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# Treatment with galantamine and time to nursing home placement in Alzheimer's disease patients with and without cerebrovascular disease

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## SUMMARY

**Objective** This study evaluated patient and treatment (galantamine and other acetylcholinesterase inhibitors (AChEIs)) factors associated with the time until nursing home placement (NHP) in patients with Alzheimer's disease (AD) with and without cerebrovascular disease (CVD).

**Methods** Re-contact follow-up study conducted in 2004 of 548 patients who had previously participated in RCTs with galantamine. Time to NHP was analyzed using Kaplan-Meier estimates and Cox regression analysed factors associated with NHP.

**Results** There were 57% of female subjects and the mean age (SE) was 73.6 ($\pm$0.33) years. Within this cohort 78% of patients had AD, and 22% had AD with CVD. Overall, 59% of subjects had a NHP (median 42.4 months 95%CI: 38.0–48.0). The Cox regression model identified higher baseline Disability Assessment in Dementia (DAD) and Mini Mental State Examination (MMSE) scores, diagnosis (AD with CVD *vs* AD), living with caregiver, country, and treatment duration with galantamine or other AChEIs as factors associated with a reduced risk of institutionalization ($p < 0.05$). For each year of treatment with galantamine or other AChEI, the risk of being admitted to a nursing home within a given period was reduced by 31% (galantamine) and 29% (other AChEI).

**Conclusions** Long-term treatment with galantamine or other AChEIs appears to be associated with a significant delay in the time to NHP in patients with AD and AD with CVD. Further prospective studies are needed to confirm these findings.


KEY WORDS — galantamine; acetylcholinesterase inhibitor; Alzheimer's disease; nursing home placement

## INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease that frequently results in residential or nursing home placement (NHP) (Yaffe *et al*., 2002). In turn, NHP is recognized to be one of the most important cost drivers in AD care (Ostbye and Crosse, 1994).

The acetylcholinesterase inhibitors (AChEIs) have been recommended as a standard treatment of AD in the Practice Parameter of the American Academy of Neurology (Doody *et al*., 2001; Doody, 2003). Double-blind, placebo-controlled RCTs of up to 6 months duration have demonstrated generally small effect sizes with statistically significant benefits on

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cognitive, functional, and global clinical outcomes with AchEIs. Data from longer-term open-label extension studies of galantamine suggest a reduced rate of cognitive decline (Raskind *et al*., 2004; Tariot *et al*., 2000; Wilcock *et al*., 2000; Rockwood *et al*., 2001; Wilkinson and Murray, 2001; Erkinjuntti *et al*., 2002; Brodaty *et al*., 2005; Loy and Schneider, 2006; Auchus *et al*., 2007).

To date a variety of study designs and approaches have been used to assess the impact of AChEIs on NHP (Knopman *et al*., 1996; Lopez *et al*., 2002; Geldmacher *et al*., 2003; Courtney *et al*., 2004). The results have been variable and have generated significant controversy about the longer-term utility of the AChEI drug class. Further data on NHP are still needed.

This current study evaluated the potential patient and treatment (galantamine and other AChEIs) factors associated with time to NHP in patients with AD, with and without cerebrovascular disease (CVD).

## METHODS

In 2004 we re-contacted subjects who had previously participated in four RCTs of galantamine conducted between 1997–2003. Figure 1 demonstrates the chronology and design of each of these RCTs: GAL-INT-1 (Wilcock *et al*., 2003), GAL-INT-2 (Rockwood *et al*., 2001), GAL-INT-6 (Erkinjuntti *et al*., 2002) and GAL-GBR-2 (Wilcock *et al*., 2003). Investigators were asked to provide data that were not available from either initial RCTs or subsequent extension studies, including data for patients who had dropped out of the trials. If the necessary information was not available in the patient's medical notes, investigators were asked to contact the patient's caregiver to collect the information. The re-contact study conformed to local and national Ethical Committee requirements.

Subjects included in GAL-INT-1, GAL-INT-2 or GAL-GBR-2 were diagnosed as having 'probable' AD

