# Clinical Factors Associated with the Preprogression Rate (PPR) in Alzheimer Disease (AD)

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## BACKGROUND

The heterogeneity of disease progression rates is common in AD. The preprogression rate (PPR) is an easily calculable index of early disease progression that can be determined at the initial visit and has prognostic value in classifying patients as rapid, intermediate, or slow decliners.[1] We wished to evaluate factors known to influence disease progression at the initial assessment, including the use of anti-dementia drugs. We hypothesized that patients who take anti-dementia drugs persistently or have greater cumulative exposure will have a slower PPR.

## OBJECTIVES

To determine if using any commercially available anti-dementia drug (including donepezil, galantamine, rivastigmine, and memantine) affects the PPR. We also evaluated patient age, sex, years of education, premorbid verbal IQ (AMNART), initial Mini-Mental State examination (MMSE) score, and the history of hypertension or diabetes.

## METHODS

We determined the PPR at the initial visit for 679 patients evaluated over the past 20 years at an academic center who were classified as having probable AD using NINCDS-ADRDA criteria.[2] The PPR or dependent variable was calculated according to the following formula: (MMSE score [expected 30] - MMSE score [initial]) / physician's estimate of symptom duration [in years]).

All patients underwent an evaluation by a neurologist and completed a standardized dementia workup. A detailed history and interview with the patient and informant, neurological and physical examinations, a neuroimaging study, neuropsychological testing, and screening laboratory studies were performed as part of the initial visit. We employ a comprehensive battery of psychometric tests to assess all patients, described elsewhere.[3]

Drug exposure to any of the four agents was ascertained for each patient at the first clinic visit by history along with review of medical records by the attending physician. Chart review was performed to evaluate possible drug exposure received during clinical research trials and to verify accuracy of information. Lapses in treatment and switching from one drug to another were also noted and recorded. The dates of drug exposure are recorded for both the starting and ending date, if applicable, so the cumulative number of months on medication can be determined for each subject. The cumulative time on drug was recorded similarly for patients on monotherapy or combination therapy. The duration of disease or the estimated time of onset of dementia is carefully estimated by a standardized procedure reported to the nearest half-year.[4]

Cumulative drug exposure was calculated by a persistency index or PI: (drug use [in years] / physician's estimate of symptom duration [in years]). Drug naïve subjects had PI= 0 and those that "ever-use-drug" had PI> 0.

Multiple linear regression analysis was used to estimate the relative contribution of cumulative exposure (PI range 0-1), ever-use-drug (PI> 0), initial Mini-Mental Status Exam score (MMSE), years of education, age, sex, hypertension history, and diabetes history to the PPR.

## RESULTS

We found that 379 of 679 patients (57%) had never taken drugs. There were 61 patients excluded from the analysis due to missing observations. The average PPR for the group of 618 subjects was 3.62 (SD 3.07) points/year on the MMSE confirming high variability in the PPR (CV 84.8%).

Significant predictors of the PPR were years of education (β= -0.10 [se= 0.03], p= 0.0017), initial MMSE (β= -0.20 [se= 0.02], p< 0.0001), and those that had ever used drug (β= -0.92 [se= 0.28], p= 0.0012). The PI, age, sex, history of diabetes or hypertension were not found to be significant. The model was extended to include the premorbid verbal IQ but there was no significant association between the AMNART and the PPR and there was loss of multiple subjects due to missing observations. The model explained 24% of variance in the PPR (adj. $R^2$= 0.2368).

**Table 1. Multiple Regression Analysis of Factors Associated with Preprogression Rates in Alzheimer Disease**

| | β | Standard Error |
|---|---|---|
| Intercept | 10.81 *** | 1.20 |
| Persistency index | 0.64 | 0.65 |
| Ever-use-drug | -0.92 ** | 0.28 |
| Years of education | -0.10 ** | 0.03 |
| Age | -0.02 | 0.01 |
| Sex (male) | -0.04 | 0.24 |
| History of diabetes | 0.17 | 0.38 |
| History of hypertension | -0.13 | 0.23 |
| MMSE | -0.20 *** | 0.02 |

*p< 0.05; **p< 0.01; ***p< 0.001; otherwise p= NS.

**Figure 1. Preprogression Rate and Years of Education**

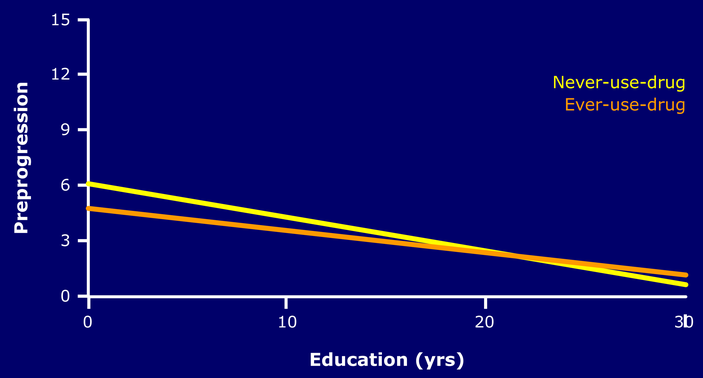
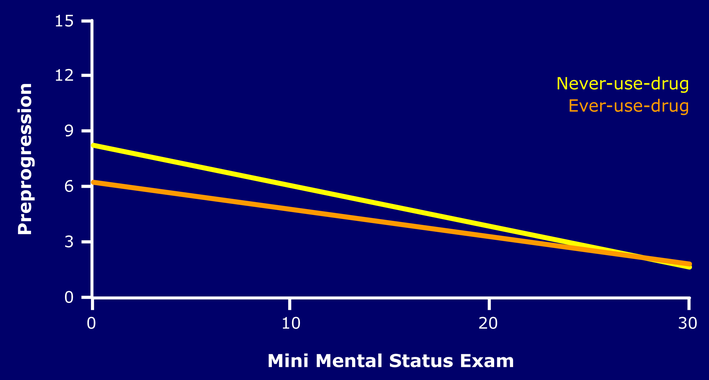



**Figure 2. Preprogression Rate and MMSE**




## CONCLUSIONS

The preprogression rate (PPR) or rate patients were progressing prior to the initial visit was lower in those who had used anti-dementia drugs versus those who never used drugs. There was no association between early disease progression on the PPR and cumulative drug exposure before the new patient visit (PI). This may have been an artifact of the high percentage of treatment naïve individuals whose PI scores were zero. Alternatively there may be other, as yet unknown differences between users and non-users of anti-dementia drugs. As previously reported, higher educational attainment and higher initial MMSE scores were also associated with slower disease progression. We would expect MMSE to be associated with the PPR since it is part of the formula. Performance on the MMSE is recognized to be influenced by education level so both these variables may be correlated. Overall the model explained only a small portion of the variance in the preprogression rate (PPR). Other factors need to be identified to explain more of the variance in early preprogression rates.

This study evaluated early disease progression from the onset of symptoms to the time patients present for an initial evaluation. A subsequent analysis was performed to determine if cumulative exposure to anti-dementia drugs over the entire course of the illness predicts observed progression rates. We hypothesized that persistent treatment or greater cumulative exposure to the antidementia drugs slows disease progression on global measures, cognitive measures, and activities of daily living. This longitudinal study also examined time to institutionalization, and survival time. These data will be presented at the annual American Neurological Association meeting October 7-10, 2007.

## REFERENCES

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