Population Dose-Response Model for ADAS-cog Scores in Patients with Alzheimers Disease by Meta-Analysis of a Mixture of Summary and Individual Data

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Abstract

A. BACKGROUND/AIMS — *Develop a population dose-response model for ADAS-cog based on both published summary statistics and individual data from one clinical trial.*

B. METHODS — *Summary statistics for ADAS-cog change from baseline were obtained from publications of the results of 55 clinical trials in which placebo, donepezil, galantamine or rivastigmine were administered to patients with Alzheimers disease The data set contained 465 sample means and 263 sample standard deviations. The data also included ADAS-cog from 196 individual patients at 6 and 12 weeks following treatment with placebo, donepezil 5 mg qd, or CP-457,920 30 qd, 60 bid or 120 mg bid, and from 613 patients following treatment with donepezil 10 mg/d or donepezil 10 mg/d plus atorvastatin for 18 months. The data was modeled using a variation of a model by Ito et al. CPT 83: S40 (2008). Key differences were modeling of both inter-trial and inter-patient variation, and use of a common drug effect model (with drug-specific parameters) for all drugs. A novel approach to the simultaneous modeling of individual and summary data was developed to estimate the parameters of a population model that may be used for simulations of individual time courses. The model was fitted using a Bayesian modeling approach (WinBUGS 1.4.3). Relatively uninformative prior distributions were used.*

C. RESULTS — *Predictive checks indicated that the model was consistent with the observed data. Simultaneous modeling of means, standard deviations and individual data, and an improved marginal variance model permitted estimation of inter-study and inter-patient variances, e.g., posterior mean inter-patient and inter-study standard deviations for progression rate were 0.038 and 0.057 points/week. The model also successfully described the net increase in sample standard deviations with time—a consequence of inter-patient variation in the progression rate not captured in previous model-based meta-analyses.*

D. CONCLUSION — *The proposed approach may be used to develop a population model that leverages both individual data and summary statistics.*

Background / Rationale

Motivation

- This modeling effort was originally motivated by a project to explore different clinical trial designs for Alzheimer's disease drug candidates via simulation.
- That required a longitudinal dose-response model for ADAS-cog suitable for simulating individual patient data.
- A longitudinal dose-response model for ADAS-cog change from baseline was previously developed by model-based meta-analysis of summary data [1], but it was not suitable for simulating individual patient data.
- Analysis of individual data from a small number of trials, though useful, would neglect the large body of evidence only available in the form of summary data.
- The desired solution: Simultaneous modeling of both summary and individual data.

But how can you rigorously combine such data in a model-based meta-analysis?

- Convert individual data to summary statistics and analyze as before
  - Same problem: can't simulate individual data from resulting model.
- For summary data treat each treatment arm like a super-patient and adjust only the residual variation for sample size.
  - Does not correctly adjust the inter-arm variation components of the model.
- Estimate the sampling distribution of summary statistics by simulation of missing individual data.
  - Very compute-intensive.
  - Not usually feasible as anything but an academic exercise.
- This led us to develop a new method.

Methods

Data summary

Summary data

- Post-baseline sample means and sample variances for ADAS-cog change from baseline from published sources
- Data set
  - Data from 55 studies / 81 treatment arms
    - 465 sample means
    - 263 sample variances

Individual patient data

- Results from two clinical trials
  - CP-457,920 dose-finding trial
    - 5 treatment arms / 196 patients:
      - Placebo: 41 patients
      - donepezil 5 mg qd: 33 patients
      - CP-457,920 30 mg qd: 44 patients
      - CP-457,920 60 mg bid: 39 patients
      - CP-457,920 120 mg bid: 39 patients
    - ADAS-cog change from baseline at 6 and 12 weeks
  - LEADe trial
    - 3 treatment arms / 613 patients
      - Placebo + donepezil 10 mg qd x 20 months: 317 patients
      - Atorvastatin + donepezil 10 mg qd x 18 months followed by placebo + donepezil 10 mg qd x 2 months: 219 patients
      - Atorvastatin + donepezil 10 mg qd x 20 months: 77 patients
    - ADAS-cog change from baseline every 3 months for 18 months

