontinuation with continuation of donepezil on risk of nursing home placement in each category of randomisation minimisation strata and time period from randomisation**

Data are n (%)/N or event rate ratio (95% CI). Error bars are 95% CIs. The dashed line shows the estimate of the unstratified event rate ratio. The comparison of the effect of memantine is not shown because we noted no overall difference on event rate, stratified or unstratified. SMMSE=Standardised Mini-Mental State Examination. *Difference between observed and expected events within each stratum; this is the log-rank statistic. †All excluding time from randomisation.

	Continue donepezil	Discontinue donepezil	Difference between groups	Add memantine placebo	Add memantine	Difference between groups
Randomly allocated patients	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 to 4·12)	4·20 (3·38 to 5·20)	..	3·58 (2·87 to 4·47)	3·84 (3·10 to 4·76)	..
Hazard ratio	Reference	1·29 (0·95 to 1·76)	..	Reference	1·08 (0·79 to 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 to 3·17)	4·42 (3·31 to 5·89)	..	3·37 (2·44 to 4·65)	3·05 (2·19 to 4·24)	..
Hazard ratio	Reference	2·09 (1·29 to 3·39)	..	Reference	0·92 (0·58 to 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 to 5·86)	3·95 (2·87 to 5·46)	..	3·79 (2·79 to 5·15)	4·73 (3·57 to 6·25)	..
Hazard ratio	Reference	0·89 (0·58 to 1·35)	..	Reference	1·23 (0·81 to 1·87)	..
Centiles of time to NHP (months)						
25%	12·7 (10·4 to 14·0)	8·9 (5·5 to 10·1)	–3·8 (–7·0 to –1·5)	10·1 (8·9 to 12·6)	11·2 (8·9 to 12·8)	1·1 (–2·7 to 4·2)
50%	21·9 (16·9 to 29·1)	16·7 (12·7 to 22·1)	–5·1 (–12·7 to 2·6)	17·5 (14·0 to 26·2)	19·6 (15·1 to 24·1)	2·2 (–5·5 to 9·3)
Probability of NHP by time after randomisation (months; Kaplan-Meier estimates)						
6	0·06 (0·03 to 0·12)	0·19 (0·13 to 0·27)	0·13 (0·04 to 0·21)	0·15 (0·10 to 0·22)	0·10 (0·06 to 0·17)	–0·05 (–0·12 to 0·03)
12	0·20 (0·14 to 0·28)	0·37 (0·29 to 0·46)	0·17 (0·06 to 0·28)	0·29 (0·22 to 0·38)	0·28 (0·21 to 0·37)	–0·01 (–0·12 to 0·10)
24	0·53 (0·43 to 0·62)	0·63 (0·54 to 0·72)	0·11 (–0·02 to 0·23)	0·56 (0·47 to 0·66)	0·59 (0·50 to 0·69)	0·03 (–0·10 to 0·16)
36	0·63 (0·54 to 0·73)	0·69 (0·60 to 0·78)	0·06 (–0·06 to 0·21)	0·66 (0·57 to 0·75)	0·67 (0·58 to 0·76)	0·01 (–0·13 to 0·15)
48	0·77 (0·68 to 0·85)	0·76 (0·67 to 0·84)	–0·01 (–0·14 to 0·13)	0·73 (0·63 to 0·82)	0·81 (0·71 to 0·88)	0·08 (–0·06 to 0·20)

The analyses separated into 0–12 months and 12–48 months periods were not preplanned, but were appropriate in the presence of non-proportional hazards. NHP=nursing home placement.

Table 3: **Summary of time to nursing home placement by donepezil group and separately by memantine group**

home placement by 12 months, which included more patients who had discontinued than had continued donepezil.

Discontinuation of donepezil treatment increased the probability of nursing home placement during the first 6 months from 0·06 to 0·19 (difference 0·13 [95% CI 0·04–0·21]) and during the first 12 months from 0·20 to 0·37 (0·17 [0·06–0·28]; table 3). This finding shows a number needed to treat of 5·88 patients for 12 months to prevent one nursing home placement. Patients who lived with their carers at baseline had a lower instantaneous risk of nursing home placement throughout follow-up compared with those who did not (HR 0·63 [95% CI 0·44–0·89]; p=0·013). This effect did not differ by treatment group (p=0·48, test for interaction) and no other baseline covariates tested were associated with nursing home placement (data not shown).

66 (22%) patients died before nursing home placement, with a further 26 (9%) deaths reported after nursing home placement (table 2). We noted no evidence for differences in time to death between groups (p=0·816 stratified; p=0·971 unstratified). In both the analysis of the composite endpoint of death or nursing home placement and the competing-risks analysis, the results were consistent with the analysis described above in which death before nursing home placement was a censoring event (data not shown).