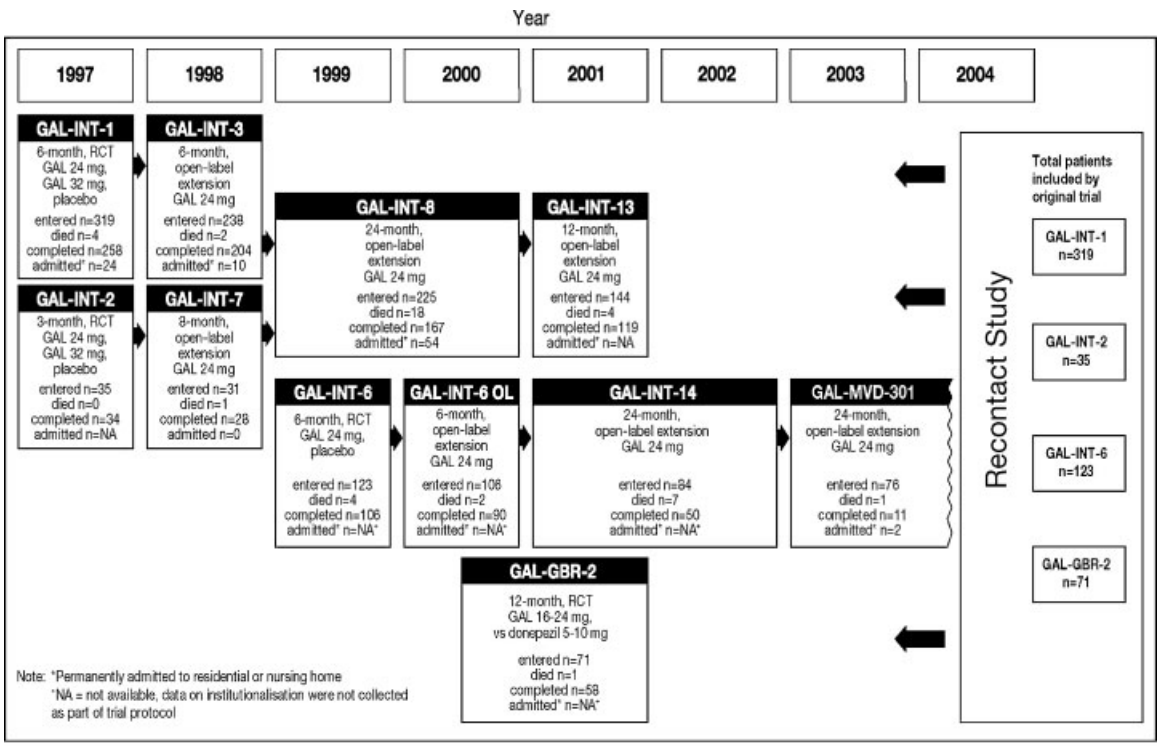


Figure 1. Overview of studies.



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according to the criteria of the NINCDS-ADRDA (McKhann *et al*., 1984). Subjects from GAL-INT-6 had AD with CVD that met the NINDCS-ADRDA criteria for 'possible' AD (McKhann *et al*., 1984) with significant radiologic evidence of CVD. Dementia severity for all patients was mild to moderate (MMSE range of 10–25) (Folstein *et al*., 1975).

A number of factors influenced the retrieval of patient data and inclusion of patients within the analyses (Figure 2). The initial factor was individual countries' participation in the re-contact study which was determined by the availability of central staff and resources within the country to conduct the re-contact protocol. A second factor related to individual centers (investigators) choice to participate in the study based on their available resources, and personnel. Non-participating countries included Australia, Germany, Israel, The Netherlands, New Zealand, Poland, South Africa, and the USA. The analyses of institutional admissions included patients with AD (with or without CVD). Subjects with 'probable' vascular dementia consistent with NINDS-AIREN criteria (McKhann *et al*., 1984) and subjects with 'uncertain diagnosis' from GAL-INT-6 were excluded. Patients already institutionalized at initial trial baseline or with missing information on institutionalization were also excluded from the analyses (Figure 2).

If the patient was institutionalized, the admission date was recorded, otherwise the date of last known contact with the patient was recorded. Additional data on AChEI treatment duration and date of death as applicable were recorded. The mortality analyses of this re-contact study have been reported separately (Feldman *et al*., 2008).

For this study's analysis of NHP, the baseline visit data were taken at the subject's entry into their initial RCT, and included their total scores on the MMSE (Folstein *et al*., 1975) DAD (Gelinas *et al*., 1999) and Neuropsychiatric Inventory (NPI) (Cummings *et al*., 1994). Continuous data from these scales are presented as mean $\pm$ standard error (SE).

A variable was created based on improvement in cognition scores to examine the association between patients' initial response to treatment following 6 months of treatment and institutional admission. Patients in GAL-GBR-2 who improved by $\geq$2 points on MMSE were defined as responders while patients in GAL-INT-1, GAL-INT-2, or GAL-INT-6 who improved by $\geq$4 points on the 11-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog11) (Rosen *et al*., 1984) were also defined as responders.

