

Disease progression meta-analysis model in Alzheimer's disease

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Abstract

Background: Various authors have evaluated disease progression in Alzheimer's disease (AD), using patient data from individual clinical studies or pooled data across various trials. We conducted a systematic review of public data sources from 1990 to 2008 for all available AChE inhibitor studies, as well as clinical studies that evaluated the rate of deterioration in AD patients. Unique to this analysis, we developed a model based on literature data to describe the longitudinal response in the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-cog) (change from baseline) in mild to moderate severity AD patients. The model was used to estimate disease progression for both placebo-treated patients and acetylcholinesterase (AChE)-inhibitor treated patients, and factors that affected disease progression.

Methods: We collected 576 mean ADAS-cog changes from baseline data points of 52 trials, representing data from approximately 19,972 patients and more than 84,000 individual observations. The model described the rate of disease progression, the evident placebo effect, and the symptomatic effect of AChE-inhibitors. Baseline ADAS-cog, Mini-Mental State Examination score, age, and year of publication were tested as covariates.

Results: The disease progression in mild to moderate AD patients across all available and relevant literature sources was estimated as 5.5 points per year. An Emax-type model best described the symptomatic drug effect of AChE inhibitors. The rate of disease progression (underlying disease progression) was no different between placebo and AChE-inhibitors groups. Baseline ADAS-cog is a significant covariate in disease progression. Baseline age was also tested as a covariate in the rate of disease progression, but the model was unable to describe any effects of age, likely because of the narrow distribution of mean age (literature-level analysis). There was no significant impact of publication year in the model.

Conclusions: Baseline ADAS-cog is a significant covariate affecting the rate of disease progression, and it describes or at least explains the different rates of deterioration evident in early or late stages of the disease. There was no significant impact of publication year in the model, suggesting that disease progression has not slowed in more recent trials.

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Keywords:

Alzheimer's disease; Disease progression; Literature data; Model-based analysis; ADAS-cog

1. Introduction

Alzheimer's disease (AD) is by far the most common cause of dementia associated with aging. It is characterized by an insidious onset and slow deterioration in cognition, functional ability (e.g., activities of daily living), behavior, and mood. An estimated 5.2 million Americans of all ages suffered from AD in 2008. By 2030, the number of people aged 65 years and over with AD is estimated to reach 7.7

million. By 2050, the number of individuals aged 65 years and over with AD could range from 11 million to 16 million, if treatments are not found [1].

Alzheimer's disease trials are conducted to demonstrate that patients receiving therapy either improve cognition, maintain cognition, or delay disability or global function caused by cognitive deterioration, compared with those who receive placebo. Proposed clinical-trial designs for symptomatic treatment, delay to disability, and disease modification, and the appropriate sample-size estimation for each of these designs, are all highly dependent on estimating the true rate of natural disease progression within a trial.

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Several methods were reported to evaluate and predict the progression of cognitive dysfunction in patients with AD, most often using the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-cog) as the primary measure of cognition. For example, Stern et al. reported on a polynomial regression model for ADAS-cog, using nontreated AD patient data ($n = 111$) [2]. Doraiswamy et al. analyzed psychometric properties, including cognitive scales, in 536 AD patients randomized to placebo in a 26-week multicenter trial [3]. Holford et al. reported on a population pharmacodynamic model to describe disease progression in tacrine studies with approximately 2500 patients [4–6]. These models described the cognitive deterioration observed in individual AD patients, and provided similar estimates of an approximately 6-point change for yearly disease progression, as measured by ADAS-cog.

We conducted a systematic review of public-data sources from 1990 to 2008 for all available acetylcholinesterase (AChE)-inhibitor studies, and for clinical studies that evaluated rate of deterioration in AD patients. The goal of this analysis was to develop a mathematical model to describe the longitudinal changes in ADAS-cog with and without AChE-inhibitor background therapy, to enable a quantitative understanding of disease progression in AD. These estimates (and associated uncertainties in the estimates) can be used as informative priors in aiding the evaluation of trial designs in future clinical trials, comparing treatment effects reported in the literature, or comparing results among studies.

2. Data selection

2.1. Search strategy and selection

The literature was searched and selected according to the approach suggested at the Quality of Reporting of Meta-Analysis Conference [7]. A systematic search of public-data sources (i.e., Medline, Embase, National Institute for Health and Clinical Excellence [NICE], and the Summary for Basis of Approvals at the Food and Drug Administration) from 1990 to 2008 was conducted. Key search terms included AChE-inhibitor names (donepezil, galantamine, rivastigmine, or tacrine), trial endpoints (e.g., ADAS-cog, Mini-Mental State Examination [MMSE], or Clinician's Interview-Based Impression [CIBIC]), and clinical-trial design descriptions (e.g., double-blind or randomized). Accordingly, 201 literature references were identified. Figure 1 depicts the search strategy and selection flow process. All titles and abstracts identified through our search strategy were carefully reviewed and screened. We made an effort to select clinical data from only reliable and controlled clinical studies with sufficient numbers of patients (i.e., more than 20). Studies included were either double-blind, single-blind, or open studies in AD patients, treated with marketed AChE-inhibitors (donepezil, galantamine, and rivastigmine) or placebo, with a treatment duration of at least 12 weeks. Clinical studies of AD patients evaluating efficacy and safety with tacrine and velnacrine (AChE-inhibitors, not marketed) and non-AChE-inhib-

itors (i.e., vitamin E, cyclooxygenase-2 inhibitors, and non-steroidal anti-inflammatory drugs [NSAIDs]) were also included in the database, but only the placebo-group data from these studies were used in the analysis. Clinical studies of patients with mild cognitive impairment (MCI) were allowed if they were double-blind studies with AChE-inhibitors, where ADAS-cog values were reported. In most cases, the literature results were reported as mean values (\pm standard error). Among various endpoints found in this body of literature, the mean values for ADAS-cog (change from baseline) were selected for our analysis, based on their prevalence in published trials and the current importance of ADAS-cog for supporting claims of efficacy. If results were presented in a figure and the values were not reported in the text (or in a table), values from the figures were extracted, by means of digitizing software (Techdig V2.0a; Ron Jones, Mundelein, IL) designed to extract data from graphs.

The following criteria were used to determine which data were included or excluded: 1) If the same results were reported in different literature sources (e.g., one was the original paper, and the other contained the same data from a review article), only the primary source was used. 2) If more than one summary value was reported with different statistical analyses or methods of imputation for missing data at the same time point, such as observed cases (OCs) and last observation carried forward (LOCF), only one value was chosen. The OC was preferred over the LOCF if available. In some articles, however, the LOCF was used for all evaluation time points (longitudinal), and both the LOCF and OC were reported at the end of the study to compare values. In this situation, the LOCF was selected for all evaluation time points within the article. Also, summary values based on completers were excluded. 3) Exploratory studies were excluded if they comprised an open study with equal to or less than 20 patients per treatment arm. 4) A study was excluded if the patient population was considered inappropriate, e.g., patients who dropped out of a previous study.

