Persistent Antidementia Drug Treatment and Survival in an Alzheimer's Disease (AD) Cohort

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Background

- Survival (life span) in people with AD is recognized to be shorter than what is expected in cognitively normal seniors and is recognized to be influenced by several factors including age, disease severity, general debility, and gender.
- An estimate of survival probability among patients with AD is needed for planning and assessing the overall impact of dementia.[1]
- Since 1993 five drugs have been marketed in the U.S. for the treatment of Alzheimer's disease (donepezil, galantamine, rivastigmine, tacrine, memantine).
- Antidementia drugs have been proven to help with the symptoms of Alzheimer's disease but their influence on long term course and life span is not known. We previously presented data that showed cognitive and functional benefits continued over many years for patients who persist in their treatment.[2]
- This study examined the use of antidementia drugs or more precisely, the persistent use of these medications and their influence on survival. This information is not available for clinical trial data because these studies have a relatively short duration of follow-up.

Study Objectives

- To assess whether persistent treatment with cholinesterase inhibitors and/or memantine affects survival time adjusting for other factors known to influence survival.

Methods

Prospective Cohort Study — Probable AD patients (meeting NINCDS-ADRDA criteria[3]) followed at the Baylor College of Medicine Alzheimer's Disease Center. The longitudinal database is approved by the IRB.

Patients — Diagnosis of probable AD with no confounding secondary diagnoses and with follow-up visits that have records of total lifetime antidementia medication exposure.

Independent Variable — Treatment with antidementia medication. We evaluated drug exposure or cumulative time on drug from the onset of symptoms[4] and determined a persistency score. The physician recorded drug exposure at the first clinic visit by history obtained from the patient and caregiver along with a review of medical records. This information was updated at each return visit to the center. A standardized from was used and treatment dates were entered in an electronic data base including the starting and ending date, if applicable, so the cumulative time on medication could be determined. Lapses in treatment or switching from one drug to another was also noted and recorded, and subtracted from the persistency score.

Dependent Variable — Cumulative survival as a function of time. Vital status was obtained from the National Death Index every six months.

Covariates — Age, sex, years of education, duration of symptoms, and baseline severity of dementia (mild, moderate, severe based on Mini Mental Status Examination score [MMSE]), and an indicator variable reflecting whether or not a patient had started on antidementia therapy before their initial visit to the ADMDC. We also evaluated the preprogression rate[5] calculated by the following formula: (MMSE score [expected 30] – MMSE score [initial]) / physician's estimate of symptom duration [in years]) in another model which excluded the duration of symptoms and baseline severity.

Analysis — Proportional hazards regression method was used to determine the association of drug treatment category (persistency score) and all-cause mortality using the upper quartile of drug persistency as the reference. Adjustments were made for the other covariates. Median survival times were calculated. The cut-off date for analysis was December 31, 2005.

Table 1. Baseline Characteristics of Patients with AD

n = 641	Value	Range
Age [yrs]	72.9 (8.5)	43 - 93
Male/Female	32% 68%	
Education [yrs]	13.6 (3.6)	0 - 29
Early Exposure Index [yrs]	0.49 (0.27)	0 - 1
Duration of Sx before initial visit [yrs]	3.7 (2.3)	0.5 - 13
Follow-up time [yrs]	3.03 (1.9)	0.8 - 13.4
Total number of visits	3.43 (1.6)	2 - 11
MMSE score	19.5 (6.6)	0 - 30

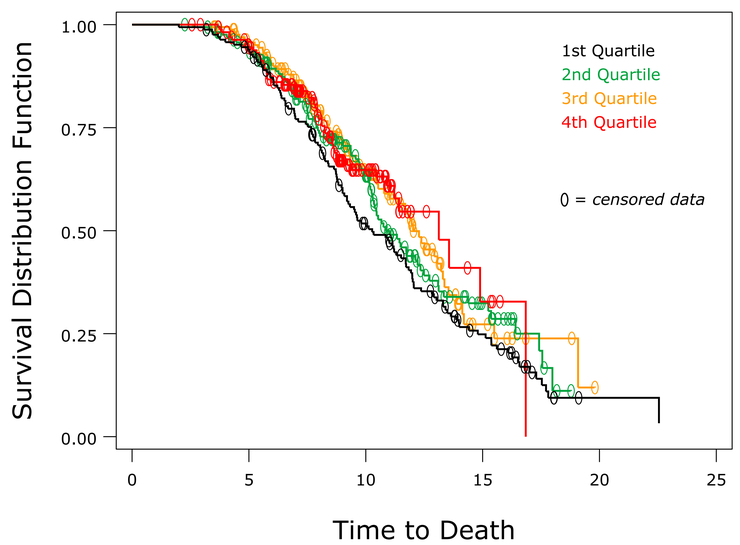
Mean (SD) for all continuous variables.

