ORIGINAL ARTICLE

Extended-Release Physostigmine in Alzheimer Disease

A Multicenter, Double-blind, 12-Week Study With Dose Enrichment

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Background: The efficacy of extended-release physostigmine salicylate, an acetylcholinesterase inhibitor, was evaluated in 850 subjects with mild-to-moderate Alzheimer disease (AD) in a multicenter trial.

Methods: Subjects initially entered a dose-enrichment phase in which they received 1 week each of physostigmine salicylate, 24 mg/d and 30 mg/d, and daily placebo. Among the subjects who completed this phase, 35.9% responded to physostigmine treatment, whereas 62.4% were considered nonresponders, and 1.6% could not be evaluated because of missing data. After a 4-week placebo-washout phase, 176 responder subjects were randomized to receive their best dose of physostigmine or placebo in a 12-week double-blind phase. Primary efficacy measures included the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog), the Clinician's Interview-Based Impression of Change With Caregiver Input (CIBIC+), and the Clinical Global Impression of Change (CGIC).

Results: In the intent-to-treat analysis of the double-blind phase, physostigmine-treated subjects scored −2.02 points better than placebo-treated subjects on the ADAS-Cog ($F_{1,167} = 6.42$ [$P = .01$]) and 0.33 points higher on the CIBIC+ ($F_{1,150} = 5.68$ [$P = .02$]). No significant improvement was observed on the CGIC or the secondary outcome measures. Nausea and vomiting were experienced by 47.0% of all physostigmine-treated subjects during the double-blind phase.

Conclusions: Physostigmine demonstrated a statistically significant benefit compared with placebo on a clinical global rating of change and an objective test of cognitive function. Given the frequency of gastrointestinal side effects, the role of this agent in clinical use remains to be determined.

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ALZHEIMER DISEASE (AD) is a progressive neurodegenerative disease that affects an estimated 4.5 million Americans.[1] It exacts a formidable emotional and financial toll on patients, caregivers, and society—with annual treatment costs in the United States as high as $100 billion.[2] Although the etiology of AD remains unknown, several lines of evidence have implicated a decline in central cholinergic neurotransmission as a critical event in cognitive dysfunction in AD. Postmortem brains with AD demonstrate an extensive loss of cholinergic neurons in the nucleus basalis of Meynert that project widely to neocortex, amygdala, and hippocampus.[3,4] Reduced activity of cortical choline acetyltransferase, the enzyme that synthesizes acetylcholine, correlates with the number of senile plaques and with cognitive impairment in patients with AD.[5]

Physostigmine reversibly inhibits the catabolic enzyme acetylcholinesterase (AChE), thereby augmenting central cholinergic neurotransmission. In animal studies, physostigmine improves memory in aged primates[6] and in primates with scopolamine-induced amnesia.[7] In numerous small clinical trials in subjects with AD, physostigmine has demonstrated improved cognitive function.[8-10] Two other AChE inhibitors (AChEIs), tacrine hydrochloride[11-13] and donepezil hydrochloride,[14] are now available in the United States for the treatment of AD. Recently, other AChEIs[15,16] have been shown to improve cognitive and global function in large-scale trials, broadly demonstrating the efficacy of AChE inhibition in AD.

The development of physostigmine as a potential treatment for AD has been hindered by its extensive first-pass metabolism and its short plasma half-life (approximately 30 minutes). A new extended-release formulation of physostigmine salicylate (Synapton) yields sustained blood levels,[17] permitting twice-daily dosing. A previous, large, multicenter

SUBJECTS AND METHODS

SUBJECTS WITH AD

Subjects with AD were recruited at 36 US centers (listed in the acknowledgment section) using a combination of clinical referral and advertising. Subjects underwent evaluation using clinical interview, mental status assessment, physical and neurologic examinations, laboratory studies, and neuroimaging. All participants met the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association[19] for probable AD. Subjects were required to be aged 45 years or older and to have a Mini-Mental State Examination (MMSE) score[20] from 10 to 26, and a modified Hachinski Ischemia Scale score[21] of no more than 4. All subjects had a reliable caregiver to ensure compliance with the protocol and were in generally good physical health for age. Subjects who required daily medications with intrinsic central nervous system activity or who had received any investigational drug within the previous 30 days were excluded. Informed consent was obtained from each subject with AD and the caregiver or legal guardian. This study was approved by the institutional review board of each of the 36 centers that contributed subjects.