Of 201 studies initially identified, 53 met our inclusion criteria. During subsequent evaluation, one of these 53 was deemed to be insufficient for further analysis. This was an open-label study where only the 52-week result (change from baseline) was available for ADAS-cog. The baseline ADAS-cog was not reported, and the dropout rate was relatively high (95 of 173 patients entering the study completed it) [8]. As a result, 52 studies were used for model development. Data points excluded from the analysis for any other reasons are reported in Results.

3. Model development

3.1. Model building and selection criteria

The overall method describe underlying disease progression was similar to that reported by Holford et al. [4–6]:

$$S(t) = S(0) + \alpha \cdot t + PD_{pbo}(t) + PD_{drug}(t) + \varepsilon$$

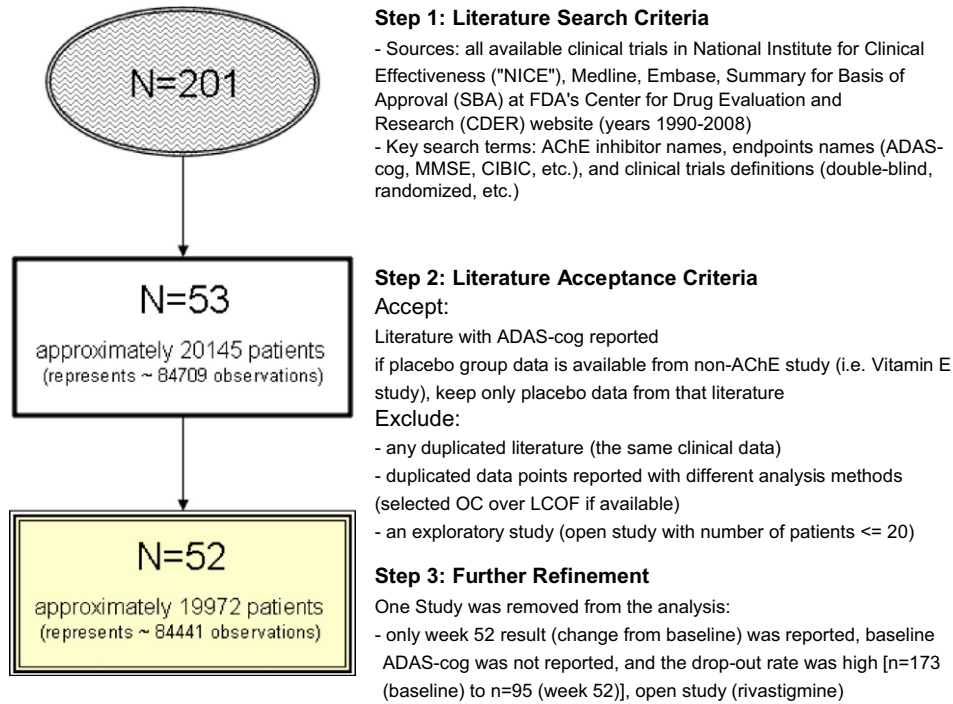


Fig. 1. Literature search strategy and selection.

where $S(t)$ is the disease state at time t after entry into a trial with baseline $S(0)$. In this analysis, $S(t)$ was the ADAS-cog change from baseline at time t , and $S(0)$ was fixed to zero. In addition, α is the rate of progression of the untreated disease, $PD_{pbo}(t)$ is a function describing the placebo effect, $PD_{drug}(t)$ is a function describing drug effect, and ϵ is a function describing the residual error. Each term of this model can be further defined, and parameter estimates can be obtained, by fitting the model to the entirety of the data available. Terms are further described below.

3.1.1. Placebo response

Within placebo control arms of AD trials, it is common to observe an initial period of weeks or months when little or no change in ADAS-cog scores is evident, suggesting that a time-dependent placebo effect may be present. The onset, offset, and overall extent of this placebo effect was successfully estimated and described in the past by the use of a first-order appearance and a first-order disappearance constant, commonly known as a Bateman-type function [4,9]:

$$PD_{pbo}(t) = \beta_p \cdot (e^{-Kel_p \cdot t} - e^{-Keq_p \cdot t})$$

where β_p is a factor defining the magnitude of the placebo effect, Kel_p is the rate constant for the offset rate of the placebo effect, and Keq_p is the rate constant for the onset rate of the placebo effect.

3.1.2. Drug response

The drug effect was modeled as an Emax-type function of time. The Emax-type model is given by the expression:

$$PD_{drug}(t) = \frac{\Delta E_{max} \cdot t}{ET_{50} + t}$$

where ΔE_{max} denotes the maximum symptomatic effect that could be obtained with each drug, and ET_{50} denotes the time at which 50% of the maximum symptomatic effect is achieved.

3.1.3. Error structure

Random effects were included on the intercept (η_1), slope (η_2), and ET_{50} (η_3) as additive errors assumed to have a normal probability distribution with a mean of 0 and variance of ω_1 , ω_2 , and ω_3 .

The residual-error structure was weighted based on the number of patients in each data point, to account for heteroscedasticity:

$$Y = F + \frac{\theta_w}{\sqrt{N}} \cdot \epsilon$$

where Y represents the observed data, F represents the predicted data based on the model, θ_w is the standard deviation, N is the number of patients (sample size), and ϵ is the additive-error component of residual variability. The variance of ϵ was fixed to 1 during estimation.

3.2. Covariate evaluation

Dose was tested as a covariate of the maximum symptomatic effect attainable (ΔE_{max}) for each drug. The dose was normalized to the clinical recommended dose for each drug

or approximate mean of the dataset. For example, the dose effect for donepezil was modeled as:

$$\Delta E_{\max_D} \cdot \left(\frac{\text{Dose}}{5}\right)^\theta$$

where ΔE_{\max} denotes the maximum symptomatic effect obtained with 5 mg of donepezil, and θ is the fitted power coefficient. For example, if the maximum symptomatic effect with 5 mg is -2 points, and if the estimated θ is 1.3, then the maximum symptomatic effect with 10 mg is calculated as $-2 * (10/5)^{1.3} = -4.92$ points.

If θ was not statistically significantly different from zero, it indicated that dose was not a significant covariate for that drug (i.e., that different doses did not affect the difference in symptomatic effect).

Covariates of interest in the dataset included year of publication, mean values for age, baseline ADAS-cog values, and baseline MMSE score. Baseline ADAS-cog was hypothesized to influence the rate of disease progression (α) (change from baseline ADAS-cog was used in this analysis, and also reflects disease severity). Age was identified a priori as an important risk factor for cognitive deterioration (rate of disease progression) in AD. Baseline MMSE score was also tested in this model, to represent severity. Year of publication was also tested on rate of disease progression (α), to examine the hypothesis that disease progression has changed as a function of time. Year of publication was tested as dichotomous covariate (before or during 2002, or later than 2002, rather than as a continuous covariate, because our main interest involved testing whether old and recent clinical studies differed in rate of disease progression. The median of publication years was 2002 (25 papers were published before 2002, and 27 papers after 2002).

