



# A meta-analytic model for Alzheimer's Disease progression incorporating both summary-level data and patient-level data

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# Key features of clinical trials in Alzheimer's Disease (AD)

## ■ Co-primary endpoints:

- A cognitive endpoint, typically the ADAS-cog.
- A “global” endpoint reflecting overall clinical condition, e.g. the Clinical Dementia Rating Scale.

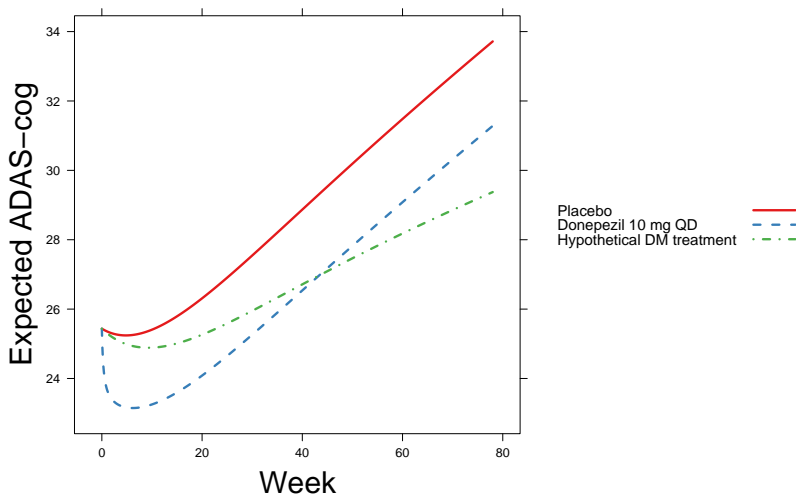
## ■ Population:

- Most therapies under development target mild to moderate severity.
- Increasing interest in milder and “pre-AD” populations, however mild population is near cusp of dynamic range of ADAS-cog.

## ■ Study duration:

- Registrational trials for e.g. Donepezil were 26-30 weeks, but 18 month trials are now standard.
- To differentiate a purely “disease modifying” (DM) drug from placebo, need to wait for cognitive decline in placebo group.

# Estimated and Hypothesized Drug Effects Over Time



# Why use modeling and simulation?

## ■ Modeling:

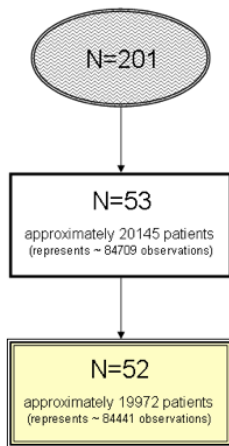
- Avoid subjective selection of historical data that support our preconceptions.
- Formal articulation of basic assumptions so they can be debated.
- Honest, data-driven assessment of uncertainty.
- More (good) data → more precise estimates (especially relevant in estimating variance components)
- A model is prerequisite to simulation . . .

## ■ Simulation:

- More realistic models can be explored
- Larger class of trial designs can be explored
- Larger set of operating characteristics can be explored (e.g. probability of a significant result *at the “best” dose* after multiplicity adjustment).
- Predictive power is more honest than conditional power [1].

# Summary data from literature

Data from systematic review of literature, assembled and published by Kaori Ito *et al* [2, 3], from which this is taken:



## Step 1: Literature Search Criteria

- Sources: all available clinical trials in National Institute for Clinical Effectiveness ("NICE"), Medline, Embase, SBAs at FDA's CDER website (years 1990-2008)
- Key search terms: AChE inhibitor names, endpoints names (ADAS-cog, MMSE, CIBIC, etc.), and clinical trials definitions (double-blind, randomized, etc.)

## Step 2: Literature Acceptance Criteria

### Accept:

Literature with ADAS-cog reported  
if placebo group data is available from non-AChE study (i.e. Vitamin E study), keep only placebo data from that literature

### Exclude:

- any duplicated literature (the same clinical data)
- duplicated data points reported with different analysis methods (selected OC over LCOF if available)
- an exploratory study (open study with number of patients  $\leq 20$ )

## Step 3: Further Refinement

One Study was removed from the analysis:

- only week 52 result (change from baseline) was reported, baseline ADAS-cog was not reported, and the drop-out rate was high [n=173 (baseline) to n=95 (week 52)], open study (rivastigmine)

# Patient-level data

- Alzheimer's Disease Neuroimaging Initiative (ADNI)  
<http://www.adni-info.org/>
  - Non-randomized, non-treatment study.
  - 2–3 year follow-up (depending on baseline status), with assessments roughly every 6 months (schedule depends on baseline status).
  - Primary endpoints are imaging and biomarker endpoints, but ADAS-cog is assessed as well.