*Analyses*

Galantamine exposure was determined by including the double-blind phase and open-label extensions, and any subsequent post-trial treatment. Kaplan-Meier survival analyses were used to explore the effect of galantamine exposure on time to institutional admission. For the Kaplan-Meier analyses, patients were classified based on their galantamine exposure as follows: $\leq$6 months (short term), $>$6 months $\leq$24 months (medium term), and $>$24 months (longer term). Six months was chosen as a threshold as it was the maximum duration of the placebo-controlled trials as well as a recommended time for patient (re) assessment according to treatment guidance (http://www.nice.org.uk/TA111), while $>$24 months was considered as a useful cut-off for longer-term treatment exposure. The medium term group was intermediate in exposure duration.

In addition, Cox regression analysis was performed to identify factors associated with the time to NHP. The initial model included duration of treatment exposure with galantamine and with other AChEIs (continuous variable [years]), age (years), sex, baseline MMSE, baseline DAD, baseline NPI, change in cognition scores in the initial treatment period (responder yes or no), diagnostic classification (AD or AD with CVD), number of concomitant diseases, living alone or with caregiver and country of residence. Using a backward selection procedure all factors with a $p$-value $>$0.10 were dropped.

To minimize the potential 'survivorship' effect for patients who remained in long-term open label studies, only data for patients in centers participating in the re-contact study were included.

*Sensitivity analyses*

We conducted a number of sensitivity analyses to examine the robustness of the results to differing assumptions and analytic methods.

To explore the potential that:

(1) Institutionalization was determining treatment duration a scatter plot of time to institutionalisation *vs* duration of galantamine exposure (both presented as continuous variables [months]) was employed (Figure 3).
(2) There was a censoring bias related to mortality among patients with differing exposures to galantamine, Cox regression analyses were conducted using time to mortality or institutional admission as a combined dependent variable.



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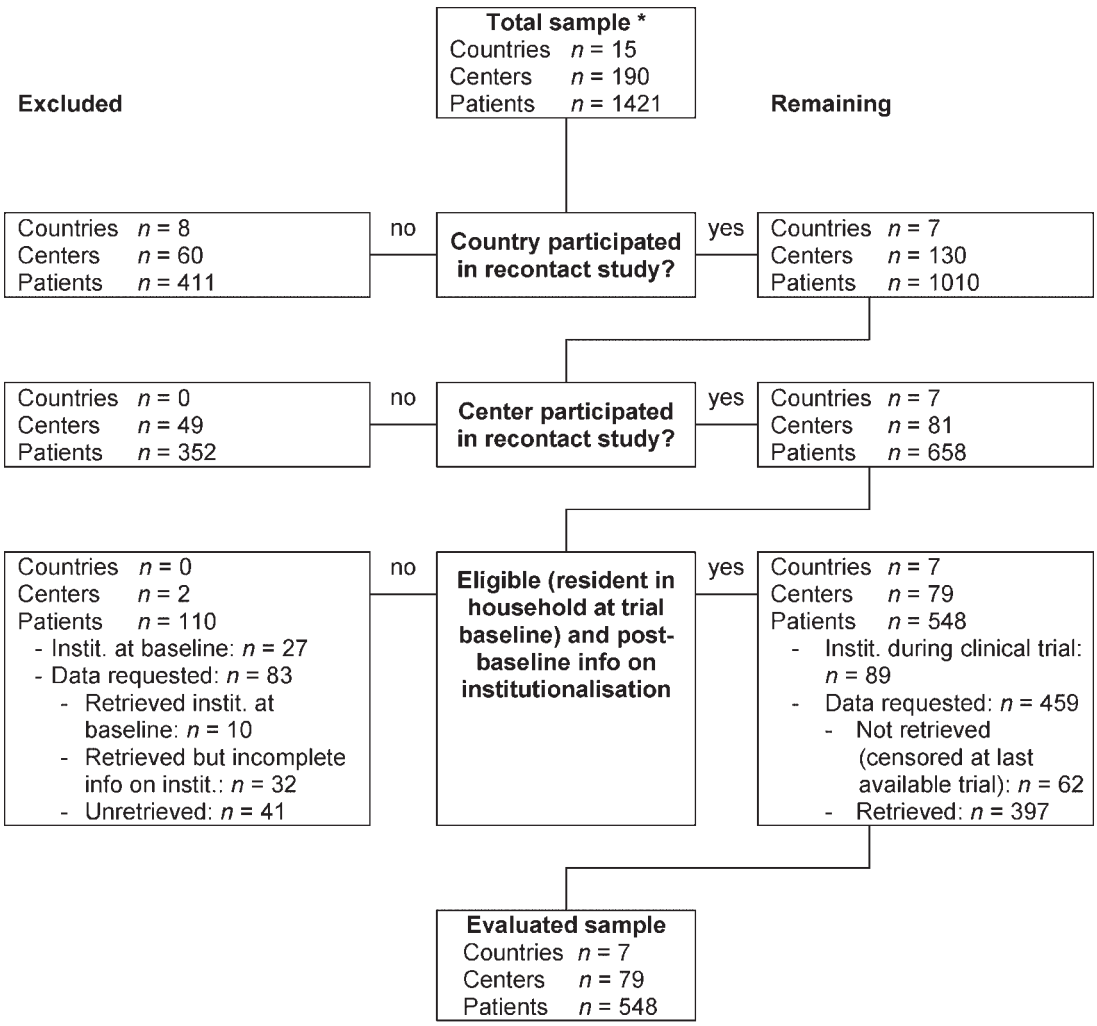