Continuous variables (age, ADAS-cog value, and MMSE score) were normalized to the approximate mean value of the whole dataset, and were incorporated into the model, using a power function described as:

$$\alpha = \alpha_{\text{pop}} \cdot \left(\frac{\text{Age}}{75}\right)^{\theta_{\text{age}}} \cdot \left(\frac{\text{ADAS}_{\text{cog}}}{25}\right)^{\theta_{\text{ADAS}}} \cdot \left(\frac{\text{MMSE}}{18}\right)^{\theta_{\text{MMSE}}}$$

where α_{pop} is the population value of the parameter, and θ_x represents the fitted power coefficients. The power function allows for the relationship between the covariates and the slope to take different nonlinear forms. Normalization to the mean of the dataset allows for a more numerically stable model. Covariates were added one by one in a stepwise manner, examining the minimum change in objective function values (MOFs) in hierarchical models, and also the precision of the parameter estimate.

For 6 of 52 trials, the mean baseline ADAS-cog was not reported. In these studies, the missing covariate was imputed, using a regression relationship between ADAS-cog value and MMSE score derived from the pooled data. A similar regression relationship between baseline

ADAS-cog value and baseline MMSE score was reported by Doraiswamy et al. [10].

Model-fitting was performed using a population-analysis approach (NONMEM Version VI, Level 1.2, ICON Development Solutions, Ellicott City, MD). Diagnostic graphics and postprocessing of NONMEM output, and simulation, were performed using the S-Plus Professional Edition (Version 7.0) for Windows XP (Insightful Corp., Seattle, WA).

3.3. Model-selection criteria and performance evaluation

Our model-building strategy was based on a modification of the different approaches discussed by Beal et al. [11], Mandema et al. [12], Maitre et al. [13], and Ette and Ludden [14]. The difference in MOFs between two hierarchical models was used as a likelihood ratio test statistic, and was approximately distributed as χ^2 , with the number of degrees of freedom equal to the difference in the number of parameters estimated between the two hierarchical models. Testing was performed at a level of $\alpha = 0.05$. For nested models that differed by one parameter, a difference in MOF of more than 3.84 favored the model with more parameters. The goodness of fit of the final model was also evaluated using graphic assessment to evaluate the adequacy of a model fit. For example, plots of observed versus predicted, and observed versus individual predicted, were evaluated for randomness around the line of unity. Plots of conditional weighted residuals versus time, and of conditional weighted residuals versus predicted, were evaluated for randomness around the zero line. These diagnostic plots were stratified (as appropriate) by drug, to ensure adequacy of the fit across different drugs. The residual plots were also used to identify potential outliers.

After the final model was identified, 100 datasets identical in structure and covariate values to the original dataset were simulated, using the parameter estimates and uncertainties from the final model to evaluate the model performance. The changes from baseline ADAS-cog time-course by drug group were generated with 90% prediction intervals simulated from the final model.

4. Results

4.1. Data characteristics

The final dataset contains 52 literature sources consisting of 576 mean values of ADAS-cog at each visit (each time point) from approximately 19,972 patients, representing approximately 84,441 individual observations for ADAS-cog. Of these 576 data points, 181 were from placebo, 173 were from donepezil, 156 were from galantamine, and 66 were from rivastigmine. The mean (range) for baseline mean age, ADAS-cog, and MMSE in the dataset were 73.9 years (58–78.9), 25.4 points (11.0–41.7), and 18.8 (11.4–27.4), respectively. Information for each study is summarized in Table 1 [15–68].

Table 1
Study design summary [15–68]

Author	Year	Study Design/Description	Drug/Dose	Treatment Duration	Baseline Age (yrs)*	Baseline ADAS-cog*	Baseline MMSE*	Total N (randomized)
Farlow et al.	1992	Randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of tacrine	Tacrine 20, 40, 80 mg	12 weeks	71	27.5	17.9	468
Knapp et al.	1994	Randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of high-dose of tacrine	Tacrine 80, 120, 160 mg	30 weeks	72.1	28.4	18.5	663
Antuono et al.	1995	Randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of velnacrine	Valnacrine 150, 225 mg	24 weeks	73.3	29.6	NA	449
Rogers et al.	1996	Randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of donepezil	Donepezil 1, 3, 5 mg	14 weeks	70.6–72.9	26.6–29.2	18–19.6	161
Schneider et al.	1996	Randomized, double blind, placebo controlled study of estrogen replacement therapy (ERT) on response to tacrine	Tacrine 80, 120, 160 mg	30 weeks	74	30.3	17.6	343
Sano et al.	1997	Double-blind, placebo controlled study of selegiline (monoamine oxidase inhibitor), alpha-tocopherol (vitamin E), or a combination of the two agents	Selegiline 10 mg/day alpha-tocopherol 2000 IU/day	2 years	73.5	NA	13.4	341
Corey-Bloom et al.	1998	Double blind study to evaluate the efficacy and safety of rivastigmine	Lower dose (1–4 mg/day) Higher dose (6–12 mg/day)	26 weeks	73.8–74.9	21.7–22.4	19.5–20	699
Rogers et al. [†]	1998	Double blind placebo controlled study	Donepezil 5, 10 mg	12 weeks	73.4–74	25.0–27.2	19.1–19.8	468
Rogers et al. [†]	1998	Double blind, placebo controlled study followed by a 6-week single blind placebo washout	Donepezil 5, 10 mg	24 weeks	72.6–74.6	26.3–27.4	19.2–19.4	473
Burns et al.	1999	Double blind, placebo controlled study followed by a 6-week single blind placebo washout	Donepezil 1, 3, 5 mg	24 weeks	71–72	NA	20	818
Forette et al.	1999	Double-blind to assess the efficacy and maximum tolerate dose	Rivastigmine 10 mg/day	18 weeks	69.5–72.5	21.7–24	19.2–19.8	114
Rosler et al.	1999	Double blind, placebo controlled study of rivastigmine	Lower dose (1–4 mg/day) Higher dose (6–12 mg/day)	26 weeks	72	23.3–23.9	NA	725
Aisen et al.	2000	Double blind, placebo controlled study of prednisone	Moderate-dose prednisone	68 weeks	72.3	21.2	22	138
Greenberg et al.	2000	Randomized, placebo-controlled double masked crossover study	Donepezil 5 mg	12 weeks	75	18.5	21.8	60
Homma et al.	2000	Double blind placebo controlled study	Donepezil 5 mg	24 weeks	69.4–70.1	22.9–26.9	16.6–17.8	268
Kumar et al.	2000	Double blind, placebo controlled rivastigmine study in AD patients with concurrent vascular risk factors	Lower dose (1–4 mg/day) Higher dose (6–12 mg/day)	26 weeks	74.3–74.8	21.2–23.3	19.2–20.2	699
Raskind et al.	2000	6-month randomized, placebo controlled trial with 6-month extension	Galantamine 24, 36 mg/day	12 months	75–75.9	24.8–25.8	19.1–19.5	636