STUDY DESIGN

The design consisted of a 3-week dose-enrichment phase, a 4-week placebo-washout phase, and a 12-week double-blind phase (**Figure 1**). During the dose-enrichment phase, subjects with AD received 1 week each of placebo and 24 and 30 mg/d of physostigmine salicylate. Physostigmine was given twice daily (bid) in a double-blind randomized sequence. Subjects who did not complete at least 1 week of physostigmine (at either dose level) and one week of placebo were discontinued from the study. As previous studies[18] have suggested that only a subset of subjects with AD benefit from physostigmine treatment, and that those who do may require individualized dosing, this dose-enrichment design was used to preselect potential physostigmine responders and their optimal dose.

Following the dose-enrichment phase, all subjects were treated with placebo for 4 weeks in a single-blind fashion (placebo-washout phase; subjects were not told about this period). This interval was designed to serve as a washout period for the dose-enrichment phase and thus to provide baseline measurements for the double-blind phase. It also permitted sufficient elapsed time to identify subjects responsive to physostigmine based on analysis of results from the dose-enrichment phase. Subjects were considered responders if they had a best dose of physostigmine, defined as a reduction of at least 3 points on the cognitive subscale of the Alzheimer Disease Assessment Scale (ADAS-Cog),[22] when the most effective tolerated dose of physostigmine was compared with placebo during the dose-enrichment phase. At the completion of the placebo-washout phase, responder subjects entered a 12-week double-blind phase during which they were randomly assigned to placebo or their best dose of physostigmine. Randomized assignment was performed centrally by the sponsor and was based on computer-generated numbers using a validated program. Nonresponder subjects were discontinued from the study.

OUTCOME MEASURES

Efficacy was assessed using 3 primary and 2 secondary measures. We included the following primary measures. (1) The ADAS-Cog[22] assesses 11 cognitive domains and is scored on a 0- to 70-point scale, with lower scores indicating

study reported the efficacy and safety of extended-release physostigmine salicylate for the treatment of mild to moderate AD for 6 weeks with doses of 18, 24, and 30 mg/d.[18] We undertook this randomized trial to determine the efficacy of doses of 24 and 30 mg/d of extended-release physostigmine salicylate for 12 weeks.

RESULTS

DOSE-ENRICHMENT PHASE

A total of 850 subjects with AD entered the dose-enrichment phase. These subjects ranged in age from 46 to 91 years (mean ± SD, 72.8 ± 8.1 years); 85.1% were aged 65 years or older. Of subjects, 94.5% were white, 3.8% were black, 1.1% were Hispanic, and 0.6% were of other ethnicity; 54.7% were women. The demographic characteristics and the baseline efficacy parameters (ADAS-Cog, MMSE, and IADL) of the 850 subjects initially enrolled in the study were similar for all treatment sequence groups (data not shown).

The disposition of all subjects who entered the dose-enrichment phase is displayed in **Figure 2**. A total of 546 subjects completed the dose-enrichment phase and entered the placebo-washout phase. Of these, 196 subjects (35.9%, or 23.0% of subjects entering the dose-enrichment phase) responded to physostigmine treatment (some at both dose levels); whereas 341 subjects (62.5%) were considered nonresponders. Nine subjects (1.6%) with missing data could not be evaluated with respect to responder status. Among the 196 responder subjects, 68 responded only to the 12-mg bid dose, 60 only to the 15-mg bid dose, and 68 to both doses. For subjects responding with equivalent ADAS-Cog reductions at both doses, the best dose was chosen on the basis of tolerability. If the doses were still equivalent, the 15-mg bid dose was considered the best dose. Of the 196 responder subjects, 20 discontinued during the placebo-washout phase due to adverse events or withdrawal of consent, leaving 176 who entered the double-blind phase.

