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Cost Effectiveness of Donepezil in the Treatment of Mild to Moderate Alzheimer's Disease

A UK Evaluation Using Discrete-Event Simulation

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Supplemental Digital Content

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Technical Appendix: Predictive Equations

Rate of Change in MMSE

Longitudinal MMSE data were available from a repository of donepezil trial data, as well as the Consortium to Establish a Registry for Alzheimer's Disease (CERAD). (See Appendix Table 1, following page.)

We examined both data sources to determine how best to use the available information. Various parameterizations of change in MMSE were explored: change from baseline, change from previous visit, and rate of change from previous visit (calculated as change from previous visits divided by years between visits). We also considered relating the change measures to time or previous MMSE. The relationship between annual rate of change from previous MMSE and previous MMSE was chosen as the basis for analysis, since the pattern observed in CERAD was consistent with what has been previously reported[1 2 3]: a slowly accelerating rate of decline for mild patients (MMSE > 18), relatively constant rate of decline for moderate patients (10-18), and a quickly decelerating rate of decline for severe patients (< 10).

The relationship between annual rate of change and MMSE in the trials was notably different, with no change or a slight improvement in those with an MMSE below 20, and potentially large declines for those above 20 (Appendix Table 1). This was believed to be due to the shorter measurement intervals, which introduces greater chance of random fluctuation. Thus, it was determined that the CERAD data would be more adequate to derive a general equation to predict patterns of MMSE change over time. The trial data were analyzed to estimate the effect of treatment on annual rate of change, which was then applied to predictions from the CERAD equation to predict patterns for treated patients.

The CERAD data included 1,094 patients classified as AD cases. Among these, 721 patients had at least 1 post-baseline MMSE measurement. This subset was used in analyses. The characteristics of these patients are summarized below (Appendix Table 2).

To account for multiple measurements of the MMSE for each patient, a linear mixed-effects model was fitted to the data. This approach takes into account correlations between observations within patients, and allows heterogeneity in patterns across patients. A piecewise linear regression model was fitted to capture the non-linear shape of the relationship between the rate of change versus previous MMSE in CERAD. This approach creates a continuous curve consisting of three connected line segments with different slopes within each segment. Special variables (PM1-PM3), derived from previous MMSE, had to be created to implement the three line segments in a way that ensures that the segments connect at the MMSE cutpoints. In addition to these variables, the model also considered the patients' age, sex, duration of disease, baseline MMSE, and rate of decline in the first year (labeled PrevRate). For the year 1 measurement, PrevRate was calculated as (BaseMMSE-30)/duration of disease; this reflects the patient's average rate of decline at the point of entry into CERAD. Variables that were not statistically significant at the 0.05 level were sequentially dropped from the model. The final MMSE equation has the following form:

$$RateofChange_{ij} = \beta_0 + \beta_1 PM_1 + \beta_2 PM_2 + \beta_3 PM_3 + \beta_4 \mathrm{Pr}evRate + \beta_5 Age + \delta_i + \varepsilon_{ij}$$

The index *i* is for subjects and *j* stands for measurement within a subject. PM_1 – PM_3 are calculated as follows:

$$PM_1 = \min(\text{PrevMMSE}, 9)$$

$$PM_2 = \max[0, \min(\text{PrevMMSE}-9, 9)]$$

$$PM_3 = \max[0, \min(\text{PrevMMSE}-18, 12)]$$

For example, a previous MMSE of 3 would yield PM_1=3, PM_2=0, PM_3=0, while a value of 24 would yield PM_1=9, PM_2=9, PM_3=6. δ_i represents a random intercept parameter, which is unique to each patient. That is, each patient has a different curve of decline which is parallel to the one given by the parameters PM_1 to PM_3. The distribution for δ_i is $\delta_i \sim N(0, \tau^2)$, where τ^2 represents the degree of variability in patterns across patients. ε_{ij} represents the residual for observation *j* in subject *i*, assumed to have a normal distribution: $\varepsilon_{ij} \sim N(0, \sigma^2)$. The random intercept parameter accounts for within-patient correlation, as its value is common to all observations for a given patient. This creates a compound symmetry correlation structure (i.e., constant correlation): $corr(RateofChange_{ij}, RateofChange_{ik}) = \rho$.