(Continued)

Table 1
Study design summary [15–68] (Continued)

Author	Year	Study Design/Description	Drug/Dose	Treatment Duration	Baseline Age (yrs)*	Baseline ADAS-cog*	Baseline MMSE*	Total N (randomized)
Tariot et al.	2000	Double blind, parallel group, placebo controlled trial	Galantamine 8, 16, 24 mg/day	5 months	76–77.7	27.8–29.4	17.7–18	978
Thal et al.	2000	Double blind, placebo controlled of acetyl-L-carnitine in early-onset AD patients	Acetyl-L-carnitine 1 g tid	1 year	58	22.9	20.6	227
Wilcock et al.	2000	Double blind, parallel group, placebo controlled trial	Galantamine 24, 32 mg/day	6 months	71.9–72.7	24.7–26.2	19–19.5	653
Doody et al.	2001	3-year open study following 12-week (study 301) and 24-week (study 302) double-blind study	Donepezil 5, 10 mg	3 years	NA	NA	NA	468 (study 301) 473 (study 302)
Farlow et al.	2001	26-week open label extension study following a 26-week double-blind, randomized, placebo controlled study	Rivastigmine 12 mg/day	52 weeks	74.2–75.4	17.9–24.4	18.7–21.5	187
Rockwood et al.	2001	Double-blind, placebo controlled trial with a flexible galantamine dose escalation	Galantamine 24–32 mg/day	3 months	75.2–74.6	24.7–25.6	19.6–19.7	386
Van et al.	2001	Randomized, placebo-controlled study of hydroxychloroquine in early Alzheimer's disease	Hydroxychloroquine (200/400 mg)	18 months	70.7	17.6	NA	168
Wilkinson et al.	2001	Double blind dose comparison	Galantamine 16, 24, 36 mg	3 months	72.7–75.4	25.7–26.9	18.2–18.8	285
Erkinjuntti et al.	2002	Double blind trial in patients with probable vascular dementia and AD combined with cerebrovascular disease	Galantamine 24 mg/day	6 months	75–75.2	22.3–24.1	NA	592
Wilkinson et al.	2002	Open label comparative study of donepezil and rivastigmine	Donepezil (up to 10 mg/day) rivastigmine (up to 12 mg/day)	12 weeks	74–74.9	20.2–20.6	20.7–21.5	111
Aisen et al.	2003	Randomized, placebo-controlled study of selective cyclooxygenase (COX) -2 inhibitor (rofecoxib) or a traditional nonselective NSAID (naproxen)	Rofecoxib 25 mg once-daily Naproxen 220 mg bid	1 year	73.8	24.2	20.8	351
Blesa et al.	2003	Post hoc analysis for advanced moderate AD patients using data extracted from two long-term galantamine studies	Galantamine 24 mg/day	12 months	NA	37.3–37.4 34–39	15.9–16 12.5–14	165 (ADAS > 30) 72 (MMSE < 14)
Krishnan et al.	2003	Double blind, placebo controlled study of the effects of donepezil on neuronal markers and hippocampal volumes in AD	Donepezil 10 mg	24 weeks	72.4–74.4	26.4–26.5	19–19.5	67
Tune et al.	2003	Randomized, double-blind, parallel-group, pilot study	Donepezil 10 mg	24 weeks	72.2–73.7	21.8–21.9	20.8–21.4	28
Wilcock et al.	2003	Rater-blinded, randomized, parallel-group study to compare galantamine and donepezil	Donepezil 10 mg/day Galantamine 24 mg/day	52 weeks	74.1–72.8	NA	14.8–15.1	182
Aguglia et al.	2004	Open label, comparative study of rivastigmine, donepezil and galantamine	Rivastigmine 6 mg twice daily Donepezil 10 mg once daily Galantamine 8 mg twice daily	6 months	77–78	23.2–25.0	20.4–21.5	242

(Continued)

Table 1
Study design summary [15–68] (Continued)

Author	Year	Study Design/Description	Drug/Dose	Treatment Duration	Baseline Age (yrs)*	Baseline ADAS-cog*	Baseline MMSE*	Total N (randomized)
Jones et al.	2004	Open label study to compare the effects of donepezil and galantamine	Donepezil 10 mg/day	12 weeks	73.8–75.1	23.1	18.3–18.4	120
Lyketsos et al.	2004	12-month open label study following 5 month double blind placebo controlled study with a 6-week washout	Galantamine 24 mg/day Galantamine 16, 24 mg/day (24 mg/day during open trial)	12 months	76.5–77	27.6–28.6	17.8–18.2	699
Raskind et al.	2004	24 months open-label extension study followed participation in either of 2 double-blind placebo controlled study with continuous open-label extension for total of 12 months	Placebo Galantamine 24 mg/day (24 mg/day during open trial)	36 months	76.1	NA	19.7	194
Reines et al.	2004	Randomized, placebo-controlled study of selective cyclooxygenase (COX) -2 inhibitor	Placebo Rofecoxib 25 mg	1 year	75	20	21	692
Brodaty et al.	2005	Double blind, parallel group, placebo and active controlled trial	Galantamine 24 mg/day Galantamine PRC [†] 24 mg/day	24 weeks	76.3–76.6	26.1–27.3	17.8–18.1	965
Feldman et al.	2005	Placebo data pooled from two 1-year, randomized, double-blind, placebo-controlled trials of glutamate antagonist (sabeluzole)	Placebo	1 year	71.9–73.3	NA	16.3–20.8	331
Karaman et al.	2005	Randomized, placebo-controlled study in advanced moderate AD	Rivastigmine (up to 12 mg/day)	52 weeks	73.4–74.1	39.3–41.6	11.4–13.2	44
Liu et al.	2005	Open study in AD patients treated with escalating dose of galantamine	Galantamine 4-8-16 mg/day	12 weeks	76.6	22.2	13.2	39
Martin et al.	2005	Open study to evaluate efficacy of rivastigmine in AD patients with rapid/slow disease progression	Rivastigmine 12 mg/day	26 weeks	73–73.7	20.7–34.9	NA	679
Petersen et al.	2005	Double-blind, placebo-controlled study of vitamin E or donepezil in subjects with the amnesic form of mild cognitive impairment	Donepezil 10 mg daily Vitamin E 2000 IU	3 years	72.9–73.1	11.03–11.28	27.3	790
Visser et al.	2005	Open label study in AD patients treated with escalating dose of rivastigmine	Rivastigmine 3-12 mg/day	26 weeks	66.7–73.1	17.7–21.3	18.5–20.6	159
Peskind et al.	2006	Double-blind, placebo-controlled study	Memantine 20 mg/day	24 weeks	77	27.3	17.2	403
Rockwood et al.	2006	4-month double-blind followed by 4-month open label extension study	Galantamine 24 mg/day	8 months	77–78	24.2–27.9	19.9–20.8	130
Suh et al.	2006	Prospective, multi-center, randomized, double-blind galatamine trial to rivastigmine the effect of the apolipoprotein E epsilon4 allele	Galantamine 16 mg/day	16 weeks	74.4–75	NA	16.3–16.7	202
Thavichachart et al.	2006	Open label study in AD patients with/without cerebrovascular disease and vascular dementia (VaD)	Galantamine 16 or 24 mg/day	24 weeks	74.5	21.78	19.7	75
Chu et al.	2007	Open-label study of galantamine therapy	Galantamine 24 mg/day	2 years	78.48	28.94	14.91	61