Modeling approach

- The model was first conceptualized in terms of the individual data model.
- The sampling distributions for the treatment means and variances were then derived from that individual data model.
- Initial model structure was adapted from the Ito et al model [1].
- Random effects structure included inter-trial and inter-unit variation (where unit = arm for summary data and unit = patient for individual data).
- Bayesian model fitting using WinBUGS 1.4.3
- Data management and analysis of MCMC samples using R
- Model evaluation primarily via graphical posterior predictive checking

Model for individual patient data

ADAS-cog change from baseline on the i^{th} occasion in the j^{th} patient in the k^{th} study:

$$
\begin{aligned}
\Delta ADAS_{ijk} &\sim N\left(\widehat{\Delta ADAS}_{ijk}, \sigma_k^2\right) \\
\widehat{\Delta ADAS}_{ijk} &= \alpha_{jk}\left(\frac{ADAS\left(0\right)_{jk}}{25}\right)^{\theta} t_{ijk} + E_{\text{placebo,ijk}} + \left(1 - I_{\text{placebo,jk}}\right) E_{\text{drug,ijk}} + \eta_{\text{intercept},jk} \\
E_{\text{placebo,ijk}} &= \beta\left(e^{-k_{el}t_{ijk}} - e^{-k_{eq}t_{ijk}}\right) \\
E_{\text{drug,ijk}} &= \left(\frac{D_{jk}}{D_{ref,jk}}\right)^{\gamma_{jk}} \frac{E_{\Delta,jk} e^{\eta_{\text{drug},k}} t_{ijk}}{ET_{50,jk} + t_{ijk}} \\
D_{ref,jk} &= \begin{cases} 5, \\ 24, \\ 6, \\ 120, \end{cases} \qquad E_{\Delta,jk} = \begin{cases} E_{\Delta,\text{donepezil}}, & \text{drug}_{jk} = \text{donepezil} \\ E_{\Delta,\text{galantamine}}, & \text{drug}_{jk} = \text{galantamine} \\ E_{\Delta,\text{rivastigmine}}, & \text{drug}_{jk} = \text{rivastigmine} \\ 0, & \text{drug}_{jk} = \text{CP-457,920} \end{cases} \\
ET_{50,jk} &= \begin{cases} ET_{50,\text{donepezil}}, \\ ET_{50,\text{galantamine}}, \\ ET_{50,\text{rivastigmine}}, \\ 1, \end{cases} \qquad \gamma_{jk} = \begin{cases} \gamma_{\text{donepezil}}, & \text{drug}_{jk} = \text{donepezil} \\ \gamma_{\text{galantamine}}, & \text{drug}_{jk} = \text{galantamine} \\ \gamma_{\text{rivastigmine}}, & \text{drug}_{jk} = \text{rivastigmine} \\ 0, & \text{drug}_{jk} = \text{CP-457,920} \end{cases} \\
\eta_{\text{intercept},jk} &\sim t\left(\eta_{\text{intercept,study},k}, \omega^2_{\text{intercept}}, df_{\text{intercept}}\right) \qquad \eta_{\text{intercept,study},k} \sim N\left(0, \psi^2_{\text{intercept}}\right) \\
\alpha_{jk} &\sim t\left(\alpha_{\text{study},k}, \omega^2_{\alpha}, df_{\alpha}\right) \qquad \alpha_{\text{study},k} \sim N\left(\widehat{\alpha}, \psi^2_{\alpha}\right) \\
\eta_{\text{drug},k} &\sim N\left(0, \psi^2_{\text{drug}}\right) \qquad \frac{1}{\sigma_k^2} \sim \text{gamma}\left(\alpha_\sigma, \alpha_\sigma \widehat{\sigma}^2\right)
\end{aligned}
$$

Model for sample means and variances

Modifications for sample mean and variance of ADAS-cog change from baseline on the i^{th} occasion in the j^{th} treatment arm in the k^{th} study:

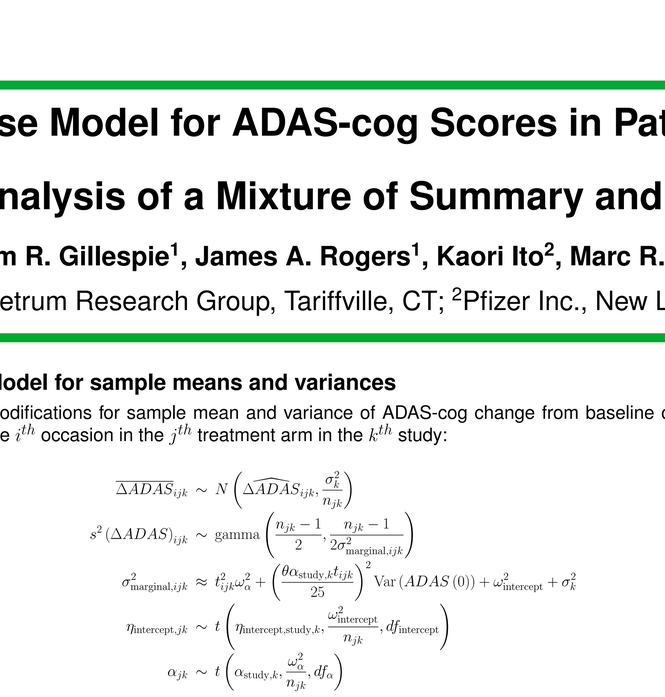
$$
\begin{aligned}
\overline{\Delta ADAS}_{ijk} &\sim N\left(\widehat{\Delta ADAS}_{ijk}, \frac{\sigma_k^2}{n_{jk}}\right) \\
s^2\left(\Delta ADAS\right)_{ijk} &\sim \text{gamma}\left(\frac{n_{jk}-1}{2}, \frac{n_{jk}-1}{2\sigma^2_{\text{marginal},ijk}}\right) \\
\sigma^2_{\text{marginal},ijk} &\approx t_{ijk}^2 \omega_\alpha^2 + \left(\frac{\theta \alpha_{\text{study},k} t_{ijk}}{25}\right)^2 \text{Var}\left(ADAS\left(0\right)\right) + \omega^2_{\text{intercept}} + \sigma_k^2 \\
\eta_{\text{intercept},jk} &\sim t\left(\eta_{\text{intercept,study},k}, \frac{\omega^2_{\text{intercept}}}{n_{jk}}, df_{\text{intercept}}\right) \\
\alpha_{jk} &\sim t\left(\alpha_{\text{study},k}, \frac{\omega^2_{\alpha}}{n_{jk}}, df_{\alpha}\right)
\end{aligned}
$$

Results

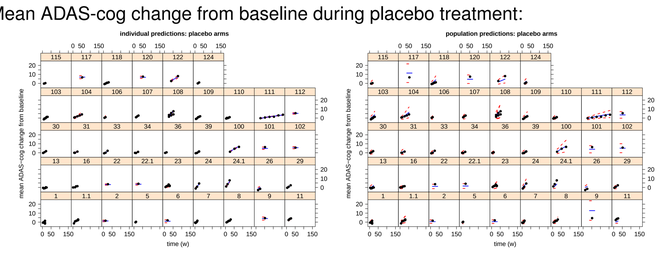
The results are based on 3 chains of 50,000 MCMC iterations each with 5,000 burn-in iterations per chain. The samples are thinned by 25 leaving a total of 5400 MCMC samples for subsequent calculations and inferences.