The estimates of the coefficients are shown in Appendix Table 3.

The coefficients estimated in the regression equation indicate that younger patients are expected to deteriorate more quickly (by an additional 0.0747 units per year). The coefficient for PM1 represents the rate of decline for patients in the severe stage; PM2 reflects the difference in rate of decline for moderate vs. severe patients, and PM3 represents the difference in rate of decline for mild and moderate. The rate of decline is slightly faster in the moderate stage (vs. severe, by 0.0042 points per additional point of MMSE), while those in the mild stage had a much slower decline. Finally, patients with faster decline in the previous period, all else being equal, are more likely to experience slower decline in subsequent periods.

Goodness of fit was assessed by comparing observed and predicted values. Appendix Figure 1 shows the observed and predicted MMSE rate of change by previous MMSE.

Modeling Treatment Effect for Donepezil

Data were available from seven clinical trials, as well as extension studies (See Appendix Table 1). The trial data included 2,700 patients completing follow-up who had at least one post-baseline MMSE measurement; about half were randomized to donepezil, and the others received placebo. Since the economic model sets the maximum time for treatment effect at one year and since placebo-controlled data were only available for up to 1 year, the data were restricted to the first 52 weeks.

The same approach used to analyze the CERAD data was used to model the trial data to ensure that the treatment effect derived from these analyses can be applied. That is a linear mixed effects regression model was fitted which included the previous MMSE indicators (PM1-PM3) and a treatment indicator. Exploratory analyses of the observed MMSE decline rate over time by treatment group suggested that the benefit of treatment was different before and after the first 20 weeks. Thus, a separate treatment indicator was included for each period. The coefficients of these terms represent the difference in rate of decline for donepezil versus placebo. The rate of decline for treated patients was 0.12 points per week slower in the first 20 weeks compared to placebo, and 0.05 points per week slower with treatment between weeks 20 and 52.

NPI

A predictive equation relating change from baseline in NPI to treatment, MMSE, baseline NPI and other relevant predictors was derived using measurements from the first 52 weeks from the trial data (Nordic, MSAD, Multinational Severe, Swedish Severe in Appendix Table 1). A longitudinal regression model was fitted to account for repeated measurements on patients by including a random intercept term.

NPI scores were scaled from 0 to 100 (and then rescaled from 0 to 144 in the simulation). The NPI estimates for both treated and untreated patients were based exclusively on the

trial data, as NPI data were not available in CERAD. Time (in weeks), age, sex, treatment, use of anti-psychotic medications, baseline and most recent NPI, baseline and most recent MMSE, and rate of MMSE decline were included as potential predictors. Variables with non-significant coefficients ($p>0.05$) were dropped from the equation. Interactions between treatment and time, and baseline NPI and time were also considered. The final equation is shown in (Appendix Table 4).

The effect of donepezil comes into play not only through the treatment coefficient (-0.6421), but also through its influence on MMSE. That is, since donepezil is associated with a slower rate of MMSE decline, treated patients will tend to have higher MMSE values. Higher MMSE at the most recent prior measurement is associated with slower decline of the NPI (0.22 points for every additional point of MMSE). Other coefficients indicated that patients of black and white race experience smaller increases in behavioral symptoms over time, but patients on psychiatric medications experience greater increases. For MMSE, the negative coefficient indicates that patients with better cognitive function are less likely to experience increases in behavioral disturbances than their more severe counterparts. The relationship between change in NPI and NPI severity is more complex as it is influenced by both baseline NPI, the influence of which gets stronger over time, and previous NPI.

Appendix Figure 2 shows the observed and predicted NPI change by time.

ADL and IADL

Various ADL/IADL scales were used to measure function in the clinical trials. After selecting the trials with the most similar scales, we took the following steps to make them comparable and analyzable across trials.

