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Hierarchical Bayesian cognitive processing models to analyze clinical trial data

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Abstract Identifying disease-modifying treatment effects in earlier stages of Alzheimer's disease (AD)—when changes are subtle—will require improved trial design and more sensitive analytical methods. We applied hierarchical Bayesian analysis with cognitive processing (HBCP) models to the Alzheimer's Disease Assessment Scale—Cognitive subscale (ADAS-Cog) and MCI (mild cognitive impairment) Screen word list memory task data from 14 Alzheimer's disease AD patients of the Myriad Pharmaceuticals' phase III clinical trial of Flurizan (a γ-secretase modulator) versus placebo. The original analysis of 1649 patients found no treatment group differences. HBCP analysis and the original ADAS-Cog analysis were performed on the small sample. HBCP analysis detected impaired memory storage during delayed recall, whereas the original ADAS-Cog analytical method did not. The HBCP model identified a harmful treatment effect in a small sample, which has been independently confirmed from the results of other γ-secretase inhibitor. The original analytical method applied to the ADAS-Cog data did not detect this harmful treatment effect on either the full or the small sample. These findings suggest that HBCP models can detect treatment effects more sensitively than currently used analytical methods required by the Food and Drug Administration, and they do so using small patient samples.

Keywords: Small samples; Episodic memory; Short-term memory; Delayed recall; γ-Secretase inhibitors

1. Introduction

In Alzheimer's disease (AD), no Food and Drug Administration (FDA) clinical trial has successfully identified a disease-modifying treatment effect [1–4]. As AD trials expand to earlier stages where functional and cognitive abilities progress more slowly over many years, better trial designs and more sensitive analytical methods are becoming increasingly important.

One analytical method that may be more powerful involves combining hierarchical Bayesian analysis with models of how cognitive processes generate cognitive test scores. We refer to this method as hierarchical Bayesian cognitive process (HBCP) modeling. HBCP models belong to the class of generative models, which specify how the observed data are generated by jointly modeling the model's parameters and the data. The parameters of the HBCP model represent key components of the underlying cognitive processes involved in generating the word list memory (WLM) test scores. Once estimated, these cognitive processing parameters can be used to predict the observed item response data. These parameters can be influenced by other factors, including treatment, cognitive test used, biomarker levels, and potentially confounding covariates. To our knowledge,

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HBCP methodology has not been previously applied in AD research.

In this study, we compared an HBCP model of WLM task performance with the analytical method used in the randomized double-blind FDA clinical trial of 1649 AD patients treated with either placebo or the γ-secretase modulator Flurizan (Myriad Pharmaceuticals, Salt Lake City, UT). These two analytical methods were compared in their ability to detect treatment effects in a subsample of 14 AD subjects from the clinical trial. This small sample was chosen because these subjects had received both the Alzheimer's Disease Assessment Scale—Cognitive subscale (ADAS-Cog) and the MCI (mild cognitive impairment) Screen (MCIS) [5,6] WLM tasks, had ADAS-Cog total score data, and had item response data for the two WLM tests. This study had three objectives: (1) to determine whether the analytical method used for total score data versus that used for item response data differed in their ability to detect treatment effects, (2) to apply HBCP modeling to the ADAS-Cog and MCIS WLM item response data to determine whether either test was more sensitive in detecting treatment effects, and (3) to apply HBCP modeling to the MCIS WLM item response data to examine changes in memory performance before, during, and after the Flurizan trial.

