Study Design Factors and Patient Demographics and Their Effect on the Decline of Placebo-Treated Subjects in Randomized Clinical Trials in Alzheimer's Disease

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Objective: To gain insight into factors affecting the rate of decline in placebo-treated subjects participating in Alzheimer's disease (AD) clinical trials.

Data Sources: Studies were identified through a MEDLINE search using a combination of 2 strategies. The first strategy searched for the term *Alzheimer's disease* and was restricted to those publications that reported a randomized controlled trial in human adults. A second strategy searched for the terms *Alzheimer's disease* and *ADAS-Cog* and restricted the results to human adults.

Study Selection: Studies were included if they reported results from a prospective, placebo-controlled, double-blind, parallel group study and used the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) as a primary outcome measure and included patients with mild to moderately severe probable AD. A total of 69 trials were identified. Three studies were removed from the analysis because of anomalous results. Two data sets were analyzed: an "intent-to-treat" set (69 trials) and a "plausible" set (66 trials).

Data Extraction: Lead or senior author, year of publication, total and placebo sample size, the use of acetylcholinesterase, maximum and minimum Mini-Mental State Examination (MMSE) score allowed, mean MMSE score and mean age at baseline, percentage of female subjects, number of investigational sites, investigational treatment, the number of treatment arms and study evaluations, study duration, percentage of patients with the genotype APOE ε4+, and the mean and SD of the change from baseline on the ADAS-Cog were recorded from each study and from the placebo-treated group specifically.

Data Synthesis: Linear regression models were used to explore the relationship between the date of publication and patient demographics. Multiple linear regression was used to explore the contributions of patient demographics and study design variables to the change from baseline score on the ADAS-Cog. Analyses suggest that patients enrolling in trials are progressively older and that trials are getting progressively longer. Other patient demographics and study design variables have not changed over time. The duration of a study was the most consistent predictor of decline in placebo-treated subjects. Increased number of investigational sites, increased number of evaluations, and milder dementia severity at baseline were associated with a loss of decline in placebo-treated subjects.

Conclusions: Study duration was the only variable that predicted decline consistently, whereas the number of evaluations, the number of sites, and baseline MMSE score are inversely proportional with decline and should be taken into account when planning future clinical trials.

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The number of investigational agents and approved drugs with novel pharmacologic approaches reaching the clinic has increased.[1] Therapeutic clinical trials that generate data supporting the clinical efficacy of these agents, including those used in Alzheimer's disease (AD), appear to be increasing in volume, size, and cost. This increase in resource utilization is quite likely due to the scientific, logistical, and regulatory complexity of conducting clinical trials in the current research environment. Given the public health implications of AD, there are also economic pressures for investigators to recruit subjects into clinical trials in a shorter and more cost-efficient fashion and to work in regions where research costs are lower.[2,3]

Three relatively large AD clinical trials (phenserine,[4] galantamine CR,[5] and rosiglitazone[6]) failed to separate from placebo on 1 or more of their primary endpoints. These studies were adequately powered to detect clinically relevant responses, were technically well designed, and were conducted to good clinical practice standards.[7] For phenserine and galantamine, the failures were unprecedented, as both compounds have a clinically proven mechanism of action. The failure of these 3 studies appears to be driven by a lack of progression in the placebo-treated subjects. The deterioration of placebo-treated patients with AD has been a sine qua non of clinical trials in this patient population and critical to the approval of several medications. Since clinical trials for the symptomatic treatment of AD tend to have very similar designs,

a plausible explanation for these failures is that the population of subjects enrolled in monotherapy trials may have changed over time.

Being able to discriminate between a negative study (clear lack of efficacy) and a failed study (failure to separate from the control group) is crucial when considering future investment in the development of a compound. The simplest technique to ensure that a study is interpretable is to include an active control (if there is one available).[8,9] However, sponsors of AD trials generally do not include active controls because they assume that placebo-treated AD patients will decline in a predictable fashion. If this assumption is no longer reasonable, it is likely that promising compounds will end up on the shelf instead of in the clinic because of failed initial clinical studies.