Six basic ADL items (toileting, feeding, dressing, grooming, ambulation, bathing) were in common among the PSMS and ADL-SEV scales in 5 trials that included mild,

moderate, and severe AD populations (Preservation of Function, Nordic, MSAD, Multinational Severe, Swedish Severe in Appendix Table 1). The individual item responses were pulled and scored with the same algorithm used in the clinical study reports to normalize for different response ranges and provide a 0 to 100 scale.[1]

Instrumental/Independent ADL (IADL) items varied more among trials. Three scales from 3 mild to severe trials (Preservation of Function, Nordic, MSAD in Appendix Table 1) had 8, 10, and 12 items (covering phone, shopping, food preparation, household tasks, finances). Though having considerable overlap in domains measured, strictly speaking there were just 4 common items among all 3 trials. Thus, we decided to take each trial's IADL scale in its entirety, normalized to 0 to 100, using the same scoring algorithm described for ADLs to adjust for different response scales and missing data.

For both ADL and IADL, scales were standardized to range from 0 to 100, and increases represent worse function.

Predictive equations for ADL and IADL change over time were derived using the same approach used to analyze NPI. Potential predictors included treatment, time, baseline and most recent ADL/IADL, baseline and most recent MMSE, baseline and most recent NPI, age, sex, treatment, and use of anti-psychotic medications.

The equation for change in ADL from baseline is shown in Appendix Table 5. Donepezil' s effect was modeled directly through the treatment effect term and the terms for patients' most recent MMSE. Older patients deteriorate more quickly, as do those on psychiatric medications, and those with more severe cognitive deficits. Patients of black race had significantly better outcomes in terms of changes in ADL scores. As with the

[1] For each patient and score Xj on item j define the transformed item score Yj = (Xj - MINj)/(MAXj - MINj), where MINj and MAXj are the minimum and maximum response levels on item j. The average of Yj over the patient's non-missing items multiplied by 100 is the patient's score. If more than 15% of the items are missing the patient score is considered missing.

NPI equations, the relationship between ADL and changes in ADL is more complex. Baseline ADL has a negative coefficient, while previous ADL has a slightly smaller coefficient, but it is positive. As patients' ADL scores increase (i.e., function deteriorates), the previous ADL score will increase, and the coefficient for previous ADL will result in accelerated future changes in ADL.

Appendix Figure 3 shows the observed and predicted ADL change by time.

IADL is modeled as IADL change from baseline. NPI was also not a significant predictor of IADL change, but both MMSE and ADL were (Appendix Table 6). As such, donepezil' s treatment effect comes into play through the treatment term, as well as patients' most recent MMSE and ADL scores. Unlike the other equations, the IADL equation also contains an interaction term, with donepezil' s effect increasing over time. IADL deterioration is greater in female patients, and patients who experience greater deterioration in ADLs and cognition.

Appendix Figure 4 shows the observed and predicted IADL change by time.

Correspondence Between Observed and Simulated Treatment Effects

In order to evaluate how well the equations predicted treatment effects, we compared the mean differences between treated and untreated patients in the simulation, with the observed differences in the source data at 24 weeks, the duration of the majority of the clinical trials. As Appendix Table 7 indicates, the size of the simulated treatment effects fell within the confidence interval of the observed differences for all four scales. Predictions for MMSE, NPI and ADL were particularly close to the observed differences. For IADL, the simulated treatment effect was smaller than what was observed in the clinical trials (1.69 versus 3.79), likely due to some imprecision in the interaction term between time and treatment effect, which indicated that donepezil' s effect on IADLs increased over time.

Caregiver Time

Caregiver time was recorded in the Nordic and MSAD trials (Appendix Table 1). Caregivers reported that they averaged about 4 to 6 hours per day helping patients with ADL and IADL activities. The relationship of caregiver time to disease progression parameters was developed from the two trials using a linear repeated measure, fixed effects model, as shown in Appendix Table 8. Caregiver time increases with worsening function in all scales, as well as age, history of psychiatric medication, and male patient or caregiver gender.