Number of subjects with request for data to be retrieved n = 542. Subjects with unretrieved data n =103; Overall retrieval rate = 81%.
*In GAL-GBR-2, only patients randomized to treatment with galantamine were included.
Instit. = Institutionalization.

Figure 2. Patient inclusion.

(3) That the results were unduly driven by admissions occurring in the initial 6 months among patients with limited exposure to galantamine, Cox regression analyses were again conducted but using admission data and treatment exposure following the initial 6-month period.
(4) Finally propensity scoring analyses were employed to explore potential differences between patients with differing levels of galantamine exposure (Rosenbaum and Rubin, 1983). The propensity analyses utilized the factors associated with patients' treatment duration with galantamine to produce a derived propensity score variable that was included in an additional Cox regression together with a variable for galantamine treatment duration.



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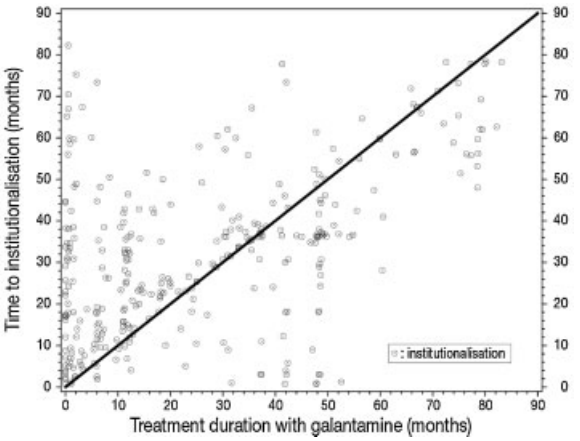


Figure 3. Time to institutionalization by exposure to galantamine.

## RESULTS

A total of 548 patients from seven countries were included (Table 1, Table 2, Figure 2) with 311 women and 237 men with mean age of $73.6 \pm 0.33$ years. Disease severity (MMSE; $p = 0.466$), behaviour (NPI; $p = 0.267$) and living status ($p = 0.632$) were not statistically different between the three treatment groups at baseline entry into their initial randomized clinical trial (Table 1). The proportions of patients demonstrating an initial treatment response on cognitive measures were very similar across the three groups ($p = 0.958$, $\chi^2$ test). There were however, statistically significant ($p < 0.05$) differences on age, number of concomitant diseases, country of residence and functional disability (DAD) present across the galantamine exposure groups. The Kaplan-Meier analyses of survival free of NHP are presented with recognition that these were not randomized subgroups but rather those within an observational cohort (Figure 4). Comparison between the 548 included patients and the 873 patients who were not included showed no significant differences on age, gender, MMSE, and time since diagnosis, or percentage of patients with AD *vs* AD with CVD ($p > 0.05$).

The re-contact study added significant follow-up information to that collected within clinical trials. Mean follow-up was 3.8 years in the overall population and 3.1 years in patients with shorter-duration of galanta-