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 three degrees of freedom for the time-varying covariate of donepezil (active *vs* placebo). Figure 4 shows the fitted hazard and survivor functions from this model, revealing how the underlying risk of nursing home placement changes with time. The risk of nursing home placement in patients discontinuing donepezil is high in the first few months, with a peak at around 6 months and steadily declining thereafter. The risk of nursing home placement in patients continuing donepezil is lower during the first 12 months than in patients discontinuing donepezil, with the peak not occurring until after 12 months and steadily declining afterwards. The curves for risk of nursing home placement were separate during the first 6–12 months, with the risk about equal for both groups from 12 months onwards.

Discussion

To our knowledge, we are the first to show a significant effect of dementia drug treatment on nursing home placement using data from a randomised, double-blind study. Discontinuation of donepezil treatment in patients with moderate-to-severe Alzheimer's disease was associated with a doubling of the instantaneous risk of placement to nursing homes during 12 months. We noted no significant difference in the risk of placement at later follow-up points, and starting of memantine treatment had no effect, either singly or in combination with donepezil, at any point in the trial. The comparison between treatment groups of time to nursing home placement was a secondary objective of the DOMINO-AD trial for which the study was not designed to have statistical power, and the analysis restricted to the first 12 months was not prespecified in the statistical analysis plan. These results should therefore be deemed exploratory and would ideally need to be substantiated in future studies. Restricted mean survival time might be a more appropriate treatment effect measure than is (average) HR in the presence of non-proportional hazards.[27] However, in view of the apparent disadvantages of withdrawal of cholinesterase inhibitor treatment,[14] data from further double-blind trials are unlikely to become available.

Cholinesterase inhibitors are symptomatic treatments for Alzheimer's disease and are not disease modifying. How might symptom worsening, associated with withdrawal of donepezil, increase risk of nursing home placement? Yaffe and colleagues[1] showed that impairment in ADL was a more important predictor of nursing home placement than cognitive impairment. In their study, Kaplan-Meier rates for nursing home placement during 1 year were 24% for patients with a Mini-Mental State Examination (MMSE)[28] score of 15–20 and 26% for patients with a score of less than 15, but 15% for those who were ADL independent and 25% for those with one or more ADL dependencies.[1] Analysis of data from a long-term clinical trial showed that, although baseline ADL score affected risk of and time to nursing home placement, decline in ADL most strongly predicted placement.[29] Withdrawal from donepezil treatment in the DOMINO-AD trial was associated with a mean 3 point BADLS disadvantage during the 12 month intervention period.[14] In view of the established effect of ADL status and loss of ADL on risk of nursing home placement,[1,29] the ADL worsening noted when patients were withdrawn from donepezil in the trial most probably represents the mechanism for early nursing home placement.

Because nursing home placement is affected by social and living circumstances, preferences, and values,[1] and because findings from a previous randomised controlled trial by some of the authors of this study (AD2000)[2] were unambiguously negative, could donepezil treatment plausibly affect nursing home placement? Three important differences exist between the AD2000[2] and DOMINO-AD[14] trials that might be relevant. First,

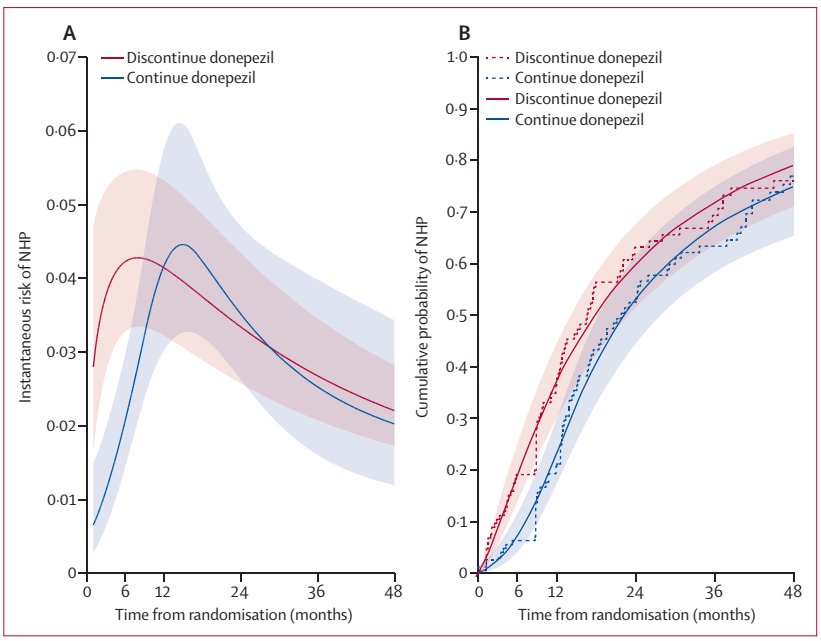


Figure 4: **Change in risk of nursing home placement with time**
(A) Fitted hazard and (B) cumulative probability of nursing home placement for the flexible parametric survival model. Solid lines show fitted estimates and the dashed lines in (B) show Kaplan-Meier non-parametric estimates. Shaded areas show 95% CIs. This post-hoc analysis shows how the hazard (instantaneous risk) of NHP changes with time. NHP=nursing home placement.