Caregiver Health Utilities

Caregivers completed the SF-36 at each visit in three of the donepezil clinical trials (Preservation of Function, Nordic, MSAD in Appendix Table 1), but in one trial patient NPI was not measured (Preservation of Function), and so this trial was dropped from the analysis. Following previous work in this area the SF-36 scores were used to estimate a utility,[4] which was then related with a linear repeated measures model to other trial outcomes to develop the equation shown in Appendix Table 9. Caregiver mean utility was about 0.8. IADL, ADL, and NPI proved to be slightly stronger predictors than MMSE; and as all are highly correlated with MMSE, MMSE added little to the model. An MMSE standard error was included for use in probabilistic sensitivity analysis.

Tables

Appendix Table 1 Aricept repository and CERAD data selected for analyses

Study	N (completers)	Length (wks)	Assessments	Cognition	Behavior	ADL	IADL	*Caregiver*
Pivotal Ph3 – 1[5]	412	12	7	MMSE	-	-	-	-
Pivotal Ph3 - 2[6]	367	24	7	MMSE	-	-	-	-
Pivotal Ph3 open –label extension[7]	353	144	15	MMSE	-	-	-	-
Preservation of Function [8]	431	54	10	MMSE	-	PSMS – ADFACS	IADL – ADFACS	*SF-36*
Nordic[9]	192	52	5	MMSE	NPI	PSMS	IADL	*CBI, SF-36*
Nordic extension[10]	< 157	156	5	MMSE	NPI	PSMS	IADL	*CBI*
MSAD[11]	240	24	6	MMSE	NPI	PSMS	IADL+	*CATS CSS SF-36*
Multinational Severe[12]	247	24	6	MMSE	NPI	ADCS-ADL-SEV	-	*CBQ CSS*

Swedish Severe[13]	249	26	3	MMSE	NPI	ADCS-ADL-SEV	-	-
CERAD Registry[14]	1,094	7 yrs		MMSE	-	-	-	-

ADL	Activities of Daily Living
ADFACS	Functional Assessment and Change Scale (a composite of ADL and IADL items.)
ADCS-ADL-SEV	Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory for Severe Alzheimer's Disease
CBI	Caregiver Burden Scale
CBQ	Caregiver Burden Questionnaire
CATS	Caregiver Time Spent Caregiving
CSS	Caregiver Stress Scale
IADL	Instrumental Activities of Daily Living
MMSE	Mini-Mental State Examination
NPI	Neuropsychiatric Inventory
SF-36	Short-Form Health Survey

Appendix Table 2 Characteristics of Patients in CERAD

Variable	N	Mean	Standard Deviation	Min	Max
Gender (Male = 1)	721	0.43	0.49	0	1
Age	721	72.3	7.91	50.5	93.2
Years of Education	720	12.5	3.7	0	26
MMSE Annual Change per year	717	3.78	2.84	0.35	22.6
MMSE	719	17.8	5.46	1	29
Age at Onset	719	67.8	8.19	47.2	88.1
Disease Duration	719	4.4	2.68	0.66	17.7

Appendix Table 3 CERAD-based fixed effects model for annual rate of MMSE change

Effect	Estimate	Standard Error
Intercept	-5.4663	0.9836
PM1	-0.4299	0.0597
PM2	-0.0042	0.0410
PM3	0.1415	0.0487
Age at Baseline	0.0747	0.0127
Previous Rate of MMSE Change	-0.0791	0.0317

* Actual model estimates used equations with at least 4 decimal places.

Appendix Table 4 Trial based model for change in NPI from baseline

Effect	Estimate	Standard Error
Intercept	5.74	1.08
Donepezil	-0.64	0.37
Weeks	0.03	0.01
Base NPI	-0.59	0.02
Base NPI x Weeks	0.0012	0.0004
Last NPI	0.24	0.02
White	-1.74	1.00
Black	-3.82	1.51
Use of Psychiatric Medications	2.34	0.44
Base MMSE	0.12	0.06
Most Recent MMSE	-0.22	0.05

* Actual model estimates used equations with at least 4 decimal places

Appendix Table 5 Trial based model for change in ADL from baseline

Effect	Estimate*	Standard Error
Intercept	1.35	1.48
Donepezil	-0.81	0.30
Weeks	0.06	0.00
Base ADL	-0.79	0.01
Previous ADL	0.71	0.01
Base MMSE	0.12	0.05
Age	0.09	0.02
Use of Psychiatric Medications	0.81	0.32
Black	-3.05	0.92
Most Recent MMSE	-0.49	0.04