Comparison of model predictions to observed data

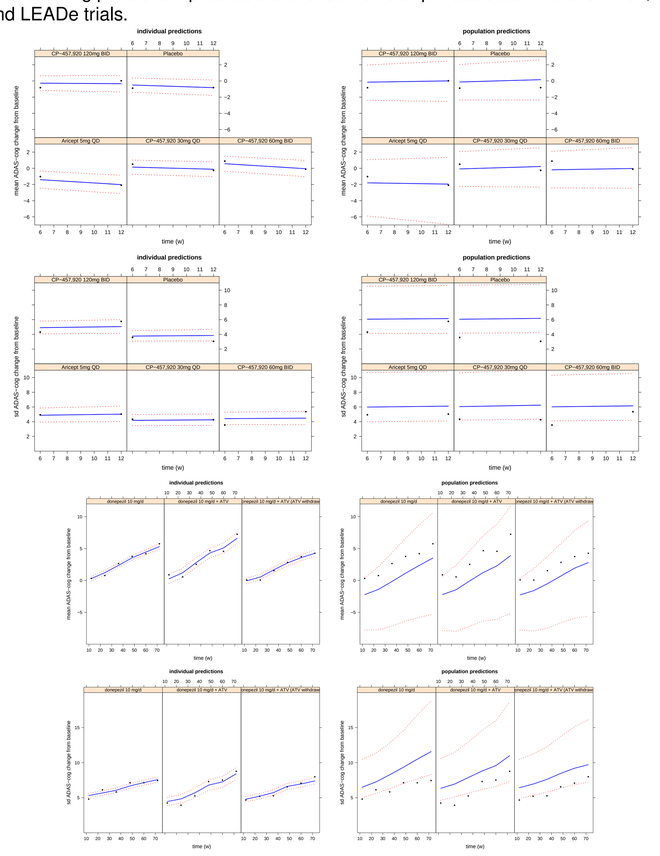
The following plots show predicted treatment mean ADAS-cog difference from placebo compared to observed values calculated from summary data. "Individual" predictions are posterior predictions (posterior median and 90% credible intervals) for hypothetical new observations in the same patients and studies. "Population" predictions are posterior predictions for hypothetical new observations in different patients and studies that share the same covariate values.



Mean ADAS-cog change from baseline during placebo treatment:



The following plots show predicted and observed sample statistics for the CP-457,920 and LEADe trials.



Conclusion

- The proposed approach may be used to develop a population model that leverages both individual data and summary statistics.
- When the individual data model is linear with respect to inter-patient random effects, the sampling distributions for treatment means and variances are derived exactly.
- When the individual data model is *not* linear with respect to inter-patient random effects, the sampling distributions for treatment means and variances are approximated in 3 senses:
  - The sampling distributions are approximated as normal for the mean and gamma for the variance.
  - The conditional expectation for the treatment mean is approximated using the individual data model in which the variances of the inter-arm random effects are sample size adjusted inter-patient variances.
  - The marginal variance is approximated via the delta method.
- Unlike other approaches used for model-based meta-analysis of longitudinal data, e.g., [2, 1], the proposed approach accounts for within arm correlation.
- It also accounts for the observed increase with time in the standard deviation of ADAS-cog change from baseline.
- Further work, e.g., analysis of simulated data sets, is needed to characterize the performance of the proposed method, particularly for models that are nonlinear with respect to the inter-patient random effects.
- This work is the basis of an open-source model sharing initiative for modeling Alzheimer's disease progression using ADAS-cog (OpenDiseaseModels.org).

References

[1] K Ito, M Rosario, S Ahadieh, B Corrigan, J French, T Fullerton, R Zhang, P Lockwood, Q Zhao, R Qiu, T Russell, T Tensfeldt. A disease progression meta-analysis model for cognitive deterioration with Alzheimers disease. *Clin Pharmacol Ther* 83: S40 (2008).

[2] JW Mandema, E Cox, J Alderman. Therapeutic benet of eletriptan compared to sumatriptan for the acute relief of migraine pain results of a model-based meta-analysis that accounts for encapsulation. *Cephalalgia* 25: 715725 (2005).

Appendix: General derivation of modeling approach

Linear case

This section describes the approach for a model that is linear with respect to the inter-patient and residual random effects, and has normally-distributed residual, inter-patient and inter-study variation.