In order to gain some insight into factors affecting the rate of decline in placebo-treated subjects participating in AD clinical trials, a retrospective analysis of publicly available data was conducted. In particular, exploratory analyses were conducted to explore whether certain baseline patient demographics and certain study design variables affect the rate of decline and whether there had been a change over time in selected patient demographics. The analyses were generally based on the following hypotheses: (1) Because more mildly affected subjects tend to progress more slowly,[10] higher Mini-Mental State Examination (MMSE) scores at baseline would predict less decline. (2) Because AD is an inexorably progressive disease, longer study duration would predict more decline. (3) Because studies requiring large numbers of investigational sites are likely to provide more variable data, larger numbers of investigational sites would blunt decline. (4) Because repeated study evaluations may be associated with sustained learning effects,[11] an increased number of evaluations would predict less decline.

METHOD

Studies were identified through a MEDLINE search using a combination of 2 strategies. The first strategy searched for the term *Alzheimer's disease* and was restricted to those publications that reported a randomized controlled trial in human adults. A second parallel strategy searched for the terms *Alzheimer's disease* and *ADAS-Cog* and restricted the results to human adults. The results of these 2 strategies were combined and manually scanned. Studies were included if they reported results from a prospective, placebo-controlled, double-blind, parallel group study and used the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) as a primary outcome measure. Furthermore, the studies needed to be in patients with mild to moderately severe probable AD.

The following data were recorded from each study and from the placebo-treated group specifically: lead or senior author, year of publication, total and placebo sample size, the use of acetylcholinesterase inhibitors, maximum and minimum MMSE score allowed, mean MMSE score and mean age at baseline, percentage of female subjects, number of investigational sites, investigational treatment, the number of treatment arms and study evaluations, study duration (weeks), percentage of patients with the genotype APOE ε4+, and the mean and SD of the change from baseline on the ADAS-Cog (SD was computed if the SEM was reported and vice-versa).

For those studies that provided the ADAS-Cog results in a graphical form, a simple linear interpolation was used to estimate the change from baseline for the placebo-treated group. For those studies that did not report a baseline MMSE score, the baseline ADAS-Cog score was converted to an equivalent MMSE score using a validated regression equation.[12] For those studies that did not explicitly report the number of investigational sites, this datum was estimated by counting the number of investigational sites acknowledged in the publication. The use of acetylcholinesterase inhibitors and the minimum and maximum allowed MMSE scores were not included in analyses due to the lack of variability in the data, and the proportion of APOE ε4+ subjects was not included in the analyses because only a few studies reported proportion of APOE ε4+ status, precluding any meaningful analysis.

The year of publication was used as an indicator of the approximate time period when a study was being conducted. A series of simple linear regressions was used to evaluate the relationship between the date of publication and patient demographics. Four backward multiple regression analyses were performed to explore which factors contributed to the change from baseline score on the ADAS-Cog (delta). Variables with nominal p values > .15 were removed from the regression models. The dependent variable was the change from baseline on the ADAS-Cog, and the independent variables included patient demographics (mean age, mean MMSE score, and proportion of females) and study variables (year of publication, number of treatment arms, number of evaluations, and number of investigational sites). Because of the potentially variable lag between study conduct and the date of publication and bias toward reporting positive studies faster than negative ones, subsequent analyses excluded the publication date. A third analysis was conducted to control for the effect of a single outlier in the study duration data. This analysis was modeled after the second analysis but excluded the study by van Gool.[13] In order to explore a model expected to be representative of future symptomatic monotherapy clinical trials, a fourth analysis replicated the second analysis but included only studies from 12 to less than 52 weeks in duration. Because higher ADAS-Cog scores indicate more severe impairment, positive slopes (β) indicate a factor associated with more rapid decline whereas negative slopes indicate factors associated with slower decline.

Number Cruncher Statistical Systems (NCSS), 2004 (Kaysville, Utah) was used to conduct all statistical analyses. Since all analyses are exploratory, no corrections for multiple comparisons were applied. Nominal significance was set at $p < .05$. Because studies with larger sample sizes are expected to provide more accurate estimates of disease progression, all regression analyses were weighted by the sample size of the placebo group.[14]

A total of 69 trials (Table 1) were identified.[4–6,13,15–79] After a manual review of the study designs and a visual inspection of the data, 3 studies[25,26,66] were identified as having anomalous results. Two data sets were therefore analyzed: an "intent-to-treat" (ITT) set that included data from all 69 trials and a "plausible" set that included all data except for the 3 studies mentioned above.