* Actual model estimates used equations with at least 4 decimal places

Appendix Table 6 Trial based model for change in IADL from baseline

Effect	Estimate*	Standard Error
Intercept	1.27	1.13
Donepezil	0.63	0.41
Weeks	0.17	0.01
Donepezil x Weeks	-0.06	0.01
Base IADL	-0.84	0.02
Base IADL x Weeks	0.002	0.0002
Previous IADL	0.84	0.01
Male	-0.67	0.30
Base MMSE	0.20	0.05
Most Recent MMSE	-0.28	0.04
Base ADL	-0.16	0.02
Most Recent ADL	0.18	0.01

* Actual model estimates used equations with at least 4 decimal places

Appendix Table 7 Comparison of differences between donepezil and untreated patients at 24 weeks in the simulation and in the donepezil clinical trials

Variable	Mean Simulation Treatment Effect	Mean Observed Treatment Effect	Lower CI for Observed treatment Effect	Upper CI for Observed Treatment Effect
MMSE	-1.92	-1.88	-2.63	-1.13
NPI	1.75	1.68	-0.35	3.70
ADL	2.55	2.59	1.10	4.09
IADL	1.69	3.79	1.25	6.32

Appendix Table 8. Equation to predict caregiver time as minutes per day

Effect	Estimate*	Standard Error
Intercept	76.41	72.82
Caregiver Age	1.80	0.69
Caregiver gender = male	93.02	25.24
Patient gender = male	85.56	26.09
MMSE	-6.47	1.29
NPI	0.58	0.35
ADL	2.66	0.50
IADL	2.61	0.47
Psychiatric medication	20.55	17.67

* Actual model estimates used equations with at least 4 decimal places

Appendix Table 9. Equation to predict caregiver health utilities

Effect	Estimate*	Standard Error
Intercept	0.90	0.05264
Caregiver Age	-0.003	0.0006
Caregiver gender = male	0.03	0.02
Patient gender = male	0.001	0.001
MMSE	0.00000	0.001
NPI	-0.001	0.0002
ADL	-0.001	0.0003
IADL	-0.0004	0.0003
Psychiatric medication	-0.01	0.01