Number of subjects	
Normal	200
MCI	400
Mild AD (MMSE 20-26)	200

- Proprietary clinical trial data sets.

# Brief History of Published AD Progression Models

- Disease progression model published by Holford and Peace [4, 5, 6].

$$E[S(t)] = S(0) + \alpha * t + E_{PBO}(t) + E_{DRUG}(Conc)$$

- Ito *et al* [2, 3] developed meta-analytic version of this model (based on summary statistics) and applied it to substantial new body of evidence. Modifications:
  - inclusion of new covariates, notably baseline severity
  - modeled drug effect directly as a function of time and dose, not using concentration as an intermediary.

$$E[S(t)] = S(0) + \alpha * t + E_{PBO}(t) + E_{DRUG}(t, Dose)$$

# Brief History of Published AD Progression Models

Gillespie *et al* (\*) derived an error structure that allows simultaneous modeling of summary-level data and patient-level data.

- Statistically sound “weighting” of residuals *and random effects* based on sampling theory.
- Accurately predicts:
  - observed correlations between time points (important in simulating adaptive trials or trials where primary analysis uses longitudinal data)
  - changes in marginal variance over time (important in simulating *any* clinical trial).

\* <http://www.metrumrg.com/images/stories/publications/ADAScog03132009.pdf>

# Where We Are Today

- In progress: “fusion” of models by Ito *et al* and Gillespie *et al*:
  - Adapting Gillespie *et al* model to respect the 0–70 constraint on the ADAS-cog (described in detail in subsequent slides).
  - Incorporating research on key covariates by Kaori Ito.
  - Application of this model to summary-level literature data and ADNI data (simultaneously).

# Subscript Notation

- Let  $ADAS_{ipk}$  denote the observed ADAS-cog score on the
  - $i^{th}$  occasion for the
  - $p^{th}$  patient in the
  - $k^{th}$  study.
- Where it is convenient, we will use the following subscripts in place of  $p$ :
  - $j = j(p)$ , denoting study arm
  - $d = d(i, p)$  denoting drug (not applicable for placebo)
  - For example,  $t_{ijk}$  denotes the time of the  $i^{th}$  visit for all patients in arm  $j$  in study  $k$ .

# Distribution of Individual Patient Scores

$$ADAS_{ipk}/70 \mid \text{patient } p \sim \text{Beta}(\theta_{ipk}\tau, (1 - \theta_{ipk})\tau).$$

This distribution is parameterized such that:

$$\begin{aligned} \mathbb{E}[ADAS_{ipk}/70 \mid \text{patient } p] &= \theta_{ipk} \\ \mathbb{V}[ADAS_{ipk}/70 \mid \text{patient } p] &= \frac{\theta_{ipk}(1 - \theta_{ipk})}{\tau + 1} \end{aligned}$$

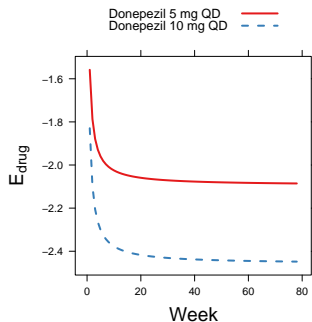
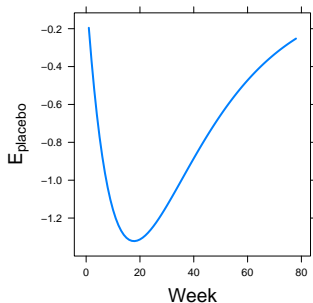
We then model the conditional expectation as:

$$\log \left[ \frac{\theta_{ipk}}{1 - \theta_{ipk}} \right] = \alpha_{pk} t_{ipk} + \eta_{\text{intercept},pk} + E_{\text{placebo},ipk} + E_{\text{drug},ipk}$$