Table 1. Baseline characteristics by exposure to galantamine

| | 0–6[a] | | 7–24[a] | | >24[a] | | All | |
|---|---|---|---|---|---|---|---|---|
| | *n* | %[b] | *n* | %[b] | *n* | %[b] | *n* | %[b] |
| Women | 80 | 63 | 79 | 51 | 152 | 57 | 311 | 57 |
| Men | 47 | 37 | 76 | 49 | 114 | 43 | 237 | 43 |
| AD | 109 | 86 | 85 | 55 | 231 | 87 | 425 | 78 |
| AD with CVD | 18 | 14 | 70 | 45 | 35 | 13 | 123 | 22 |
| | *n* | mean ± SE | n | mean ± SE | *n* | mean ± SE | *n* | mean ± SE |
| Age (years)* | 127 | 74.3 ± 0.68 | 155 | 75.1 ± 0.60 | 266 | 72.4 ± 0.47 | 548 | 73.6 ± 0.33 |
| Time since diagnosis (years) | 109 | 1.0 ± 0.14 | 85 | 0.9 ± 0.11 | 231 | 0.8 ± 0.07 | 425 | 0.9 ± 0.06 |
| No. of concomitant diseases* | 127 | 2.3 ± 0.18 | 155 | 2.9 ± 0.17 | 266 | 2.1 ± 0.11 | 548 | 2.4 ± 0.08 |
| DAD* | 122 | 62.3 ± 2.15 | 149 | 58.3 ± 2.15 | 262 | 69.4 ± 1.50 | 533 | 64.7 ± 1.09 |
| NPI[c] | 32 | 13.5 ± 2.70 | 101 | 11.3 ± 1.06 | 90 | 9.9 ± 0.98 | 223 | 11.1 ± 0.73 |
| MMSE | 127 | 19.3 ± 0.31 | 155 | 19.2 ± 0.32 | 266 | 19.6 ± 0.23 | 548 | 19.4 ± 0.16 |

| | 0–6[a] | | 7–24[a] | | >24[a] | | All |
|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | *n* |
| Residential status of patient and caregiver** | | | | | | | |
| Living together | 66 | 72.5 | 38 | 79.2 | 129 | 76.8 | 233 |
| Patient living alone | 25 | 27.5 | 10 | 20.8 | 39 | 23.2 | 74 |
| Status unknown | 36 | | 107 | | 98 | | 241 |

[a]Months of exposure to galantamine.
[b]Percentage based on column total.
[c]Not used in GAL-INT-1.
*$p < 0.05$ for comparison between subgroups (*F*-test).
**$p = 0.632$ for comparison between residential status groups.



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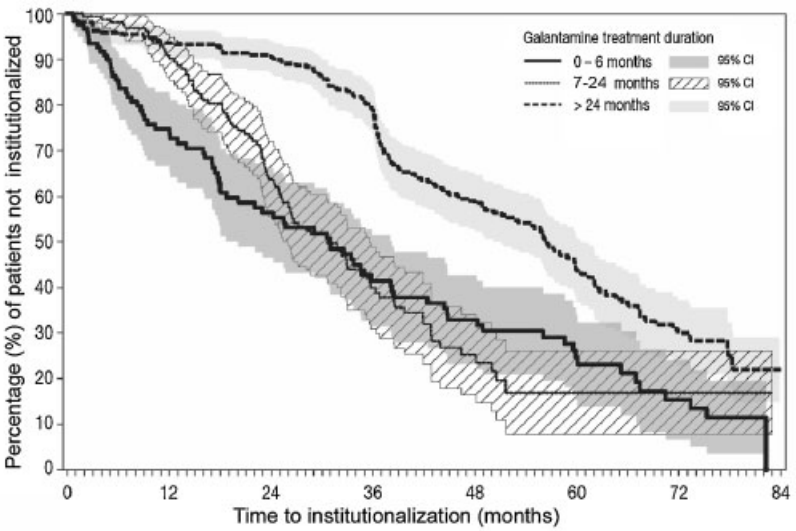
Table 2. Distribution of patients in subgroups by exposure to galantamine

| Subgroup | 0–6[a] | | 7–24[a] | | >24[a] | | All | |
|---|---|---|---|---|---|---|---|---|
| | *n* | %[b] | *n* | %[b] | *n* | %[b] | *n* | %[b] |
| Responder on cognitive score[c] | 25 | 25 | 39 | 26 | 69 | 26 | 133 | 26 |
| GAL-INT-1 | 94 | 74 | 50 | 32 | 175 | 66 | 319 | 58 |
| GAL-INT-2 | 6 | 5 | 5 | 3 | 24 | 9 | 35 | 6 |
| GAL-INT-6 | 18 | 14 | 70 | 45 | 35 | 13 | 123 | 22 |
| GAL-GBR-2 | 9 | 7 | 30 | 19 | 32 | 12 | 71 | 13 |
| Canada | 26 | 21 | 39 | 25 | 58 | 22 | 123 | 22 |
| Denmark | 1 | 1 | 8 | 5 | 3 | 1 | 12 | 2 |
| Finland | 27 | 21 | 28 | 18 | 72 | 27 | 127 | 23 |
| France | 17 | 13 | 14 | 9 | 21 | 8 | 52 | 9 |
| UK | 32 | 25 | 53 | 34 | 48 | 18 | 133 | 24 |
| Norway | 12 | 9 | 5 | 3 | 8 | 3 | 25 | 5 |
| Sweden | 12 | 9 | 8 | 5 | 56 | 21 | 76 | 14 |
| All | 127 | 100 | 155 | 100 | 266 | 100 | 548 | 100 |