Model for individual patient data

Dependent variable y_{ijk} on the i^{th} occasion in the j^{th} patient in the k^{th} study:

$$
\begin{aligned}
y_{ijk} &\sim N\left(\widehat{y}_{ijk}, \sigma_k^2\right) \\
\widehat{y}_{ijk} &= f\left(t_{ijk}, x_{jk}, \theta, \mathbf{H}_{jk}, \mathbf{K}_k\right) \\
&= f_0\left(t_{ijk}, x_{jk}, \theta, \mathbf{K}_k\right) + \sum_{m=1}^{n_{\mathbf{H}}} f_m\left(t_{ijk}, x_{jk}, \theta, \mathbf{K}_k\right) \eta_{mjk}
\end{aligned}
$$

where

x_{jk} ≡ independent variables for the j^{th} patient and k^{th} study, e.g., assigned treatment
θ ≡ model parameters
$\mathbf{K}_k = \{\kappa_{1k}, \kappa_{2k}, \cdots, \kappa_{n_{\mathbf{K}}k}\}$ = inter-study random effects for k^{th} study
$\sim N\left(0, \Psi\right)$
$\mathbf{H}_{jk} = \{\eta_{1jk}, \eta_{2jk}, \cdots, \eta_{n_{\mathbf{H}}jk}\}$ = inter-patient random effects for j^{th} patient in k^{th} study
$\sim N\left(0, \Omega\right)$ where Ω is a diagonal matrix

Modifications for sample mean and variance

Since $y_{ijk}|\mathbf{H}_{jk}, \mathbf{K}_k \sim N\left(\widehat{y}_{ijk}, \sigma_k^2\right)$, the sample mean $\overline{y}_{ijk}$ on the i^{th} occasion in the j^{th} treatment arm in the k^{th} study is also normally distributed:

$$
\overline{y}_{ijk} \sim N\left(\widehat{y}_{ijk}, \frac{\sigma_k^2}{n_{jk}}\right)
$$

where

$$
\begin{aligned}
\widehat{y}_{ijk} &= f\left(t_{ijk}, x_{jk}, \theta, \overline{\mathbf{H}}_{jk}, \mathbf{K}_k\right) \\
&= f_0\left(t_{ijk}, x_{jk}, \theta, \mathbf{K}_k\right) + \sum_{m=1}^{n_{\mathbf{H}}} f_m\left(t_{ijk}, x_{jk}, \theta, \mathbf{K}_k\right) \overline{\eta}_{mjk} \\
\overline{\eta}_{mjk} &\sim N\left(0, \frac{\omega_m^2}{n_{jk}}\right)
\end{aligned}
$$

In this case $\widehat{y}_{ijk}$ represents the expected value conditioned on treatment arm j and study k. Similarly the distribution of y_{ijk} conditioned only on study k is normally distributed, i.e., $y_{ijk}|\mathbf{K}_k \sim N\left(f_0\left(t_{ijk}, x_{jk}, \theta, \mathbf{K}_k\right), \sigma^2_{\text{marginal},ijk}\right)$. It follows that the normalized sample variance $\left(\left(n_{ijk}-1\right)s^2\left(y\right)_{ijk}\right) \Big/ \sigma^2_{\text{marginal},ijk}$ is $\chi^2\left(n_{ijk}-1\right)$ distributed or equivalently:

$$
s^2\left(y\right)_{ijk} \sim \text{gamma}\left(\frac{n_{jk}-1}{2}, \frac{n_{jk}-1}{2\sigma^2_{\text{marginal},ijk}}\right)
$$

where $\sigma^2_{\text{marginal},ijk}$ is the variance of y_{ijk} conditioned on study k. An expression in terms of the model parameters is derived below:

$$
\begin{aligned}
\sigma^2_{\text{marginal},ijk} &= \text{Var}\left(y_{ijk}|\mathbf{K}_k\right) \\
&= \text{Var}\left(\text{E}\left(y_{ijk}|\mathbf{H}_{jk}, \mathbf{K}_k\right)|\mathbf{K}_k\right) + \text{E}\left(\text{Var}\left(y_{ijk}|\mathbf{H}_{jk}, \mathbf{K}_k\right)|\mathbf{K}_k\right) \\
&= \sum_{m=1}^{n_{\mathbf{H}}} f_m\left(t_{ijk}, x_{jk}, \theta, \mathbf{K}_k\right)^2 \omega_m^2 + \sigma_k^2
\end{aligned}
$$

Nonlinear case

This section describes the approach for the more general case where the model may be nonlinear with respect to the inter-patient and residual random effects, and has normally-distributed residual, inter-patient and inter-study variation.