RESULTS

The studies by Akhondanzeh[25,26] were excluded for the following reasons: (1) the differences in response detected in each study (~13 ADAS-Cog–point difference between treatment groups) are implausible given the putative cholinergic mechanism of action of these herbal extracts; (2) the lack of any cholinergic side effects, given the putative cholinomimetic mechanism of action of both extracts; (3) methanol extracts from *Salvia officinalis* have been shown to have affinity for benzodiazepine receptors[80]; (4) *Melissa officinalis* has been reported to have sedating and calming effects, negative effects on cognition, and very weak affinity for cholinergic receptors[81]; and finally, (5) the results from these 2 studies (in terms of the time course for the ADAS-Cog and Clinical Dementia Rating-Sum of Boxes and side effect profile) are nearly identical in spite of the fact that herbal extracts tend to vary widely in terms of their affinity for cholinergic receptors.

The study by Weyer[66] was excluded for the following reasons: (1) the improvements in the ADAS-Cog score in the placebo-treated group (4.5 points) is implausible given the natural history of AD and the duration of the study; (2) the effect size seen in the 90-mg arm (6.5 points) is implausible given the pharmacology of idebenone; (3) the magnitude of improvement in the placebo group increased in proportion to baseline severity (ADAS-Cog score ≥ 20: 5.3 points, ADAS-Cog score ≥ 50: 7.9 points), which is another biologically implausible effect; and (4) the treatment effects noted in this study were not replicated in a later study.

Descriptive statistics from the 69 studies are displayed in Table 2 and exploratory scatter plots of patient demographics and study design variables by year of publication are displayed in Figures 1 and 2. Please note that Figure 2 uses a logarithmic y-axis in order to present the study design variable data in a single graph. With regard to patient demographics, scatter plots for both data sets suggest that age has increased during the period covered by this review but that the mean baseline MMSE score and the proportion of female subjects have not. In terms of study design variables, the number of treatment arms appears to be relatively constant over time, whereas the duration of studies, the number of evaluations, and the number of sites vary considerably over time.

Effect of Date of Publication on Subject Demographics

Linear regression analyses detected a statistically significant positive correlation between the year of publication and mean age at baseline (ITT sample: $\beta = 0.399$, $N = 69$, $t = 3.99$, $p = .0002$; plausible sample: $\beta = 0.393$, $N = 66$, $t = 3.825$, $p = .0003$). No trends were detected between the year of publication and the mean MMSE score at baseline (ITT sample: $p = .289$, plausible sample: $p = .324$) or in the proportion of female subjects in the studies (ITT sample: $p = .35$, plausible sample: $p = .25$).

Effect of Date of Publication on Study Design Variables

A series of simple regression analyses detected a statistically significant positive correlation between the date of publication and the duration of a study (ITT sample: $\beta = 1.032$, $N = 69$, $t = 2.17$, $p = .034$; plausible sample: $\beta = 1.059$, $N = 66$, $t = 2.16$, $p = .034$) but failed to detect correlations with other study design variables.

Effects of Subject Demographics and Study Design Variables on Symptomatic Progression: Multiple Regression Analyses

Analysis 1 (all variables included). Brief description: This analysis included all of the subject demographics, study design variables, and year of publication as predictive variables (ITT sample: $N = 69$, adjusted $R^2 = 0.61$; plausible sample: $N = 66$; adjusted $R^2 = 0.764$).