[a]Months of exposure to galantamine.
[b]Percentage based on column total.
[c]Data were unavailable from 34 patients.

mine treatment (Table 3). Furthermore, the re-contact study revealed a total of 361 admissions in the participating centers *vs* 90 recorded within the clinical trial protocols at those centers. Sixty-five patients had recorded exposure to rivastigmine or donepezil following their participation in the galantamine trials with mean treatment exposure of 26 months. Few patients had recorded memantine ($n = 19$, mean duration: 7 months) or other symptomatic treatments for AD ($n = 21$, mean duration: 20 months).

Overall, 59% of the eligible sample had a permanent institutional admission recorded with the remaining 224 patients being censored (due to mortality or end of follow-up). The median time to institutionalization was 42.4 months [95% Confidence Intervals (CI): 38.0–48.0 months]. Significant differ-




Displayed are the Kaplan-Meier plots for the time to institutionalization in the 3 subgroups according to their exposure to galantamine (0-6 months: n = 127; 7-24 months: n = 155, and >24 months: n = 266) including 95% confidence intervals (CI).

Figure 4. Time to institutionalization by exposure to galantamine.



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ences between the three galantamine exposure groups were observed (Figure 3) ($p < 0.0001$, log-rank test). Median time to institutionalization was 30.9 months for the short-term exposure group (95% CI: 20.1–38.2 months, 48/127 patients censored), 30.6 months for the intermediate exposure group (95% CI: 26.0–35.6 months, 63/155 patients censored), and 56.4 months for the long-term exposure group (95% CI: 51.1–60.5 months, 113/266 patients censored).

In the initial Cox regression model, treatment with galantamine or other AChEIs, baseline DAD and MMSE total scores, diagnosis (AD or AD with CVD), living alone and country were identified as significant factors ($p < 0.05$). A reduced model was estimated using backward selection of covariates removing factors with $p > 0.10$ (sex, number of concomitant diseases, baseline NPI, response on cognition scores), producing consistent results (Table 4).

The model estimated that for each year of treatment with galantamine the risk of being admitted to a nursing home was reduced by 31%. A similar risk reduction (29%) was estimated for other AChEIs. For both baseline functional disability (DAD) and cognition (MMSE) higher baseline values were associated with significant reductions in risk of admission. For example, for patients with 10 point better scores on baseline DAD the risk of admission was reduced by 19% (95% CI: 11–26%). Similarly a 1 point higher score on baseline MMSE was associated with estimated risk reduction of 7% (95% CI: 3–11%). Living alone significantly increased the risk of NHP by 76% (95% CI: 25–147%). For patients with AD with CVD the risk of being institutionalized was 44% lower (95% CI: 10–65%) *vs* patients with AD. Country of residence was also a significant factor.

In order to investigate the hypothesis that institutionalization itself determined treatment discontinuation with galantamine, we used a scatter plot to examine the pattern of galantamine exposure *vs*. time pre- and post-admission (Figure 3). Interestingly many patients continued galantamine treatment after admission, while others who ceased treatment remained in households for some months following discontinuation.

Cox regression analyses that employed mortality or admission as a dependent variable produced consistent results. Estimated hazard rates for each year of galantamine exposure (HR 0.660 [95% CI 0.622–0.700] in the analyses using combined mortality/institutionalisation endpoint were similar *vs*. the original analyses (HR 0.690 [95% CI 0.647–0.735]). Similarly, when Cox regression analyses of permanent institutional admission excluded admissions and treatment exposure in the first six months results were consistent (HR 0.692 [95% CI 0.647–0.740] *vs* the original analyses (HR 0.690 [95% CI 0.647–0.735]). HRs for other covariates again also remained generally consistent in both of these additional models.