(Continued)

Table 1
Study design summary [15–68] (Continued)

Author	Year	Study Design/Description	Drug/Dose	Treatment Duration	Baseline Age (yrs)*	Baseline ADAS-cog*	Baseline MMSE*	Total N (randomized)
Aisen et al.	2008	Randomized, double-blind, controlled clinical trial of high-dose of folate, vitamin B6, and vitamin B12 supplementation in mild to moderate AD patients	High-dose vitamin supplements	18 months	76.3	22.51	20.95	409
Rockwood et al.	2008	Open-label long-term extension of two placebo-controlled clinical trials	Galantamine 12 mg/day	36 months	74.7	22.6	20	240

* Reported as mean values for study or each treatment arm.

† Duplicated by Doody et al., 2001, but data are complementary.

‡ PRC = prolonged-release capsule.

4.2. Post hoc data inclusions and exclusions

Two data points were excluded from the analysis because of an extreme deviation. These two data points were obtained during week 174 from a study of donepezil reported by Doody et al. [35]. During week 174, only 9 of the original 363 patients (302 study) and 45 of the 279 patients (301 study) who entered into the open-study phase remained after completion of the double-blind phase. These two points clearly deviated from the other observed mean values reported for larger sample sizes at other time points in the trial. The rest of the values from this trial were retained.

4.3. Final model

Figure 2 shows the time-course of ADAS-cog (change from baseline) with 90% confidence intervals (CIs) for each treatment group from the 100 simulations. The parameter estimates of the final model are presented in Table 2. The standard diagnostic plots for mixed-effects models showed no obvious discrepancies with the model. These results indicate that the model prediction is reasonable for both the point estimates and the distributions.

The placebo effect in the trials was described with a Bateman-like function, with parameter estimates for β_p of -2.1 , for Kel_p of $0.00306 \text{ week}^{-1}$, and for Keq_p of 0.127 week^{-1} . In clinical terms, the half-time to reach the maximum placebo effect was 5.6 weeks (calculated as $\ln(2)/0.127$), and the half-time to diminish the placebo effect was 22.7 weeks (calculated as $\ln(2)/0.0306$), indicating that the maximum placebo effect in trials included in the analysis occurred at around 11 weeks, and disappeared within 1 year. These estimates are longer than previously hypothesized from patient-level analyses, where the placebo effect was estimated to fade to zero after about 6 weeks [4,9]. These differences are perhaps attributable to a lack of data points available during the first few weeks, making estimations of the onset of placebo effect imprecise, with limited data available after 6 months to estimate precisely the offset of placebo effect.

The time-course of symptomatic effects of AChE-inhibitors was well-described, using an Emax-type model. The dose effect was not significant for galantamine treatment, probably because of the small dose range reported in the literature. The ET_{50} was estimated from 1.42 to 13.1 weeks, indicating that the maximum symptomatic effects of AChE drugs is obtained between 3 to 26 weeks.

The underlying disease-progression slope (α) from the model was estimated as a 5.5-point deterioration/year in ADAS-cog values, consistent with the previously held understanding of disease progression in mild-to-moderate AD patients.

Baseline ADAS-cog value was the only covariate found to have a significant effect on slope (α). The power coefficient was estimated as 0.669. In clinical terms, disease progression was a function of baseline severity, with more severe populations demonstrating more severe deterioration in cognitive function, compared with less severe populations, according

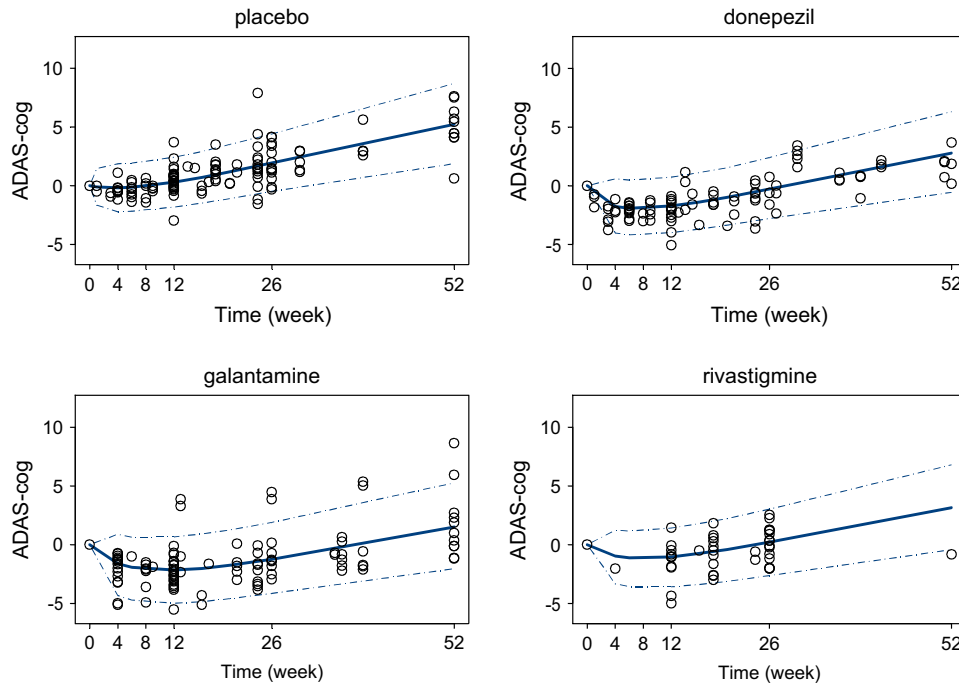


Fig. 2. Time-course of ADAS-cog from 100 simulated datasets according to treatment group. Solid line, mean estimate; dashed line, 90% predicted intervals.

to ADAS-cog (within the range of values available in the dataset). For example, if a baseline ADAS-cog value is 35 (i.e., cognitive function is worse than the population mean of 25), the slope estimate is 6.88 points/year deterioration (calculated as $5.49 \times (35/25)^{0.669}$, where 5.49 is the population mean-slope estimate from the model), and if a baseline ADAS-cog value is 15, then the slope estimate is 3.9 points/year. These results are summarized in Table 2B.