In the ITT sample, the result of this multiple regression analysis indicates that only the duration of the clinical trial was a statistically significant contributor to the change from baseline ($\beta = 0.135$, $t = 10.35$, $p < .001$). In the plausible sample, the result of this multiple regression analysis indicates that the year of publication ($\beta = –0.084$, $t = –2.08$, $p = .042$), study duration ($\beta = 0.145$, $t = 14.06$, $p < .001$), and the number of study evaluations ($\beta = –0.35$, $t = –3.01$, $p = .004$) were statistically significant contributors to the change from baseline and that the number of sites ($\beta = –0.01$, $t = –1.72$, $p = .09$) trended towards significance. The analysis of variance (ANOVA) for the regression model was statistically significant ($F = 53.71$, $p < .001$).

Analysis 2. Brief description: This analysis included all of the subject demographics and study design variables but due to publication lags, excluded the year of publication as a predictive variable (ITT sample: $N = 69$,

Table 1. Demographic Information From the 69 Studies That Met Initial Literature Search Criteria

Trial	Year	Duration, wk	N	Arms, No.	Sites, No.	Evaluations, No.	Mean Age, y	Mean MMSE Score	Female, %	Delta*
Memantine[79]	2006	24	403	2	42	6	77.0	17.2	57.4	1.1
Cerebrolysin[15]	2006	24	279	4	3	4	73.9	19.8	65.5	2.27
Rosiglitazone[6]	2006	26	122	4	67	4	71.8	21.00	63.0	–0.4
Atorvastatin[16]	2005	52	31	2	1	5	78.9	20.50	35.5	4
Ginkgo biloba[17]	2005	26	513	3	44	5	77.5	18.2	52.0	0.9
Rivastigmine[18]	2005	52	20	2	1	5	73.4	13.20	55.0	4.45
Galantamine[5]	2005	26	320	3	73	5	76.3	18.08	64.0	1.3
Phenserine[4]	2005	26	76	3	24	5	74.6	19.00	64.0	0.2
Galantamine[19]	2004	16	66	4	17	2	76.8	15.40	75.8	4.7
Donepezil[20]	2004	24	57	2	17	5	75.1	24.30	60.0	0.5
Colostrinin[21]	2004	15	52	2	6	2	72.1	20.00	67.0	5.3
Rofecoxib[22]	2004	52	346	2	31	6	75	21.00	52.0	5.44
Doxycycline/rifampin[23]	2004	24	50	2	5	3	75.9	19.10	50.0	2.9
Rofecoxib[24]	2003	52	111	3	40	6	73.8	20.80	55.9	5.7
Salvia officinalis[25]	2003	16	15	2	3	9	72.8	19.30	40.0	5.53
Melissa officinalis[26]	2003	16	15	2	3	9	73.7	18.03	42.9	5.6
Clioquinol[27]	2003	36	16	2	1	5	72.5	18.76	47.0	6.5
Idebenone[28]	2003	52	129	4	39	4	74.9	20.50	51.0	6.3
Choline alfoscerate[29]	2003	24	129	2	5	3	71.7	17.60	73.2	2.9
Donepezil[30]	2003	24	33	2	2	5	72.4	19.00	70.0	3.2
DHEA[31]	2003	24	30	2	9	3	77.2	21.90	47.0	1.4
Nimesulide[32]	2002	12	19	2	1	2	74	22.70	47.0	–0.5
Ondansetron[33]	2002	24	64	3	22	3	73.2	19.30	58.0	0.6