Finally results again appeared similar for galantamine exposure when Cox regression analyses including a propensity score variable were conducted (HR

Table 3. Duration of follow-up and of treatment by exposure to galantamine

| Follow-up | 0–6[a] | 7–24[a] | >4[a] | All |
|---|---|---|---|---|
| | $n = 127$ | $n = 155$ | $n = 266$ | $n = 548$ |
| Cumulative [patient years] | 398 | 448 | 1247 | 2093 |
| Mean [years] | 3.13 | 2.89 | 4.69 | 3.82 |
| SE [years] | 0.22 | 0.12 | 0.09 | 0.08 |
| Maximum [years] | 7.05 | 6.92 | 7.18 | 7.18 |
| Treatment with galantamine | $n = 127$ | $n = 155$ | $n = 266$ | $n = 548$ |
| Cumulative [patient years] | 17 | 169 | 1056 | 1242 |
| Mean [years] | 0.13 | 1.09 | 3.97 | 2.27 |
| SE [years] | 0.01 | 0.03 | 0.08 | 0.08 |
| Minimum [years] | 0 | 0.5 | 2 | 0 |
| Maximum [years] | 0.5 | 2 | 6.9 | 6.9 |
| Treatment with other AchEIs | $n = 31$ | $n = 22$ | $n = 12$ | $n = 65$ |
| Cumulative [patient years] | 88 | 38 | 17 | 142 |
| Mean [months] | 33.99 | 20.50 | 16.70 | 26.23 |
| SE [months] | 4.17 | 3.61 | 3.65 | 2.58 |
| Minimum [months] | 1 | 1 | 1 | 1 |
| Maximum [months] | 77 | 53 | 36 | 77 |

[a]Months of exposure to galantamine.



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Table 4. Cox regression analyses of time to permanent institutional admission

| Variable | Hazard Rate | 95% CI | Probability |
|---|---|---|---|
| Years of treatment with galantamine | 0.690 | 0.647–0.735 | <0.0001 |
| Years of treatment with other AChEI | 0.714 | 0.631–0.809 | <0.0001 |
| Baseline DAD | 0.983 | 0.977–0.990 | <0.0001 |
| Baseline MMSE | 0.934 | 0.902–0.968 | 0.0002 |
| AD with CVD *vs* AD | 0.562 | 0.349–0.904 | 0.0175 |
| Living alone | 1.757 | 1.252–2.465 | 0.0011 |
| Not known whether living alone ($n = 241$) | 1.146 | 0.786–1.672 | 0.4784 |
| Age [years] | 1.015 | 0.999–1.032 | 0.0614 |
| Country | | | <0.0001 |
| Canada *vs* Finland | 0.756 | 0.525–1.090 | |
| Denmark *vs* Finland | 0.357 | 0.109–1.170 | |
| France *vs* Finland | 0.714 | 0.431–1.182 | |
| UK *vs* Finland | 0.299 | 0.192–0.465 | |
| Norway *vs* Finland | 1.679 | 1.008–2.798 | |
| Sweden *vs* Finland | 1.668 | 1.172–2.375 | |

Using backward selection with $p < 0.10$ as criterion for staying in the model, the following factors with $p \geq 0.10$ were dropped: gender, number of concomitant diseases, baseline NPI, short term responded in cognitive score.

0.737 [95% CI 0.692–0.786] in the propensity scoring analyses *vs* HR 0.690 [95% CIs 0.647–0.735] in the original analyses).

## DISCUSSION

This study addresses the important AD milestone of time to NHP among AD patients with and without CVD. It also investigates the influence of both AChEI treatment and other important clinical factors on NHP. The study design included a re-contact study of former trial participants from initial registration RCTs of galantamine as well as some later RCTs (1997–2004). It provides additional data on the time to NHP in a sizeable sample of AD patients.

These results indicate that close to 60% of the patients re-contacted had been permanently admitted to NHP within a median time of 42 months. In common with previous research, cognitive and functional severity indicators and resident alone status significantly impacted the time to NHP (Heyman *et al*., 1997; Opit and Pahl, 1993). Not surprisingly, strong country effects on NHP rates were seen. For example, patients in the UK had a significantly lower predicted risk of NHP *vs*. with patients with similar characteristics and treatment patterns in the northern Scandanavian countries, reflecting perhaps differences in the availability of nursing home beds, and financial and other policies influencing admissions. Each year of treatment with galantamine was associated with a reduction in risk of admission of just under a third with similar risk reductions predicted for post-galantamine trial use of other AChEIs.

The strengths of this study include the relatively large sample of patients with NHP data up to seven years after their participation in the initial RCTs. This sample supported the examination of a number of potentially important NHP determinants. The inclusion of patients with AD without and with CVD broadens the potential generalizability of the study findings given that a significant portion of AD patients are recognized to have coexisting CVD (Feldman *et al*., 2003).