Baseline MMSE score and baseline ADAS-cog value were both evaluated as covariates affecting the disease-progression slope. The model-fitting was statistically better with baseline ADAS-cog than with baseline MMSE, based on the objective-function decrease in the NONMEM analysis. We attempted to incorporate both baseline MMSE and baseline ADAS-cog on the slope. However, the model was ill-conditioned because of the high correlation between baseline ADAS-cog and MMSE (Fig. 3, top left). Thus, baseline ADAS-cog was selected in the final model as a covariate describing the effect of baseline severity on the slope. Age and year of publication did not have statistically significant effects on disease progression. For exploratory purposes, study design (open study vs. double-blind study) or missing-data imputation method (LOCF vs. OC) were also tested as covariates on the disease progression slope, but neither was statistically significant.

5. Discussion

Acetylcholinesterase-inhibitors have beneficial effects on the cognitive, functional, and behavioral symptoms of AD, and AChE-inhibitors are recommended as first-line treatment in patients with mild-to-moderate AD. However, the literature suggests that the available antidementia drugs only pro-

vide symptomatic improvement, and do not address the underlying pathology of AD. Their effects on cognition, executive functioning, and behavior are only temporary, because patients who demonstrate initial improvement in cognition will ultimately regress to and then beyond their pre-drug baseline. None of these available antidementia agents are considered to exert disease-modifying effects that can halt the progression of AD and stop cognitive decline.

Based on the available literature from 1990 to 2008 for AChE-inhibitors (donepezil, galantamine, and rivastigmine), a model for longitudinal response in AD patients of mild to moderate severity was developed. Drug effect was modeled in terms of Emax-type over time for each drug, with a description of drug effect reaching a plateau, and of maximum effect occurring over time (synonymous with a symptomatic effect). We also tested linear and sigmoid-Emax models for each drug during model development, but the Emax model best described the data.

The rate of disease progression (α) was estimated as 5.5 points per year (± 0.229 , standard error) for a patient population with a mean baseline ADAS-cog value of 25. The results were similar to those of Holford et al. [5] (6.17 points/year, with baseline ADAS-cog estimate of 28.7) and Doraiswamy et al. [3] (3.38 points/26 weeks, with baseline ADAS-cog of 28.4), based on data from a single drug-development program. The slope estimate from our meta-analysis is slightly slower, which is largely explained by our slightly lower baseline ADAS-cog value.

We performed analyses during model development to test whether any difference in disease-modifying effect was evident via AChE-inhibitor treatment (different slope from placebo), but this difference was not significant. This finding

Table 2
Model parameter estimates (A) Final parameter estimates

Parameter	Estimate (SE)	
Disease progression		
Baseline (points)	0 fix	
Slope (α) (points/year)	5.49	(0.299)
Baseline ADAS-cog effect on slope	0.669	(0.357)
Placebo effect		
β	-2.1	(0.946)
Kel (week $^{-1}$)	0.0306	(0.00956)
Keq (week $^{-1}$)	0.127	(0.0551)
Drug effect		
Donepezil		
ΔE_{max} (points)	-2.26	(0.296)
ET_{50} (weeks)	1.42	(1.21)
Dose effect (dose/5 mg) 0	0.231	(0.0948)
Galantamine		
ΔE_{max} (points)	-4.88	(0.498)
ET_{50} (weeks)	13.1	(3.8)
Rivastigmine		
ΔE_{max} (points)	-1.6	(0.566)
ET_{50} (week)	9.37	(9.88)
Dose effect (dose/6 mg) 0	1.17	(0.58)
Random effect		
(η_1) on intercept	0.669	(0.282)
(η_2) on slope	0.0391	(0.0137)
(η_3) on ET_{50}	1.33	(0.735)
Standard deviation	8.51	(0.823)

Abbreviations: α = rate of change of ADAS-cog; β = coefficient of placebo effect; Kel , the rate constants for the offset of the placebo effect; Keq , the rate constants for the onset rate of the placebo effect; ⁰, fitted power coefficient; ET_{50} = half-time to reach maximum drug effect.

is consistent with the belief that AChE-inhibitors have only symptomatic effects, and may not exert a disease-modifying effect. Moreover, we do not have enough placebo data information from over a sufficient length of time (3 to 6 months for a double blind study) to differentiate the slope difference between placebo and drug.

Baseline ADAS-cog value was found to be a significant covariate in rate of disease progression. The results indicate that the milder the baseline cognitive impairment in a population observed within a trial, the slower the disease progression, and that the more severe the cognitive impairment, the faster the deterioration. For example, if the baseline ADAS-cog is 10, 20, 30, or 40 points, the slope estimate from the model is 2.97, 4.73, 6.20, or 7.52 points/year, respectively. These findings are consistent with the current understanding of cognitive deterioration as assessed by ADAS-cog, i.e., cognitive deterioration is slow during early stages of AD or MCI, and more rapid during the middle stages. It should be noted that only one clinical study with MCI was included in this analysis. A number of clinical trials in the literature evaluated the efficacy of AChE-inhibitors in MCI patients, but only one paper met our predefined search criteria. Other papers reported modified ADAS-cog values (ADAS-cog/13-item version, ADAS-cog/MCI) [69–71] or different endpoints (standardized Z-score for a cognitive test battery) [72]. Furthermore, as a treatment population reaches the upper and

(B)
Slope estimate according to baseline ADAS-cog

Baseline ADAS-cog	Baseline MMSE*	Slope estimate (points/year)	95% CI
10	>27	2.97	2.39–3.56
15	25	3.90	3.31–4.49
20	22	4.73	4.14–5.31
25	19	5.49	4.90–6.08
30	17	6.20	5.62–6.79
35	14	6.88	6.29–7.46
40	<12	7.52	6.93–8.10

* Baseline MMSE was approximately calculated based on linear regression relationship with baseline ADAS-cog.

lower edges of the ADAS-cog scales, these relationships are likely to break down because of the nature of the scale itself to manifest ceiling and floor effects as the scale reaches its edges.

These results, obtained from study-level data, are in agreement with emerging results [73] of the Alzheimer's Disease Neuroimaging Initiative (<http://www.loni.ucla.edu/ADNI/>). All these results indicate that cognitive deterioration is slower during early-stage AD, and more rapid during moderate AD.

In addition, the results of our analysis may provide important insights into the expected rate of cognitive decline in patients enrolled in clinical trials of putative disease-modifying therapies. In principle, these therapies are expected to alter the slope of cognitive decline, unlike the AChE-inhibitors. For symptomatic agents, the rate of cognitive decline is expected to parallel that of untreated patients with the same underlying therapy, after a stabilization period. The duration of this stabilization period is predicted by the results of this analysis, and suggest that several months on background AChE-inhibitor therapy are needed to rule out any contributions of this background to changes in ADAS-cog values. The time required to reach the maximum effect with an AChE-inhibitor is estimated to be 3 to 26 weeks according to the ET_{50} values, suggesting that a treatment effect is stable by approximately 6 months.