Cerebrolysin[34]	2002	24	95	2	14	4	71.2	20.90	56.0	1.02
Galantamine[35]	2001	12	125	2	43	3	74.6	19.60	53.6	0.7
Cerebrolysin[36]	2001	16	70	2	9	4	73.5	17.50	51.4	1.1
Hydroxychloroquine[13]	2001	72	86	2	4	3	70.7	22.49	54.0	8.1
Galantamine[37]	2001	12	87	4	8	3	74.2	18.70	59.0	1.6
Estrogen[38]	2000	16	21	2	5	3	78	19.00	100.0	0.5
Donepezil[39]	2000	24	112	2	54	7	69.4	16.60	66.0	0.11
Prednisone[40]	2000	52	69	2	22	5	72.3	22.00	50.7	6.3
Eptastigmine[41]	2000	25	114	3	26	4	72.3	17.80	66.0	2.92
Galantamine[42]	2000	24	213	2	33	4	75.3	19.20	61.5	2
Galantamine[43]	2000	20	286	4	57	4	77.1	17.70	62.2	1.7
Acetyl-L-carnitine[44]	2000	52	116	2	31	3	58	20.21	47.0	7.5
Lu 25-109[45]	2000	24	126	4	28	4	76	20.10	56.0	1.16
Physostigmine[46]	2000	12	93	2	36	3	71.4	18.40	33.0	1.06
Galantamine[47]	2000	24	215	3	86	4	72.7	19.30	61.3	2.4
Donepezil[48]	1999	24	274	3	82	5	71	20.00	55.0	1.5
Metrifonate[49]	1999	26	203	3	71	5	72	18.70	65.5	1.5
Physostigmine[50]	1999	24	44	3	27	4	69	18.60	45.5	–1.4
Metrifonate[51]	1999	26	87	2	22	5	74.5	18.70	67.8	2.89
Metrifonate[52]	1999	6	133	3	15	4	75	18.50	54.1	0.5
Eptastigmine[53]	1999	24	164	3	36	3	70.8	17.00	66.0	2.7
Rivastigmine[54]	1999	26	239	3	45	4	72	19.90	59.0	1.45
Citicoline[55]	1999	12	17	2	NA	2	73	16.39	64.7	0.25
Misoprostol[56]	1999	25	15	2	1	4	73.9	17.80	47.0	1.93
Physostigmine CR[57]	1999	24	117	3	24	4	73.8	18.90	47.9	2.6
Rivastigmine[58]	1998	26	235	3	22	4	73	19.70	59.0	4
Eptastigmine[59]	1998	25	105	3	26	4	68.3	18.30	70.0	3
Metrifonate[60]	1998	26	24	2	1	4	71.7	19.80	50.0	1.67
Metrifonate[61]	1998	26	135	2	23	4	73.7	19.40	54.5	2.5
Metrifonate[62]	1998	12	120	4	27	5	72	NA	47.5	0.5
Donepezil[63]	1998	24	162	3	20	5	72.6	19.20	61.0	1.82
Donepezil[64]	1998	12	153	3	23	5	74	19.80	61.0	0.4
Linopirdine[65]	1997	26	189	2	20	7	71.5	19.60	53.0	3
Idebenone[66]	1997	26	100	3	6	4	70	18.10	69.0	–4.5
Sabeluzole[67]	1997	48	33	3	2	5	70.1	18.5	84	6.7
Xanomeline[68]	1997	28	83	4	17	5	75	19.80	57.0	1.35
Metrifonate[69]	1996	12	23	2	1	2	72.3	19.30	39.1	1.1
Besipirdine[70]	1996	12	91	3	15	4	71.1	18.50	51.0	1.33
Donepezil[71]	1996	12	40	4	10	6	70.6	18.20	52.5	0.7
Physostigmine CR[72]	1996	6	183	2	40	4	69.1	18.00	49.0	0.63
Acetyl-L-carnitine[73]	1996	52	212	2	24	5	71	19.60	55.0	7
Velnacrine[74]	1996	6	152	2	17	2	71.5	16.82	58.0	–1
BMY-21502[75]	1996	12	35	2	1	4	72	23.50	59.4	–0.5
Velnacrine[76]	1995	24	152	3	13	6	73.3	17.90	65.0	1.28
Tacrine[77]	1994	30	181	4	33	6	72.7	18.20	53.0	2
Tacrine[78]	1992	12	77	6	23	5	71	18.2	49.0	1.0