Model for individual patient data

Dependent variable y_{ijk} on the i^{th} occasion in the j^{th} patient in the k^{th} study:

$$
\begin{aligned}
y_{ijk} &\sim N\left(\widehat{y}_{ijk}, \sigma_k^2\right) \\
\widehat{y}_{ijk} &= f\left(t_{ijk}, x_{jk}, \theta, \mathbf{H}_{jk}, \mathbf{K}_k\right)
\end{aligned}
$$

where

x_{jk} ≡ independent variables for the j^{th} patient and k^{th} study, e.g., assigned treatment
θ ≡ model parameters
$\mathbf{K}_k = \{\kappa_{1k}, \kappa_{2k}, \cdots, \kappa_{n_{\mathbf{K}}k}\}$ = inter-study random effects for k^{th} study
$\sim N\left(0, \Psi\right)$
$\mathbf{H}_{jk} = \{\eta_{1jk}, \eta_{2jk}, \cdots, \eta_{n_{\mathbf{H}}jk}\}$ = inter-patient random effects for j^{th} patient in k^{th} study
$\sim N\left(0, \Omega\right)$ where Ω is a diagonal matrix

Modifications for sample mean and variance

Approximate equations for the sampling distributions of the sample means $\left(\overline{y}_{ijk}\right)$ and variances $\left(s^2\left(y\right)_{ijk}\right)$ are derived by first approximating the model using a first order Taylor series and then deriving the relationships as described above for the linear case. Begin by approximating $\widehat{y}_{ijk}$ for individual patients with a first order Taylor series where the inter-patient random effects (η's) are expanded about their expected values, i.e., 0:

$$
\begin{aligned}
\widehat{y}_{ijk} &= f\left(t_{ijk}, x_{jk}, \theta, \mathbf{H}_{jk}, \mathbf{K}_k\right) \\
&\approx \widehat{y}_{\text{approx},ijk} = f\left(t_{ijk}, x_{jk}, \theta, 0, \mathbf{K}_k\right) + \sum_{m=1}^{n_{\mathbf{H}}} f_{\eta_m}\left(t_{ijk}, x_{jk}, \theta, 0, \mathbf{K}_k\right) \eta_{mjk}
\end{aligned}
$$

where f_{η_m} is the derivative of f with respect to η_m. Proceeding as before the approximate equations used for fitting the sample means and variances follow.

$$
\begin{aligned}
\overline{y}_{ijk} &\sim N\left(\widehat{y}_{ijk}, \frac{\sigma_k^2}{n_{jk}}\right) \\
s^2\left(y\right)_{ijk} &\sim \text{gamma}\left(\frac{n_{jk}-1}{2}, \frac{n_{jk}-1}{2\sigma^2_{\text{marginal},ijk}}\right)
\end{aligned}
$$

where

$$
\begin{aligned}
\widehat{y}_{ijk} &= f\left(t_{ijk}, x_{jk}, \theta, \overline{\mathbf{H}}_{jk}, \mathbf{K}_k\right) \\
\overline{\mathbf{H}}_{jk} &\sim N\left(0, \frac{\Omega_m}{n_{jk}}\right) \quad \text{or equivalently} \quad \overline{\eta}_{mjk} \sim N\left(0, \frac{\omega_m^2}{n_{jk}}\right) \\
\sigma^2_{\text{marginal},ijk} &= \sum_{m=1}^{n_{\mathbf{H}}} f_{\eta_m}\left(t_{ijk}, x_{jk}, \theta, 0, \mathbf{K}_k\right)^2 \omega_m^2 + \sigma_k^2
\end{aligned}
$$

Application to the ADAS-cog model

The ADAS-cog model is further complicated by the use of t-distributions to describe the distributions of inter-patient random effects. The approach derived above is strictly valid only in the case where the inter-patient random effects are normally distributed. As a result the application of this method to the ADAS-cog model represents an additional approximation beyond that required to deal with the nonlinearity.

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