# Fixed Effects for Placebo and Drugs

$$E_{\text{placebo},ipk} = \beta \left( e^{-k_{el}t_{ijk}} - e^{-k_{eq}t_{ijk}} \right)$$

$$E_{\text{drug},idk} = \left( \frac{D_d}{D_{\text{ref},d}} \right)^{\gamma_d} \frac{E_{\Delta,d} t_{idk}}{ET_{50,d} + t_{idk}}$$



# Hierarchical Random Effects

- Inter-study random effects

$$\alpha_{\text{study},k} \sim \text{N} \left( \mu_{\alpha}, \psi_{\alpha}^2 \right)$$

$$\eta_{\text{intercept},\text{study},k} \sim \text{N} \left( \mu_{\text{intercept}}, \psi_{\text{intercept}}^2 \right)$$

- Inter-patient random effects

$$\alpha_{pk} \mid \text{study } k \sim \text{N} \left( \alpha_{\text{study},k}, \omega_{\alpha}^2 \right)$$

$$\eta_{\text{intercept},pk} \mid \text{study } k \sim \text{N} \left( \eta_{\text{intercept},\text{study},k}, \omega_{\text{intercept}}^2 \right)$$

- As shown by Gillespie *et al*, this covariance model correctly predicts the growth of the marginal variance over time.

# Distribution of Sample Statistics

$$\overline{ADAS}_{ijk}/70 \mid \text{arm } j \sim \text{Beta} \left( \bar{\theta}_{ijk} (n_{jk} \tau_k + n_{jk} - 1), (1 - \bar{\theta}_{ijk}) (n_{jk} \tau_k + n_{jk} - 1) \right), \text{ where,}$$

$$\bar{\theta}_{ijk} = \frac{1}{n_{jk}} \sum_{p:j(p)=j} \theta_{ipk}$$

Now define these "shorthand" random effects:

$$\bar{\alpha}_{jk} \equiv \frac{1}{n_{jk}} \sum_{p:j(p)=j} \alpha_{pk}$$

$$\bar{\eta}_{\text{intercept},jk} \equiv \frac{1}{n_{jk}} \sum_{p:j(p)=j} \eta_{\text{intercept},pk}$$

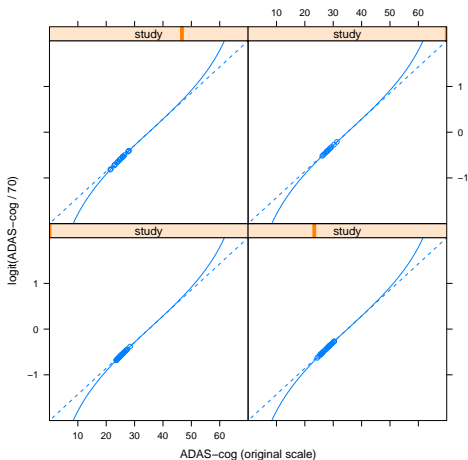
$$\overline{\text{logit}[\theta]}_{ijk} \equiv \bar{\alpha}_{jk} t_{ijk} + \bar{\eta}_{\text{intercept},jk} + E_{\text{placebo},ijk} + E_{\text{drug},ijk}$$

And invoke the approximate linearity of the logit over the range of interest:

$$\text{logit}[\bar{\theta}]_{ijk} \approx \overline{\text{logit}[\theta]}_{ijk}$$

# Linear Approximation to Logit

*Points shown are observed sample means from 4 studies; all time points and all study arms are shown*



# Distribution of Sample Statistics (cont'd)

Our model for  $\overline{ADAS}_{ijk}/70$  results in approximately the correct gain in conditional precision, relative to a single observation:

$$V[\overline{ADAS}_{ijk}/70 \mid \text{arm } j] = \frac{\bar{\theta}_{ijk}(1 - \bar{\theta}_{ijk})}{n_{jk}(\tau_k + 1)} \approx \frac{V[ADAS_{ipk} \mid \text{patient } p]}{n_{jk}}$$