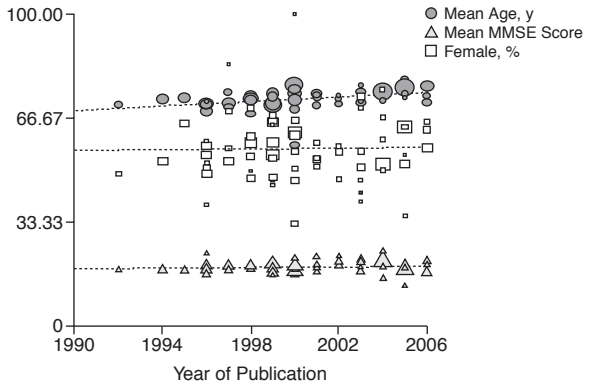
*Delta: Change from baseline on the Alzheimer's Disease Assessment Scale-Cognitive subscale (a positive number denotes clinical worsening).
Abbreviations: DHEA = dehydroepiandrosterone, MMSE = Mini-Mental State Examination, NA = not available.

Table 2. Descriptive Statistics

Variable	No. of Studies	Mean	Median	Standard Deviation	Minimum	Maximum
Year of publication	69	2000.20	2000.00	3.23	1992	2006
Duration, wk	69	25.36	24.00	13.50	6	72
Placebo, N	69	112.04	100.00	79.01	12	346
Total, N	69	326.55	300.00	235.23	30	978
Arms, No.	69	2.70	2.00	0.85	2	6
Sites, No.	69	23.19	22.00	20.71	1	86
Evaluations, No.	69	4.35	4.00	1.42	2	9
Mean age, y	69	72.94	72.80	2.91	58	78.9
Mean MMSE score	68	19.10	19.00	1.77	13.2	24.3
Female, %	69	0.57	0.56	0.11	0.33	1.0
Delta*	69	2.26	1.60	2.36	–4.5	8.1

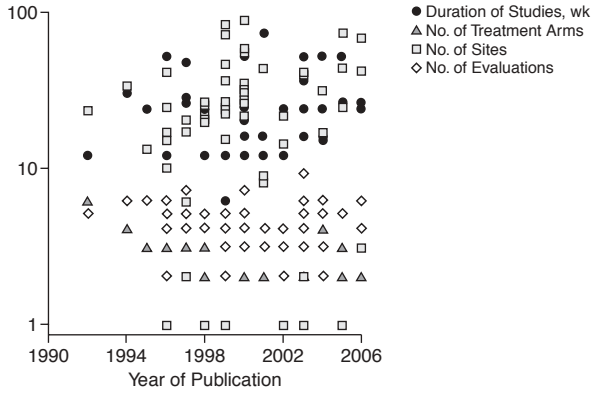
*Change from baseline on the Alzheimer's Disease Assessment Scale-Cognitive subscale.
Abbreviation: MMSE = Mini-Mental State Examination.

Figure 1. Scatter Plots of Patient Demographics (mean age, mean Mini-Mental State Examination [MMSE] score, and proportion of females) by Year of Publication[a]



[a]Plot-point size is proportional to the size of the placebo-treated population. Regression lines are least squares estimates.

Figure 2. Scatter Plots of Study Design Factors (arms, sites, evaluations, and duration) by Year of Publication[a]



[a]Please note the y-axis is logarithmic.

adjusted $R^2 = 0.61$; plausible sample: N = 66, adjusted $R^2 = 0.75$).

In the ITT sample, the result of this multiple regression analysis indicates that only the duration of the clinical trial was a statistically significant contributor to the change from baseline ($\beta = 0.135$, $t = 10.25$, $p < .001$). In the plausible sample, the result of this multiple regression analysis indicates that study duration ($\beta = 0.136$, $t = 13.47$, $p < .001$), study sites ($\beta = –0.0125$, $t = –2.18$, $p = .034$), and the number of study evaluations ($\beta = –0.285$, $t = –2.39$, $p = .02$) were statistically significant contributors to the change from baseline. The ANOVA for the regression model was statistically significant ($F = 51.5$, $p < .001$).

Analysis 3. Brief description: This analysis excluded the publication date and the study by van Gool,[13] as it is a statistical outlier in terms of study duration (ITT sample: N = 68, adjusted $R^2 = 0.57$; plausible sample: N = 65, adjusted $R^2 = 0.739$).

In the ITT sample, the result of this multiple regression analysis indicates that only the duration of the clinical trial was a statistically significant contributor to the change from baseline ($\beta = 0.138$, $t = 9.4$, $p < .001$). In the plausible sample and consistent with the previous analysis, this analysis indicates that study duration ($\beta = 0.142$, $t = 12.81$, $p < .001$), the number of investigational sites ($\beta = –0.013$, $t = –2.31$, $p = .02$), and number of evaluations ($\beta = –0.327$, $t = –2.67$, $p = .0098$) were statistically significant contributors to change from baseline. The ANOVA for the regression model was statistically significant ($F = 49.26$, $p < .001$).