* actual model estimates used equations with at least 4 decimal places

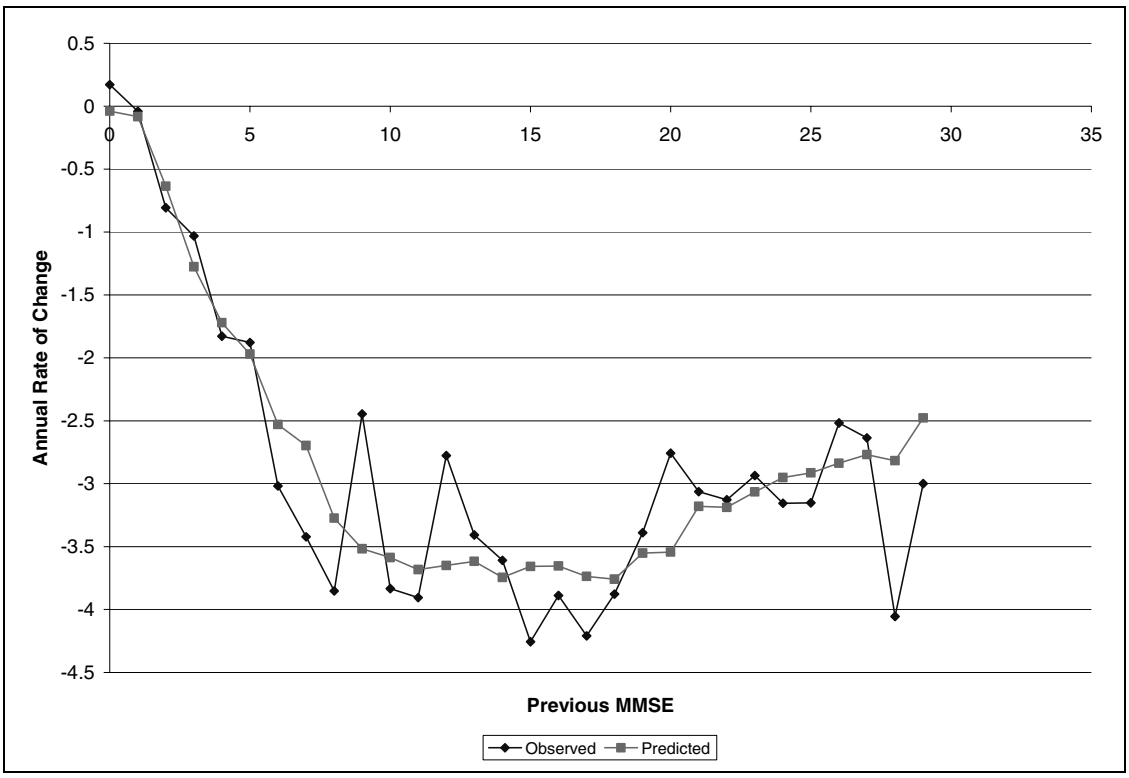

Figure 1 Observed and Predicted MMSE Rate of Change by Previous MMSE

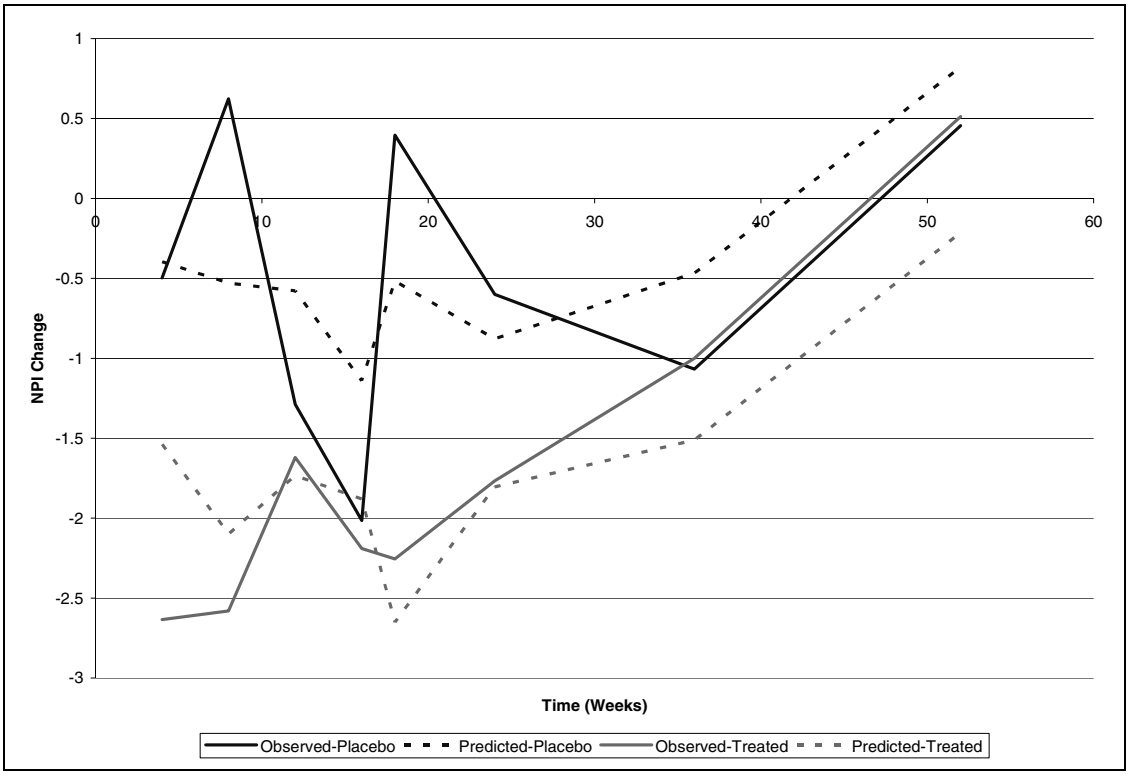

Figure 2 Observed and Predicted Change in NPI from baselined by Time

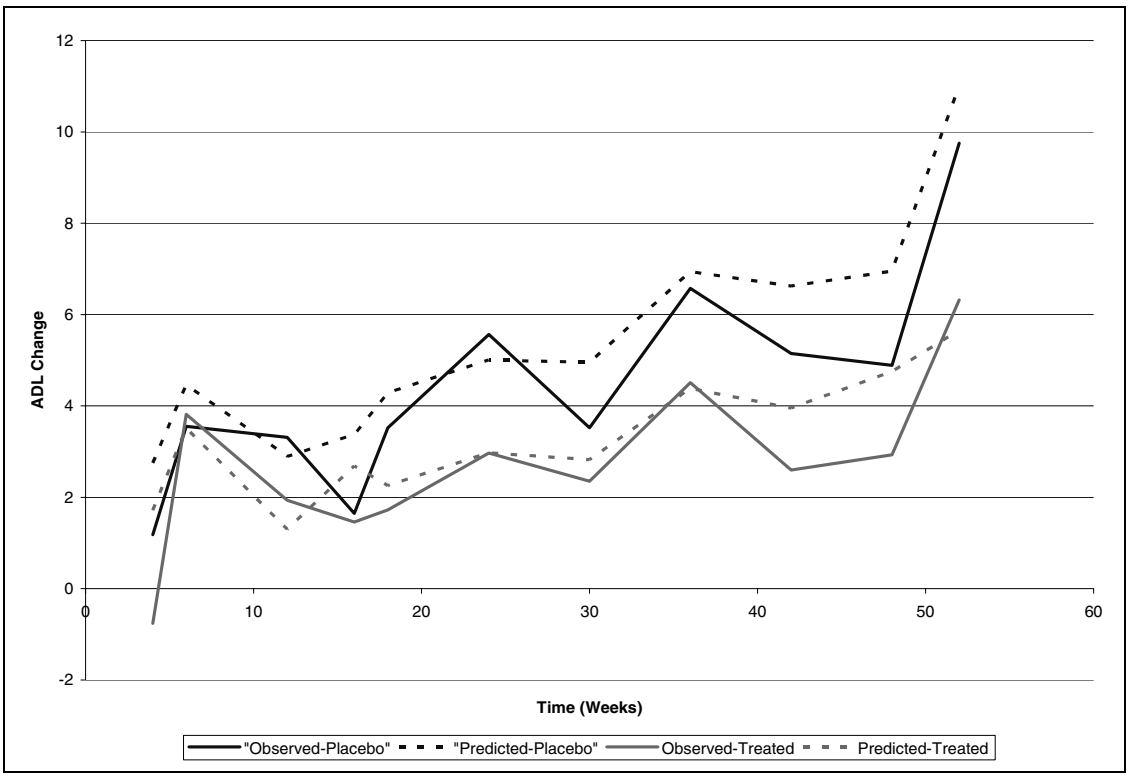

Figure 3 Observed and Predicted Change in ADL from baselined by Time

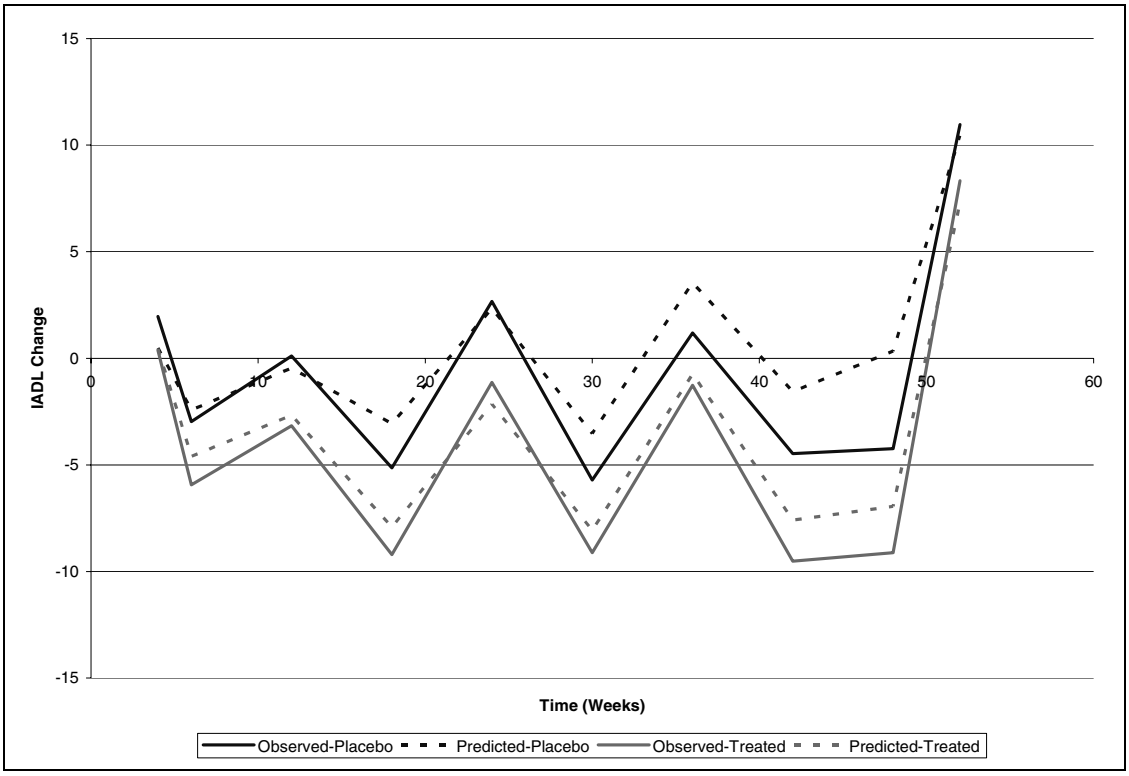

Figure 4 Observed and Predicted Change in IADL from baselined by Time.

Appendix References

1 Stern RG, Mohs RC, Davidson M, et al. A longitudinal study of Alzheimer's disease: measurement, rate, and predictors of cognitive deterioration. Am J Psychiatry 1997;151: 390–396.

2 Mendiondo MS, Ashford JW, Kryscio RJ, et al. Modelling Mini Mental State Examination changes in Alzheimer's disease. Stat Med 2000;19:1607-16.