DOUBLE-BLIND PHASE

Characteristics at screening of the 176 subjects who entered the double-blind phase are summarized in **Table 1**. No statistically significant differences were observed between the subjects assigned to placebo or physostigmine treatment in this phase. The demographic characteristics of these subjects were also essentially similar to the characteristics of those originally entering the dose-enrichment phase, with the exception of sex; 62.5% of

better cognition. The ADAS-Cog was administered weekly during the dose-enrichment phase and every 3 weeks during the double-blind phase. All ADAS-Cog psychometricians were required to attend a training session at the initial investigators' meeting and to pass a reliability test. (2) The Clinician Interview-Based Impression of Change With Caregiver Input (CIBIC+)[23] involves a rating of global change based on a structured interview of the subject with AD and the caregiver by an experienced clinician unbiased by other outcome measures or adverse events. The CIBIC+ uses a 7-point Likert scale (higher scores indicate improvement) in which each subject is rated along the continuum from "very much worse" to "very much improved." It was performed every 6 weeks during the double-blind phase. (3) The Clinical Global Impression of Change (CGIC)[24] also involves a rating of global change by the study clinician (site investigator) based on data from the subject with AD and the caregiver (including side effects) but without reference to ADAS-Cog scores or CIBIC+ ratings. The CGIC used the same 7-point scale as the CIBIC+ (higher scores indicate improvement) and was performed every 3 weeks during the double-blind phase.

Secondary outcome measures included the MMSE score (range, 0-30; higher scores indicate better cognition) and Instrumental Activities of Daily Living (IADL) score (range, 4-32; lower scores indicate better functioning).[25] These were administered at the baseline and final visits during the double-blind phase.

STATISTICAL ANALYSIS

Efficacy analyses were based on the cohort of subjects with AD identified as responders during the dose-enrichment phase and randomized for the double-blind phase. No analyses were performed comparing dose effects, but only comparing physostigmine (combining both dose levels) and placebo. Statistical analyses included an intent-to-treat (ITT), last observation carried forward (LOCF) approach that used the last observation made while the subject was still considered a study participant. A completers (observed cases) analysis was also performed for those subjects completing the double-blind phase.

The physostigmine and placebo treatment groups were compared with respect to change from baseline on the ADAS-Cog, MMSE, and IADL using analysis of covariance models with baseline score as the covariate. Since the CIBIC+ and CGIC are assessed as change from baseline, a similar analysis of variance model without covariates was used for these measures. Type III sums of squares were used throughout for testing hypotheses (2-tailed, $\alpha = .05$). The CIBIC+ and CGIC were also analyzed as categorical data, using the Cochran-Mantel-Haenszel (CMH) test. Too few subjects were enrolled at each center to measure center effects. When significant treatment effects were observed, an effect size index[26] was computed as the difference between the physostigmine- and placebo-treated group means divided by the pooled SD of both groups. Demographic differences were compared using independent *t* tests. All statistical analyses were performed using a statistical package (SAS; SAS Institute Inc, Cary, NC).

The monitoring plan called for analyses when 25%, 50%, 75%, and 100% of the planned number of subjects completed the double-blind phase, using an O'Brien-Fleming boundary.[27] However, this plan allowed for changes in the timing and frequency of analyses according to the approach of Lan and DeMets.[28] Thus, analyses actually took place at approximately the 36% and 64% points. As there were only 2 treatment groups, adjustment of multiple testing was limited to the interim analysis plans. Unless otherwise indicated, data are given as mean ± SD.

subjects entering the double-blind phase were men, compared with 45.3% men entering the dose-enrichment phase. This preferential selection of men for the double-blind phase accrued partly from the higher percentage of women discontinuing the dose-enrichment phase due to adverse events (43.2% of women vs 19.5% of men), as well as the higher percentage of men completing the dose-enrichment phase who entered the double-blind phase as responders (36.8% of men vs 26.7% of women). No analysis was undertaken of body weight in relation to adverse events or responder status. Among the responders who entered the double-blind phase, the best dose was 12 mg bid for 95 subjects (54.0%), and 15 mg bid for 81 subjects (46.0%).