2. Methods

2.1. Flurizan trial synopsis

The Myriad Pharmaceuticals' Flurizan phase III FDA clinical trial was a multicenter, randomized, double-blind, placebo-controlled trial enrolling 1684 mild AD patients at 133 trial sites in the United States between February 21, 2005, and April 30, 2008 [2]. Flurizan, 800 mg, or placebo was administered twice daily. Concomitant treatment with cholinesterase inhibitors and memantine was permitted. Patients were assessed for primary and secondary outcome measures at baseline and then 3, 6, 9, 12, 15, and 18 months later. The primary cognitive outcome was the change in the total score on the subscale of the ADAS-Cog (80-point version) from baseline to 18 months. The primary functional outcome was the Alzheimer Disease Cooperative Studies—Activities of Daily Living (ADCS-ADL) scale scores. Additional prespecified slope analyses explored the possibility of disease modification. The analysis included 1649 patients, of whom 1046 completed the trial. Using an intent-to-treat analysis, Flurizan had no beneficial effect on the coprimary outcomes based on least squares means (ADAS-Cog, 0.1 points change [95% confidence interval, 95% CI = −0.9 to 1.1]; $P = .86$; ADCS-ADL, −0.5 points change [95% CI = −1.9 to 0.9]; $P = .48$). The Clinical Dementia Rating scale (CDR) Sum of Boxes score was the only significant secondary outcome ($P = .046$) and indicated that the Flurizan group experienced a more severe decline in memory storage than the placebo group over the 18 months of the study (mean ± standard deviation of change in the CDR Sum of Boxes score: placebo, 2.43 ± 3.12; Flurizan, 2.91 ± 3.21).

2.2. Sample of the present study

The present study included all patients (n = 14) from the Shankle Clinic (Newport Beach, CA) who participated in the Flurizan trial. These patients had total ADAS-Cog score data in addition to item response data for the WLM tasks of the ADAS-Cog and the MCIS. Such data were not available for the full Flurizan trial sample. Eight of the 14 patients received placebo, and six received Flurizan. Table 1 compares the characteristics of each treatment group. Nonparametric tests (median test for ratio variables and Pearson χ^2 for ordinal or nominal variables) were used to determine whether the treatment groups differed in any of the characteristics examined.

2.3. Analysis of ADAS-Cog total score data

Analysis of the ADAS-Cog total score data was performed using the intent-to-treat population, which consisted of the sample of 14 patients. These patients received at least 1 dose of study medication. Participants initially randomized to the 400-mg group were pooled with the 800-mg group. A last-observation-carried-forward method was used to impute missing data for the main change-from-baseline analysis of each ADAS-Cog total score end point. A missing value was replaced with a value that was the same number of standard deviations (SDs) from the treatment group mean at that time point as that participant's last observed value (z score = [observed value − treatment group mean)/treatment group SD]. This imputation method accounts for AD being a progressive disease and for the data that may not be missing at

Table 1
Characteristics of the 14 Alzheimer's disease patients who participated in the Flurizan clinical trial

	All	Placebo	Flurizan	*P* value
Sample size*	14	8	6	.79
Age†, μ ± σ	73.2 ± 9.5	72.4 ± 7.9	74.4 ± 12.6	.42
% Female*	53.9%	50.0%	60.0%	.73
Education†, μ ± σ	14.8 ± 2.8	15.9 ± 2.9	13.2 ± 1.8	.10
Memory Performance Index score†, μ ± σ	36.9 ± 16.6	37.4 ± 17.9	36.3 ± 15.3	.57
% Functional Assessment Staging Test stage 2,3 (n)*	3 (21.4%)	3 (37.5%)	0 (0.0%)	.24
% Functional Assessment Staging Test stage 4 (n)*	11 (78.6%)	5 (62.5%)	6 (100%)	.24
Pretrial duration†, μ ± σ	24.1 ± 13.3	23.1 ± 13.0	25.5 ± 14.8	.59
Trial duration†, μ ± σ	16.5 ± 3.4	17.6 ± 1.1	15.2 ± 4.9	.47
Posttrial duration†, μ ± σ	20.5 ± 8.5	21.7 ± 8.5	19.0 ± 9.0	.59
Total duration†, μ ± σ	61.2 ± 19.2	62.3 ± 20.8	59.7 ± 18.6	.59

Nonparametric tests were used to determine whether the treatment groups differed in any of the characteristics examined.

*Pearson χ^2 nonparametric test was used for ordinal or nominal variables.

†Median nonparametric test was used for ratio or integer variables.