Aging is obviously an important risk factor for dementia, and baseline age was tested as a covariate in rate of disease progression. The model was unable to describe any effect of age, likely because of the narrow distribution of mean age in the studies included. For most studies included, the mean age distribution was from 70 to 78 years old, with one extreme outlier of 58 years old (Fig. 3).

The analyses also found that the baseline ADAS-cog value and baseline MMSE score are strongly related (Fig. 3, top left). The intercept and slope estimate (95% CI) derived from linear regression were 60.9 (59.6–62.3) and –1.85 (–1.92 to –1.78), respectively. These results are also consistent with those reported by Doraiswamy et al. [10], using patient-level data ($ADAS-cog = 72.2 - 2.41 * MMSE$). Although slight differences exist for the intercept and slope estimates between these analyses, these differences are most likely attributable to the different ranges of data in each dataset analyzed. However, the results demonstrate that the

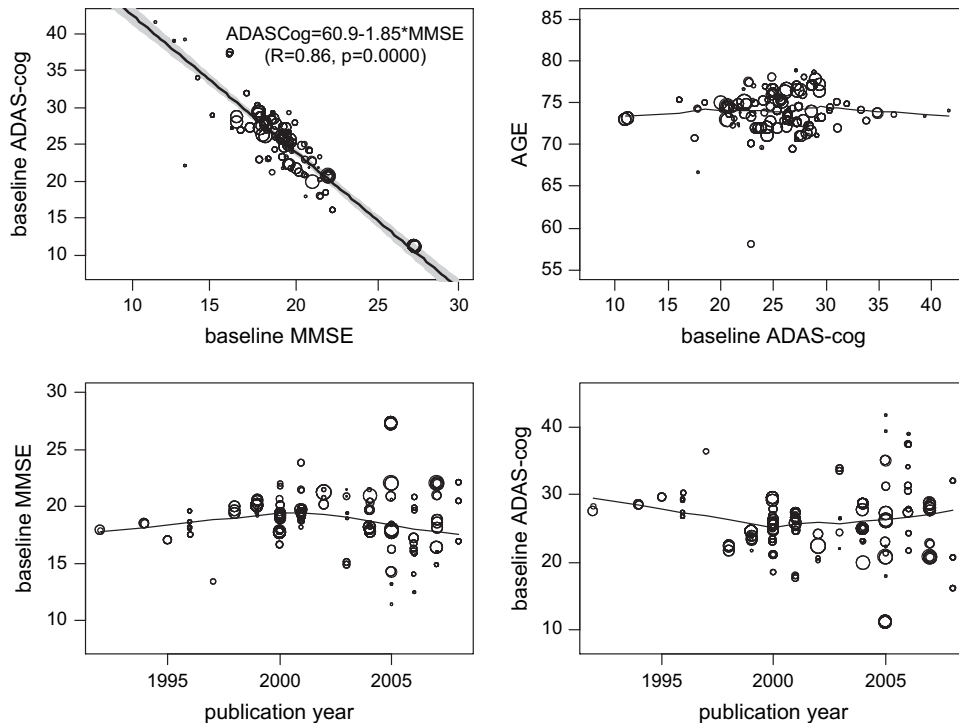


Fig. 3. Baseline characteristics (top left, linear regression; others, loess lines). Size of open circle represents clinical-trial sample size (each open circle is drawn in proportion to number of patients in trial arm).

correlation between ADAS-cog and MMSE is the same, regardless of whether study-level or patient-level data are used.

Another question concerns whether cognitive deterioration may be slower in present AD clinical trials than in the past. Potential reasons for this phenomenon include: 1) inadequate sensitivity of the standard scales used for measuring cognition in these trials in patients with mild AD (ceiling effects); 2) milder disease severity and differences in coexisting medical conditions between populations recruited now, compared with those in earlier trials; and 3) in recent trials of putative disease-modifying agents, a more frequent use of background therapies, including approved AD drugs (cholinesterase inhibitors and Memantine) by populations recruited into clinical trials. In 2008, at the International Conference on Alzheimer's Disease Meeting (in Chicago, IL), two scientific presentations addressed this issue, using different data sources and different methods of analysis [74,75].

Schneider et al. searched published and unpublished sources of randomized, double-blind, placebo-controlled AD clinical trials of 6 months' duration or longer [74]. They found 103 trials conducted between 1991 and 2005, and obtained information from 87. From these, they extracted information about trial size, countries, number of sites, treatment allocation ratios, enrollment dates, age, gender, and scores on two standard measures of cognition (MMSE and ADAS-cog). They found no changes in amounts of cognitive decline across the 15-year period of the trials. They found that smaller placebo groups were associated with a lower likelihood of cognitive worsening over the course of a trial. Pla-

cebo-group sample sizes of less than 100 had a 37% chance of showing no significant change, whereas samples greater than 200 all showed significant worsening at after 6 months. In 12-month studies, 95% of placebo groups where sample sizes were greater than 100 showed a significant decline.

Jones et al. also conducted a meta-analysis, but used individual patient data from randomized, double-blind, placebo-controlled studies of donepezil for AD between 1990 and 1999 [75]. Data were available for 3403 patients who participated in 13 randomized, double-blind, placebo-controlled AD trials. Data were grouped according to year of initiation of trials. Group 1 contained studies initiated from 1990 to 1994, and group 2 contained studies initiated from 1996 to 1999. The results indicated that patients with AD who entered the later clinical trials appeared experience a slower rate of decline in memory and other cognitive processes. Changes from baseline MMSE and ADAS-cog scores up to week 24 were compared between groups 1 and 2 for placebo only, and then between donepezil and placebo. Decline in MMSE score from baseline to week 24 was significantly greater among placebo patients in group 1 (−1.28 points) compared with group 2 (−0.56 points, $P = 0.024$). Placebo decline in ADAS-cog values was also greater in group 1 than group 2, but the difference was not significant.