Analysis 4. Brief description: This analysis included studies from 12 to less than 52 weeks in duration as a representative range for symptomatic studies. The publication date was excluded (ITT sample: N = 57, adjusted $R^2 = 0.014$; plausible sample: N = 53, adjusted $R^2 = 0.25$).

In the ITT sample, none of the independent variables were statistically significant contributors to the change from baseline on the ADAS-Cog. In the plausible sample, study duration ($\beta = 0.108$, $t = 3.56$, $p = .0008$), the number of evaluations ($\beta = –0.366$, $t = –2.66$, $p = .011$), and

number of investigational sites ($\beta = -0.014$, $t = -2.28$, $p = .027$) were all statistically significant predictors of the change from baseline. The baseline MMSE score now approaches statistical significance ($\beta = -0.202$, $t = -1.87$, $p = .067$), with higher baseline MMSE scores predicting slower decline. The ANOVA for the regression model was statistically significant ($F = 5.23$, $p = .0014$).

DISCUSSION

The analyses reported here suggest that the mean age of subjects in clinical trials has increased over the 14-year period spanned by the studies included in this report. The increasing age may be explained by various factors, including increased participation of elders in clinical research and the general aging of the population.[82] One explanation for the stronger effect of age and apparent lack of effect on the MMSE score may be that inclusion criteria in clinical studies are more restrictive regarding the MMSE score than age. The effect on age and MMSE score needs to be interpreted with caution since some studies[13,38,44] were designed to study effects in specific subsets of patients and because some studies were exploratory studies. Subjects enrolling in exploratory studies are likely to be younger and more mildly affected than subjects in Phase III studies given the more complicated and invasive nature of exploratory studies.

The multiple regression analyses indicate that study duration is the only factor that consistently predicts a decline in placebo-treated subjects. The same regression models using the plausible data set (using 66 out of 69 studies) suggest that larger number of sites and number of study evaluations predict a reduced decline in placebo-treated subjects. This effect appears to be robust since it is not affected by the span of time covered in the publication factor and is not affected by the removal of the study with the longest duration. The year of publication had a statistically significant negative effect on the change from baseline on the ADAS-Cog score in analysis 1, supporting the idea that, in the context of other variables, there has been a loss in the decline of placebo-treated subjects over time. This result needs to be interpreted with caution because the lag between study conduct and publication is variable and because of a likely publication bias toward publishing studies with positive outcomes more rapidly than those that fail.

Consistent with the initial working hypotheses, these analyses suggest that as the number of investigational sites in a study goes up, the magnitude of decline in the placebo-treated group goes down. Using data from the studies included in this review, there appears to be a very strong relationship between the size of a study and the number of sites it uses. One would expect larger studies (and by inference studies with more sites) to provide a more precise estimate of the rate of decline. However, the analyses being discussed here are not looking at the precision of the estimate but rather its accuracy. It is plausible that by increasing the number of sites, the heterogeneity of patients, investigators, and raters is also increased and leads to a loss of accuracy. In order to untangle the effect of study size from that of site number, one would have to conduct an experiment in which studies of equal size are conducted with a range of investigational sites and vice-versa.

The results of the regression analyses also suggest that increased number of evaluations were associated with a loss of decline. By analogy to the argument about the effect of increased number of sites, one could certainly argue that more evaluations are likely to yield more precise estimates of the rate of decline. However, an analysis exploring the correlation between the SEM of the change from baseline on the ADAS-Cog and the number of study evaluations failed to detect any significant correlation, suggesting that increasing numbers of evaluations are not associated with increased precision. One must then consider that repeated testing creates sustained learning effects that affect the accuracy of the estimate. Study sponsors rely on the placebo group and the use of alternate forms to control for learning or practice effects. However, it is unclear if the learning or practice effects are constant or if the use of alternate forms eliminates these effects.[83] The neuropsychological literature is replete with recommendations to use alternate versions of neuropsychological batteries in order to minimize learning and practice effects.[84] It is possible that clinical researchers in AD believe that practice or learning effects in subjects participating in AD studies are not relevant given their obligate amnestic deficit; however, the results of these analyses and a previous study suggest otherwise.[11]

