Exposure to Anti-dementia Drugs Slows Clinical Progression of Alzheimer's Disease (AD)

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Introduction

Recommendations on the management of dementia published by the American Academy of Neurology advised that cholinesterase inhibitors (ChEI) should be standard of care for treatment of mild to moderate Alzheimer's disease (AD).[1] This review predates the Food and Drug Administration approval of memantine for use in moderate to severe AD in 2003 and donepezil in severe stage AD in 2006. The current available drugs are regarded as having only symptomatic effects but some researchers believe that these drugs will continue to play an important role in patient management even when more disease modifying therapies materialize due to uncertainty about the extent of regenerative capacity in the AD brain. The commercially available medications have been demonstrated to confer benefits favoring cognition and patient function in controlled studies lasting from 3 to 6 months up to 1 year in duration.

Background

The impact of anti-dementia drugs should be judged not only by the short term effect size, but also by how long patients continue to benefit. There are no current guidelines for duration of therapy with donepezil, rivastigmine, galantamine, and memantine.

Objectives

To assess whether greater cumulative exposure to anti-dementia drug (from first symptom until death or censoring) reduces clinical progression of AD as measured by neuropsychological testing.

Methods

We prospectively evaluated 641 probable AD patients followed at our center over a 20 year period, many of whom remain in active follow-up. All members of this cohort agreed to participate in a database approved by the IRB at BCM and met criteria for the diagnosis of probable AD as determined by the NINCDS-ADRDA.[2] A total of 679 patients were eligible but 38 were missing an important covariate and were excluded from the analysis. All patients underwent an evaluation by a neurologist and completed a standardized dementia workup.[3] The duration of illness was carefully estimated by the physician at the new patient visit by a standardized procedure reported to the nearest half-year.[4] Patients return to the center annually and have the battery of neuropsychological tests repeated. The small percentage (<20%) who cannot return to the center are assessed on a subset of measures by telephone and vital status is assessed every 6 months. We analyzed basic demographic and psychometric characteristics of the cohort, time and number of visits and the vital status at censoring date.

Exposure — Drug exposure to the antidementia drugs was ascertained for each subject and quantified. Drug exposure information was recorded by the physician 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. The majority of patients received prescriptions for their antidementia drugs through the center. The dates of drug exposure were recorded in the database and included both 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. Exposure to memantine, tacrine, donepezil, galantamine, and/or rivastigmine was calculated in months of use if one or more of these drugs were taken.

Persistency Index — Persistent drug exposure was calculated by a persistency index (total PI): total years of drug use divided by the total years of disease symptoms. The regression coefficient associated with the variable "cumulative months on ChEI and/or memantine" indicated the amount of change in cognitive performance associated with a unit change in duration of ChEI and/or memantine exposure.

Early Exposure Index — The use of drug prior to the initial visit (covariate) was determined to control for the effects of early treatment and/or the propensity to take medication. The Early Exposure Index was determined by the total years of drug use divided by the total years of disease symptoms prior to the initial visit.

Neuropsychological Testing — Cognitive and functional testing were performed at baseline and annually with Mini Mental State exam (MMSE), Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS), Baylor Profound Mental State exam (BPMSE), Clinical Dementia Rating Scale Sum of Boxes (CDR-SB), Physical Self-Maintenance Scale (PSMS), and Independent Activities of Daily Living scale (IADL).

Analysis — Random effects linear regression modeling was used to examine impact of cumulative anti-dementia drug exposure (total PI) on change in the slope or rate of decline for the neuropsychological tests. The primary model included time from the first visit, total PI, interaction of these two terms and symptom duration. We then adjusted for baseline severity, duration of AD, age, sex, years of education, and the cumulative exposure to antidementia drugs prior to initial visit (Early Exposure Index).

Results

Benefits were seen on both cognitive and functional measures. There was significantly slower decline (with, without) adjustment on the MMSE ($p<0.01$, $p<0.05$), ADAS ($p<0.01$, $p<0.05$), BPMSE ($p<0.01$, $p<0.01$), and PSMS ($p<0.01$, $p<0.01$). No significant treatment effects on the slope of decline were found for the IADL and CDR-SB. Persistent exposure to the anti-dementia drugs was associated with a significantly slower rate of decline on all of the cognitive measures and basic activities of daily living. Treatment did not influence the rate of decline of a measure of complex activities of daily living or global dementia rating. However, differences on these latter two measures associated with the persistency index at the first visit were retained over time.

The magnitude of the treatment effect was thought to be clinically significant. Each 10% increment in the total PI was associated with an increased MMSE score 0.5 points and slowed decline by 0.8 points/year; reduced ADAS score 0.6 points and slowed decline by 0.2 points/year; slowed decline on the BPMSE by 0.2 points/year; reduced PSMS score 0.2 points and slowed decline by 0.09 points/year; reduced CDR-SB score 0.5 points; and reduced IADL score 0.5 points. (See graphs)

At censoring 54% of the cohort had expired and 46% were alive.