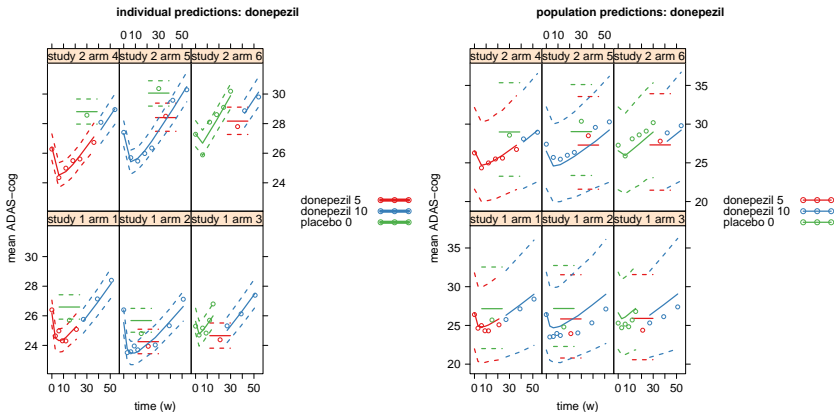
We also get the correct gain in marginal precision by modeling the average random effects as:

$$\begin{aligned} \bar{\alpha}_{jk} \mid \text{study } k &\sim N(\alpha_{\text{study},k}, \omega_{\alpha}^2/n_{jk}) \\ \bar{\eta}_{\text{intercept},jk} \mid \text{study } k &\sim N(\eta_{\text{intercept},\text{study},k}, \omega_{\text{intercept}}^2/n_{jk}) \end{aligned}$$

# Draft Priors (sensitivity analysis still needed)

$$\begin{aligned}
 E_{\Delta, \text{drug}} &= \frac{(1 + b_{\text{drug}}) E_{\text{drug}}^*}{b_{\text{drug}}} \\
 \log(E_{\text{drug}}^*) &\sim N(0, 0.1) \\
 ET_{50, \text{drug}} &= \frac{t^*}{b_{\text{drug}}}; \quad t^* = 12 \text{ weeks} \\
 b_{\text{drug}} &\sim U(0, 100) \\
 \gamma_{\text{drug}} &\sim U(0.01, 10) \\
 \mu_{\alpha} &\sim N(0, 100) \\
 \mu_{\text{intercept}} &\sim N(0, 100) \\
 AUC_{\text{placebo}} &\sim U(0, 100) \\
 \beta &= -AUC_{\text{placebo}} / \left( \frac{1}{k_{el}} - \frac{1}{k_{eq}} \right) \\
 k_{el} &\sim U(0, 2) \\
 k_{eq} - k_{el} &\sim U(0, 2) \\
 \psi_{\text{intercept}} &\sim U(0, 10) \\
 \omega_{\text{intercept}} &\sim U(0, 10) \\
 \psi_{\alpha} &\sim U(0, 10) \\
 \omega_{\alpha} &\sim U(0, 10) \\
 \mu_{\sigma} &\sim U(0, 1000)
 \end{aligned}$$

# Example Posterior Predictive Checks



# Transparent and Public Vetting of Models

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## Welcome to OpenDiseaseModels.org

Please read this page and the [Overview](#) section before doing anything else.

OpenDiseaseModels.org is an open-source disease/systems model development project. Analogous to open-source software development projects, the goal of this effort is to develop better, more useful models in a transparent and public collaborative forum.

### Motivation

The motivation for OpenDiseaseModels.org is driven by the following principles:

1. Development of disease/systems models is an extremely resource-intensive effort.
2. Pre-competitive insight and resources shared across companies/institutions will lead to better systems models than could be developed by a single institution.
3. Open models, which are transparently developed and publicly vetted, will be more widely accepted and will be better positioned to impact the entire scientific/biomedical/health community.

# Closing Thoughts: Statisticians and Modeling

- Most statisticians wanting to get more involved in modeling work should focus on learning three things:
  - computing
  - computing
  - computing
- On the other hand, we don't want to become computer technicians. Don't lose sight of the special body of knowledge and insight that has developed in the statistics discipline.
  - Think carefully about variances and correlations (they do matter!)
  - Think carefully about the data that *aren't* there (missing data; selection effects; confounding).
  - Think carefully about how data will ultimately be analyzed to make decisions.

# References



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