Two interim analyses were performed. On the basis of achieving the previously determined α level of the O'Brien-Fleming criteria ($P \leq .0116$) for the ADAS-Cog comparison, the study was terminated after the second interim analysis.

EFFICACY ANALYSIS AND ITT LOCF POPULATION

Of the 176 subjects with AD initially randomized for the double-blind phase, 173 were considered valid for the ITT LOCF in that they received at least 1 dose of the protocol-designated treatment and had at least 1 posttreatment outcome assessment. One subject randomized to receive physostigmine and 2 subjects randomized to receive placebo discontinued the double-blind phase with no efficacy assessments. Results of the ITT LOCF analysis for the ADAS-Cog, CIBIC+, and CGIC are displayed in **Table 2**. The ADAS-Cog scores of the placebo-treated subjects worsened (ie, scores increased) by 1.06 ± 5.17 points, whereas those of physostigmine-treated subjects improved by –0.96 ± 5.22 points, resulting in a –2.02 point difference favoring physostigmine ($F_{1,167} = 6.42$ [$P = .01$]; effect size index, 0.39). A drug-placebo difference in ADAS-Cog was apparent by 3 weeks and continued to increase over time (**Figure 3**).

Similarly, CIBIC+ ratings of physostigmine-treated subjects were unchanged (0.00 ± 0.88 points), whereas those of placebo-treated subjects deteriorated by –0.33 ± 0.82 points, resulting in a 0.33-point mean improvement in CIBIC+ ($F_{1,150} = 5.68$ [$P = .02$] by ANOVA; $\chi^2_1 = 5.51$ [$P = .02$] by CMH; effect size index, 0.39) after 12 weeks of treatment. A trend toward improvement in CIBIC+ emerged after 6 weeks of treatment (physostigmine, 0.10 ± 0.86; placebo, –0.16 ± 0.79; mean improvement, 0.26 points) ($F_{1,149} = 3.73$ [$P = .06$] by ANOVA; $\chi^2_1 = 3.66$ [$P = .06$] by CMH). For the CGIC, the placebo-treated subjects declined by –0.30 ± 0.84

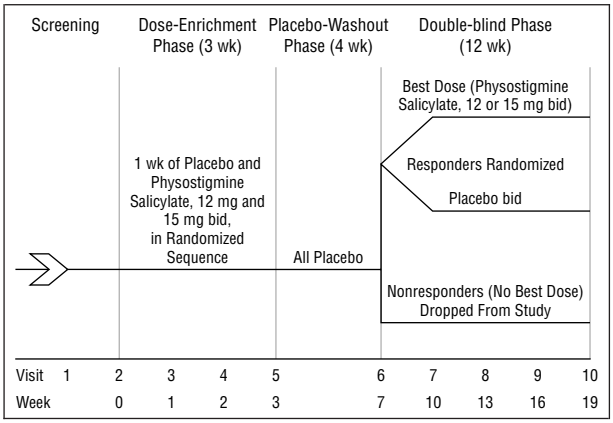

Figure 1. *Study design. Bid indicates twice daily.*

points, whereas physostigmine-treated subjects declined by –0.12 ± 0.87 points. However, the resulting 0.18-point adjusted mean improvement in CGIC was not statistically significant ($F_{1,170}$ = 1.87 [*P* = .17] by ANOVA; χ^2_1 = 1.86 [*P* = .17] by CMH).

Table 2 also summarizes the results of the secondary efficacy variables as an ITT LOCF analysis. No statistically significant differences between physostigmine and placebo treatments were obtained for the MMSE (0.62-point improvement; $F_{1,156}$ = 1.55 [*P* = .22]) or IADL (–2.23-point improvement, negative score better; $F_{1,160}$ = 1.31 [*P* = .25]).