Year of publication was also evaluated in our analysis as a covariate in rate of disease progression, to test the hypothesis that standard of care for AD may be improving with time (as reflected by later publications) and altering the rate of disease progression. Year of publication may not accurately

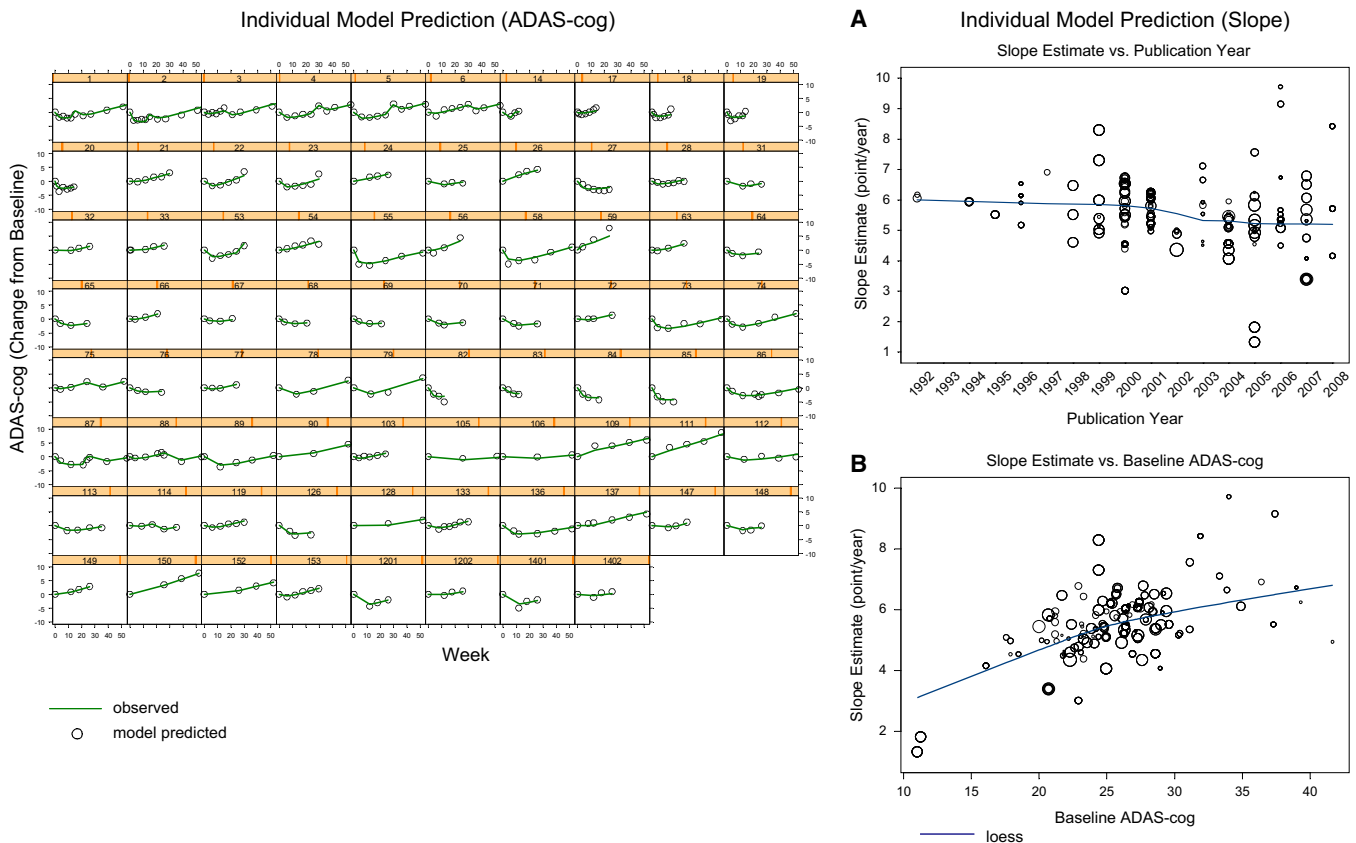


Fig. 4. Individual model prediction of ADAS-cog (**left**) and individual model prediction of slope (**right**). Individual slope estimates are plotted versus (A) year of publication (**top right**) and (B) baseline ADAS-cog value (**bottom right**). Size of open circle at right represents clinical-trial sample size (each open circle is drawn in proportion to number of patients in trial arm).

reflect the year of the study, but it was not possible to collect the actual years of study enrollment in all the literature reported. Therefore, year of publication was the only available information for capturing the period of treatment for studies in our analysis. The results showed that year of publication was not a significant factor. In addition, the predicted slope for each treatment arm was obtained from the model fit (Fig. 4, left), and the slope estimate was plotted against year of publication to visualize rate of disease progression over time (Fig. 4, top right). Two data points with less than a 2-point/year disease progression in 2005 are from a study of MCI patients with a baseline ADAS-cog of approximately 11. The data in Fig. 4 (top right) indicate no trend as a function of publication year, with a reasonable distribution of disease progression rate of approximately 6 points/year. The slope estimates, on the other hand, show an increasing trend as a function of baseline ADAS-cog (Fig. 4, bottom right), which is consistent with our findings in the model. These results indicate that a reasonable distribution of disease progression rates could be described as 3 to 8 points/year, and that the severity of patients included in a study at the beginning of the study is likely to be a much more important factor than the year of a study in predicting disease progression.

Study design (open vs. double-blind trial) and statistical methods (OC vs. LOCF) were also evaluated, but were not

found to be significant factors in describing disease progression (results not shown). The results in Fig. 2 and the relatively short period of time that placebo effects were estimated to be present also suggest that open-label data may be informative in understanding long-term disease trajectories. Many of the longer studies (>6 months) presented in these figures were open-label studies. This consideration is important, given that most placebo arms of treatment-naïve studies are limited to a 6-month duration for ethical reasons, and for the most part, long term drug-free disease-progression data are difficult to obtain. In the present analysis, only two studies were identified in the dataset where the study design allowed patients to take AChE-inhibitors as background therapy. All other studies enrolled patients without background AChE-inhibitor therapy.

The limitations of this sort of meta-analysis should be considered. Because the literature typically only reports mean values (and standard errors), the model was unable to detect the influence of potentially important covariates. For example, the distribution of mean age in our metadata was very narrow (Fig. 3, top right), although a reasonable individual age range of patients must have been included in the most of the trials. Other covariates that may have an impact on cognitive deterioration, e.g., duration of education, apolipoprotein-E genotype, and gender, were not readily available.

These covariates were reported in some of the literature, but not all, and only as means or percentages of a population, making analysis difficult.

Despite these limitations, a model-based understanding of disease progression can provide a basic platform for integrating knowledge from various sources into one common understanding. It also provides a more quantitative way to test hypotheses across all available information, and allows for a more scientific basis for drug development [76]. Another potential benefit of a model-based approach is that more informative clinical trial designs can be developed using optimal design techniques. For example, Henning et al. reported on the optimization of length of treatment period, to obtain reliable estimates of drug effects in long-term disease progression studies, based on a disease-progression model [77]. After the model is developed, newly emerging data can simply be added to the model, and parameter estimates can continue to be updated and refined. In cases where individual patient-level data are available, these parameter estimates can be used as informative priors to assist in trial design, or to combine information from the literature with patient-level data [78]. Ideally, meta-analyses would be completed with patient-level data pooled from various studies, and various coalitions are attempting to achieve this goal.

In conclusion, disease progression in mild-to-moderate AD patients across all available and relevant sources in the literature is estimated as 5.5 points per year. An Emax-type model best describes the symptomatic drug effect for AChE-inhibitors (donepezil, galantamine, and rivastigmine). Baseline ADAS-cog value is a significant covariate in disease progression (α), and describes or at least explains the different rates of deterioration evident in early or late stages of the disease. Differences in various analyses that were previously presented may be attributable to differences in underlying disease severity in the datasets used.

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