Baseline Characteristics of AD Patients

n = 641	Value	Range
Age [yrs]	72.9 (8.5)	43-93
Male/Female	32% 68%	
Education [yrs]	13.6 (3.6)	0-29
EEI [yrs]	0.49 (0.27)	0-0.99
Duration of Sx^ [yrs]	3.7 (2.3)	0.5-13
Follow-up time [yrs]	3.03 (1.9)	0.77-13.4
Total # visits	3.43 (1.6)	2-11

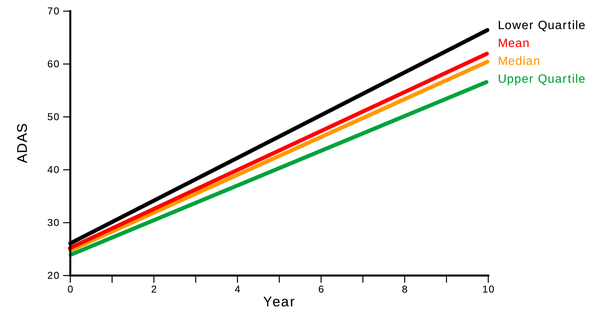
Mean (SD) for all continuous variables.
EEI = Early Exposure Index.
^before initial visit

Baseline Neuropsychological Tests

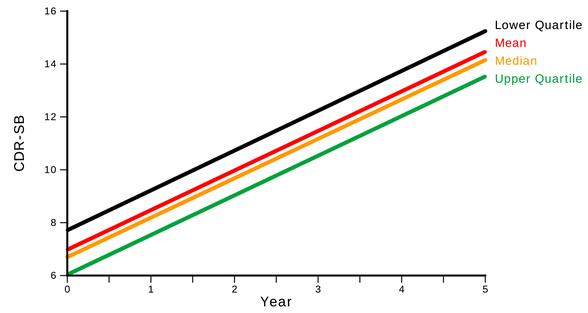
n = 641	Score	Range
MMSE	19.5 (6.6)	0-30
ADAS-Cog	24.3 (12.4)	1-68
BPMSE	19.6 (6.0)	0-25
CDR-SB	6.7 (4.0)	0.5-18
IADL	15.5 (6.5)	2-31
PSMS	7.9 (3.1)	6-25

Mean (SD) for all continuous variables.

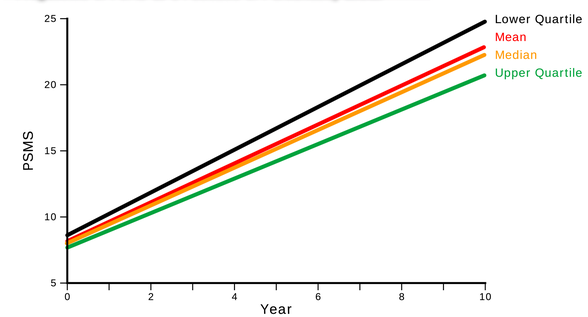
Progession of ADAS as a Function of Persistency Index



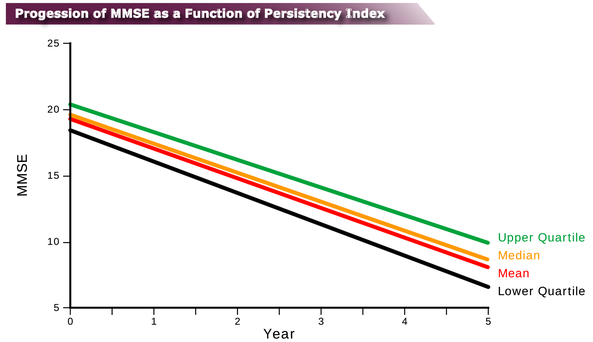
Progession of CDR-SB as a Function of Persistency Index



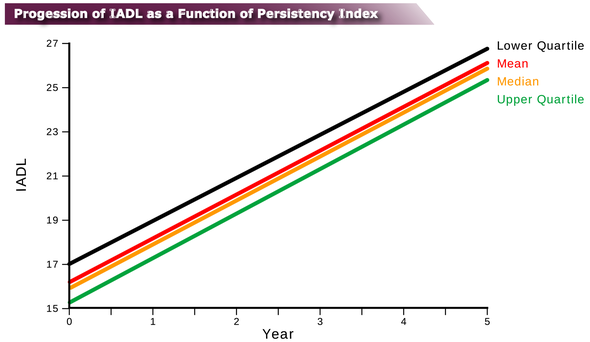
Progession of PSMS as a Function of Persistency Index



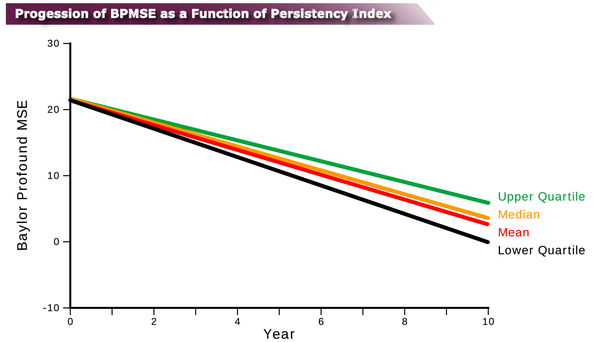
Progession of MMSE as a Function of Persistency Index



Progession of IADL as a Function of Persistency Index



Progession of BPMSE as a Function of Persistency Index



Conclusions

- Significant benefits from persistent therapy were demonstrated in AD patients followed longitudinally in a clinical practice setting.
- Benefits were found even in those with advanced disease.
- This study suggests that patients who persistently use antidementia drugs derive cognitive and functional benefits compared to those who receive less persistent therapy.

References

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Disclosure

The work was performed at Baylor College of Medicine Alzheimer Disease and Memory Disorders Center. Research support for this study came from the Cynthia Mitchell Endowment and Forest Pharmaceuticals, Inc.