There are, however, potentially important study limitations to consider. This sample was restricted to those countries and centers willing and able to participate, some years after their sites had closed out the initial RCTs. For administrative other reasons, there were eight countries and that did not participate in this re-contact study reducing the sample size and also creating the potential for a selection bias. To address this possibility, we compared the baseline clinical and demographic factors of patients included and excluded from the re-contact study and we did not identify any significant differences, though other unidentified important factors may exist. As this is an analysis of retrospectively collected data without randomized allocation to treatment groups, there are other potential sources of bias including survivorship effects. In this regard, we noted that our exposure groups had similar cognitive severity, neuropsychiatric symptoms at entry, and initial cognitive response rates. The longest exposure group however, had a higher level of functional ability at entry measured on the DAD. While this DAD difference is statistically significant the magnitude of difference is not likely to fully explain the magnitude of difference in the time to



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NHP (Feldman *et al*., 2006). Furthermore, the Cox regression analyses which took this potential source of bias into account did not alter the risk reduction associated with galantamine treatment. Additionally, we conducted further sensitivity analyses on this data using propensity scoring which gave us similar results. Interestingly, the duration of galantamine exposure did not seem to have been influenced by early response on cognitive measures, with similar proportions of responders in low and high exposure groups. An additional sensitivity analysis showed no censoring bias due to mortality or bias due to early admissions (first 6 months) among patients with low exposure to galantamine.

A further consideration that arises from this study is whether galantamine may have been stopped when subjects were institutionalized, leading to the observed effect of a correlation between time to institutionalization and exposure to galantamine in the absence of a drug effect. Our analyses indicate that there was a more heterogeneous pattern between admissions and treatment exposure, where many patients received continued treatment following admission, while other patients who stopped treatment remained outside institutional care.

Overall, the range of sensitivity analyses that we conducted to address the potential sources of bias and to examine the consistency of the data showed similar results. Unobserved biases still cannot be fully excluded within the present design and must be taken into account in considering these data.

Recognizing these potential limitations, our results are nevertheless important. They are consistent with other observational studies that have used either matched samples of AChEI treated or untreated groups (Lopez *et al*., 2002, 2005) or follow-up data from randomized trials (Knopman *et al*., 1996; Geldmacher *et al*., 2003; Feldman *et al*., 2004). This consistency of results, however, does not override the concerns about potential sources of bias within these study designs. The current study contrasts with the lack of effect of donepezil on the time to NHP observed in the AD2000 trial (Courtney *et al*., 2004). However, AD2000 also had significant potential biases from re-randomization and annual wash-out phases which meant that initial randomization groups did not reflect actual treatment exposures with large scale switches of placebo patients to NHS AChEI prescribing or discontinuation of treatment in the active arm (Courtney *et al*., 2004). In fact, at the end of the first year of the study when patients were relatively adherent to randomised treatments, results observed for donepezil were relatively consistent with this study (14% admissions for placebo *vs* 9% for donepezil; see Figure 2 page 2110 of Courtney *et al*., 2004).

Taken together, these studies using NHP as an AD milestone underscore the methodological challenges and limitations of ascertaining whether including AD treatments effectively delay the time to NHP. An optimal design and approach is still required to address this challenge.

KEY POINTS

- Galantamine and other AChEIs appear to delay the time to nursing home placement in patients with Alzheimer's disease.
- Further prospective studies are needed to confirm these findings.

## CONCLUSION

In this observational study, long-term treatment with galantamine or another AChEI appears to be associated with a significant delay in the time to NHP in patients with AD and AD with CVD. Further prospective studies are needed to confirm these findings.

## CONFLICT OF INTEREST

Within the past 2 years, Howard H. Feldman has had a financial interest/arrangement or affiliation with one or more of the following organizations: Pfizer, Eisai, Janssen Pharmaceutica NV, JJPRD, Lilly, Astra Zeneca, Sanofi Synthelabo, Glaxo Smith Kline (grant/research support external); Pfizer, Eisai, Novartis, Janssen Pharmaceutica NV, JJPRD, Servier, Sanofi Synthelabo, Glaxo Smith Kline, Myriad, Targacept, Lundbeck, Forest, Axonyx (consultant); Pfizer, Eisai, Janssen Pharmaceutica NV, JJPRD, Novartis, Forest (CME programs).

Tuula Pirttila has received research funding from Janssen Pharmaceutica NV and also been a paid consultant to Janssen Pharmaceutica NV. Jean Francois Dartigues has received grants/honorarium from Janssen Cilag, Eisai, Lundbeck, Ipsen and Novartis. Brian Everitt has been a paid consultant to Janssen Pharmaceutica NV. Mr. Van Baelen has been a paid consultant to Janssen Pharmaceutica NV. Shane Kavanagh is employed by Janssen Pharmaceutica NV and has stock in Johnson and Johnson. Susanne Schwalen was employed by Janssen Cilag when this research study and paper were conducted.



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