Table 2. Factors Associated with Increased Risk of Death in AD

Variable	Parameter (Standard Error)	HR	95% CI	p
Quartile:†				
1st vs. 4th	0.88 (0.19)	2.40	1.66, 3.47	<.0001
2nd vs. 4th	0.78 (0.19)	2.19	1.50, 3.20	<.0001
3rd vs. 4th	0.41 (0.19)	1.50	1.04, 2.17	<.05
Duration of Sx [yrs]	-0.33 (0.03)	0.72	0.68, 0.77	<.0001
Stage disease:				
Severe vs. Mild	0.54 (0.19)	1.71	1.19, 2.47	<.01
Moderate vs. Mild	0.33 (0.13)	1.39	1.09, 1.78	<.01
Drug use before initial visit	0.65 (0.14)	1.91	1.46, 2.50	<.0001
Male sex	-0.62	0.54	0.43, 0.68	<.0001
Education [yrs]	0.01	0.99	0.54, 1.02	=.43
Age	0.04	1.04	1.03, 1.06	<.0001

† Quartiles refer to persistency of antidementia therapy with 1 being the lowest and 4 the highest quartile of exposure.

Figure 1. Time to Death by Persistency Score (1st, 2nd, 3rd, and 4th Quartiles)



Results

- 641 patients met inclusion criteria (see baseline characteristics in Table 1).
- 53% of the cohort died and 47% were censored with a mean follow-up time of 3.0 ± 1.9 years. Range of follow-up 0.77 to 13.4 years.
- The average proportion of time on drug over the whole study period was 0.49 (SD 0.3) and by quartile was 0.33 (25th%), 0.55 (50th%), 0.70 (75th%), and 0.99 (100th%).
- Over the entire course of the study 12% never took any antidementia drugs.
- The median difference in survival between the lowest quartile group and the most persistent users or highest quartile group was 3.12 years.
- Male sex (p<.0001), age (p<.0001), moderate vs. mild (p<.01) and severe vs. mild (p<.01) stage disease, drug use before the initial visit (p<.0001) were associated with higher mortality. Longer duration of symptoms at the initial visit was associated with a decreased risk of death (p<.0001).
- Patients whose PI fell in the lowest three quartiles had a significantly increased relative risk of death compared to the highest quartile of drug use with adjustments: HR (1st) = 2.4 (95% CI 1.7-3.5, p<.0001); HR (2nd) = 2.2 (95% CI 1.5-3.2, p<.0001); HR (3rd) = 1.5 (95% CI 1.0-2.2, p<.05) (see Figure 1).
- When the model included the preprogression rate instead of baseline MMSE and duration of symptoms, drug use before the initial visit was not associated with increased risk of death (p=0.17), suggesting that rapid progressors were more likely to use drug early. The persistency score (continuous variable) remained inversely and significantly associated with decreased risk of death: HR = 0.6, (95% CI 0.39-0.89, p<.05).

Conclusions

- Greater persistent therapy with antidementia drugs was significantly associated with prolonged survival in an AD cohort with adjustment for covariates.
- Persistent drug therapy appears to help Alzheimer's patients live longer and the mechanism may be related to overall improvement of cognition and function resulting from current symptomatic therapies.
- Additional studies are needed to confirm these results.

Strengths

- Large number of patients followed over a relatively long period
- Reflects actual clinical practice, as patients came to the center at various times following first symptoms and were often treated in the community initially.

Limitations

- Observational study
- Selection factors associated with long term drug use cannot be ruled out as an alternative explanation for the findings
- High dose Vitamin E use as part of an antidementia drug regimen[6] was recently reported to be associated with improved survival in a long term study, and many of our patients also take high dose vitamin E. The present study was limited to use of prescription drugs approved for AD treatment.

References

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