3 Mohs RC, Schmeidler J, Aryan M. Longitudinal studies of cognitive, functional and behavioural change in patients with Alzheimer's disease. Stat Med 2000:1401–1409.

4 Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ 2002;21:271–92.

5 Rogers SL, Doody RS, Mohs RC, et al. Donepezil improves cognition and global function in Alzheimer disease: a 15-week, double-blind, placebo-controlled study. Donepezil Study Group. Arch Intern Med 1998;158(9):1021-1031.

6 Rogers SL, Farlow MR, Doody RS, et al. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. Neurology 1998;50(1):136-145.

7 Doody RS, Geldmacher DS, Gordon B, et al. Open-label, multicenter, phase 3 extension study of the safety and efficacy of donepezil in patients with Alzheimer disease. Arch Neurol 2001;58(3):427-433.

8 Mohs RC, Doody RS, Morris JC, et al. A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. Neurology 2001;57(3):481-488.

9 Winblad B, Engedal K, Soininen H, et al. A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. Neurology 2001;57(3):489-495.

10 Winblad B, Wimo A, Engedal K, et al. 3-year study of donepezil therapy in Alzheimer's disease: effects of early and continuous therapy. Dement Geriatr Cogn Disord 2006;21(5-6):353-363.

11 Feldman H, Gauthier S, Hecker J, et al. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. Neurology 2001;57(4):613-620.

12 Black SE, Doody R, Li H, et al. Donepezil preserves cognition and global function in patients with severe Alzheimer disease. Neurology 2007;69(5):459-469.

13 Winblad B, Kilander L, Eriksson S, et al. Donepezil in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo-controlled study. Lancet 2006;367(9516):1057-1065.

14 Consortium to Establish a Registry for Alzheimer's Disease (CERAD). 2003. Available from URL: http://cerad.mc.duke.edu/Default.htm. [Accessed 2009 March 6]