Lastly, one has to take into consideration that the current practice in these types of trials is to evaluate patients at fixed intervals such that longer trials inevitably have more evaluations. This would be particularly difficult to interpret if the duration of studies and the number of evaluations were tightly correlated and predicted effects in the same direction. In the case of these studies, the correlation between study duration and number of evaluations, albeit statistically significant ($t = 2.33$, $p = .023$), is relatively weak ($R^2 = 0.075$) and predicts effects in opposite directions.

The results of the analyses of studies ≥ 12 and < 52 weeks long using the plausible data set are of particular interest. Within these analyses, the baseline MMSE score emerged as a negative predictor of decline in the placebo-treated population. The finding that milder severity at baseline predicts less decline is not surprising and lends credence to the validity of the remainder of the analysis and to the notion that there has been a gradual loss in the rate of placebo decline over time.[85]

Several limitations should be considered when interpreting the results of this review. The retrospective and exploratory nature of these analyses should lead the reader to

interpret the results with caution. Determining which studies represented anomalous results was a post hoc event for which the author is solely responsible. With regard to the validity of the data, one of the assumptions underpinning some of the analyses is that the year of publication approximates the period of time during which the study was being conducted. Unfortunately, only a few of the studies reported in the literature disclose when the study started and finished. Based on some of the studies included in this report, publication lags ranged from 3 to 7 years with a clear separation between those studies that were positive and those that were not, consistent with a known publication bias.[86]

Another limitation relates to the reporting of the distribution of research sites. The heterogeneous reporting of the number and distribution of sites participating in a clinical trial precludes analyses about whether the total number of sites or the number of sites in a given region is the better indicator of progression. Because of regional variations in patient care, caregiving systems, access to medications, and expertise in clinical research, more information about the distribution of sites is necessary to control for these differences in the design and conduct of studies and in the selection and training of investigators and raters. It is also important to interpret the results of this retrospective study with caution in the light of the known publication bias against the publication of negative or failed studies. It is likely that there are a number of substantial (in terms of size or duration) failed studies that have never been reported in the peer-reviewed literature. The advent of clinical trial registries and the requirement to publish results regardless of outcome should rapidly reduce the number of these "stealth" studies.

Future clinical trials in AD may benefit from the use of these data to model the predicted placebo decline. Specifically, power and sample size calculations need to take into account the potential for slower decline in placebo-treated patients. Study sponsors may find these data useful as a way to verify that a placebo-treated population did not behave anomalously. Finally, analyses such as these would be greatly enhanced if study sponsors agreed to report certain patient demographics in a uniform fashion. Items such as a family history of AD, completion of a certain level of education, prior exposure to antidementia compounds, and nutritional status are easy to collect and constitute only a small subset of factors that can influence response to therapy.[87,88]

The results of these analyses call for study sponsors to be more transparent and judicious about the duration, number of sites, and number of evaluations required for clinical trials. The desire to compensate for slow enrollment in clinical trials in AD by increasing the number of investigative sites may result in an underpowered study. Study sponsors should consider recruitment techniques and collaborative approaches with clinical investigators to reduce the number of clinical sites required for a given study. Likewise, study sponsors should investigate novel testing techniques to reduce learning and practice effects.[89]

Drug names: atorvastatin (Lipitor), donepezil (Aricept), doxycycline (Oracea, Monodox, and others), estrogen (Premarin, Cenestin, and others), galantamine (Razadyne), hydroxychloroquine (Plaquenil and others), memantine (Namenda), misoprostol (Cytotec and others), ondansetron (Zofran and others), rifampin (Rimactane, Rifadin, and others), rivastigmine (Exelon), rosiglitazone (Avandia), tacrine (Cognex).

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Alzheimer's Disease and Related Disorders section. Please contact Eric M. Reiman, M.D., at Eric.Reiman@bannerhealth.com.