DOMINO-AD examined the effects of withdrawal of established donepezil treatment,[30] whereas AD2000 investigated the effects of treatment being commenced. Second, the mean MMSE score of patients entering AD2000 was 19 points, and for DOMINO-AD was 9 points. The participant populations were therefore very different in terms of dementia severity and proximity to the time of greatest risk of nursing home placement. Only 9% of patients given donepezil and 14% of those given placebo in AD2000 moved into a nursing home in the first 12 months, and nursing home placement could possibly have been too rare an event for a treatment effect to be noted. Third, the magnitude of treatment effect on cognition and ADL was greater in DOMINO-AD than in AD2000. During 2 years, AD2000 participants who received donepezil were a mean of 0·8 MMSE points and 1·0 BADLS points better than were those on placebo,[2] whereas the mean 12 month drug–placebo differences for donepezil in DOMINO-AD were 1·9 MMSE points and 3·0 BADLS points.[14] Although the AD2000 investigators showed no overall effect on nursing home placement, they did find that BADLS and NPI scores and age were strong independent predictors of nursing home placement and, using a multivariate model, predicted that a 2–3 point improvement in BADLS with donepezil would have reduced the proportion of nursing home placement 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 unmasked after 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 prespecified primary analysis, considering the whole follow-up period (with use of a stratified log-rank test), we noted a significant effect of continuation of donepezil compared with withdrawal and substitution of placebo. However, the piecewise modelling we carried out thereafter was not a prespecified analysis, so this factor should be borne in mind for interpretation of the results. Furthermore, withdrawal from the study drug was significantly more common in participants assigned to discontinue donepezil than in those assigned to continue,[14] which should also be borne in mind. A strength of our data was that DOMINO-AD was designed as a pragmatic study to answer questions about treatment of typical patients with Alzheimer's disease within 15 secondary care memory centres for people with dementia across England and Scotland, and the inclusion and exclusion criteria were fairly unselective, to both help participant recruitment and ensure study generalisability.

The potential economic benefits of prevention or delay of nursing home placement in patients with Alzheimer's disease are clear:[13,31] in the UK, this prevention or delay would reduce costs to public expenditure, even if it would increase imputed costs of unpaid care, but important positive effects on patient quality of life would also occur. A survey of caregivers showed that patients regarded nursing home placement as a major negative determinant of quality of life, with more than two-thirds rating delay of nursing home placement as "extremely important" or "very important" in maintenance of quality of life.[32] The decrease in quality of life for people with dementia associated with nursing home placement, 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 possible. Our data suggest that withdrawal of cholinesterase inhibitor treatment in moderate-to-severe Alzheimer's disease brings forward the timing of nursing home placement during the following 52 weeks, but that this effect does not operate at later points during further 3 year follow-up. This notion is consistent with the effects of slight symptomatic improvement in cognition and function associated with these drugs.

Contributors

All authors contributed to design and conduct of the trial and drafting of the report. RHo was the Chief Investigator for the DOMINO-AD trial, prepared the first draft of the report, and submitted the report for publication. PPJP did statistical analyses.

Declaration of interests

ABa reports paid participation in an advisory board for Lundbeck unrelated to the submitted work, payment for lectures by Lundbeck, Otsuka, Pfizer, Novartis, Eli-Lilly, and Janssen-Cilag, and meeting expenses from Lundbeck, Otsuka, Pfizer, and Eli-Lilly. CB reports grants from Lundbeck and Acadia, and personal fees from Lundbeck, Acadia, Roche, Orion, GlaxoSmithKline, Otsuka, Heptares, and Lilly. SB reports research grants and paid consultancy for Abbvie, payment for lectures by Lundbeck, Nutricia, and Lilly, and payment to his institution (University of Sussex) for secondment to the UK Department of Health. PB reports grants from the Medical Research Council during the conduct of the study and personal fees from TauRx outside the submitted work. ABu reports personal fees from the *International Journal of Geriatric Psychiatry*, NHS England, various lectures and talks, occasional court reports, King's College London, and the UK Driver and Vehicle Licensing Agency, outside the submitted work. DF reports grants from the Medical Research Council and Alzheimer's Society during the conduct of the study and personal fees and non-financial support from Eisai and Pfizer and Lundbeck outside the submitted work. RHo reports grants from the Medical Research Council UK and Alzheimer's Society UK and non-financial support from Pfizer and Lundbeck during the conduct of the study. RobJ reports grants from the Medical Research Council and Alzheimer's Society and travelling expenses from the Nottingham Healthcare Trust. RoyJ reports grants from the UK Medical Research Council and Alzheimer's Society during the conduct of the study, and grants, personal fees, and non-financial support from Eli Lilly, Servier, and Pfizer, and personal fees and non-financial support from Nutricia, Lundbeck, Novartis, Merz, AC Immune, and Roche Pharmaceuticals, outside the submitted work. CK reports personal fees from Lundbeck and Lilly outside the submitted work. JO'B reports personal fees from General Electric Healthcare, TauRx, and Cytox, and grants and personal fees from Avid and Lilly, outside the submitted work. PPJP reports grants from the Medical Research Council during the conduct of the study. All other authors declare no competing interests.

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