The sample sizes vary for different outcome measures in Table 2 (range, 70-82 for the physostigmine group and 82-90 for the placebo group) because some measures were scheduled less frequently during the double-blind phase (and had not been repeated if a subject discontinued prematurely) or were not performed when scheduled (particularly, the CIBIC+).

EFFICACY ANALYSIS AND COMPLETERS

The data were also analyzed considering only those subjects with AD who completed the double-blind phase (observed-cases analysis). This represented about 85% of the subjects who were included in the ITT LOCF analysis (ie, 64 and 80 subjects for the physostigmine and placebo groups, respectively, for ADAS-Cog). The results (**Table 3**) parallel the ITT LOCF analysis and show a statistically significant improvement favoring physostigmine for ADAS-Cog (difference between groups, –2.31 points; $F_{1,141}$ = 7.10 [*P* = .009]; effect size index, 0.45) and CIBIC+ (difference between groups, 0.31 points; $F_{1,137}$ = 4.67 [*P* = .03] by ANOVA; χ^2_1 = 4.55 [*P* = .03] by CMH; effect size index, 0.37) but not for CGIC (difference between groups, 0.25 points; $F_{1,144}$ = 3.11 [*P* = .08] by ANOVA; χ^2_1 = 3.06 [*P* = .08] by CMH). Since the secondary efficacy variables were performed only at the beginning and end of the double-blind phase, no completers analysis was performed separate from the ITT LOCF analysis.

The sample sizes vary for different outcome measures in Table 3 (61-66 for the physostigmine group and 78-80 for the placebo group) because some measures were not performed when scheduled (particularly, the CIBIC+).

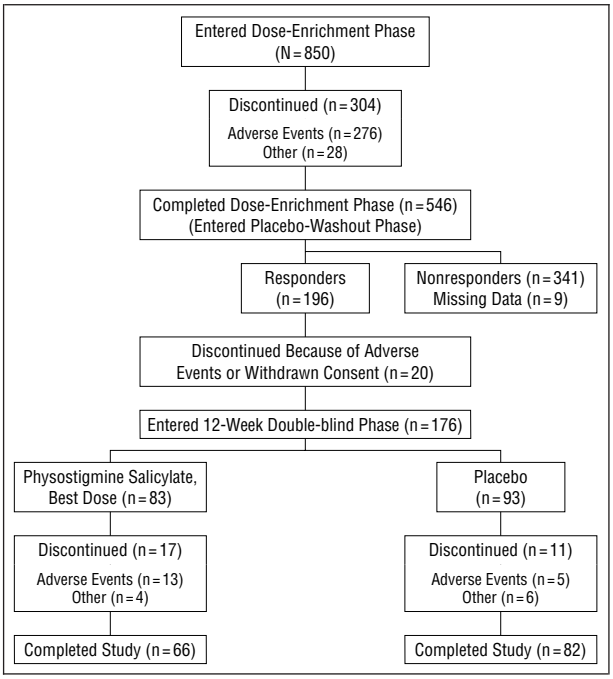

Figure 2. *Disposition of subjects.*

SAFETY ANALYSIS

The most frequent adverse events with physostigmine were in the gastrointestinal tract, as would be expected for an AChEI. All 176 subjects randomized for the double-blind phase received at least 1 dose of the protocol-designated treatment and were included in the safety analysis for this phase. Adverse events reported by at least 5% of subjects during the double-blind phase are shown in **Table 4**. They included nausea (47% physostigmine- vs 1% placebo-treated subjects), vomiting (47% physostigmine- vs 3% placebo-treated subjects), dizziness, diarrhea, sweating, abdominal pain, anorexia, and asthenia. Although most of these events were judged to be possibly or probably related to the study drug, most were mild or moderate in severity. Several adverse events appeared to be dose related, as listed in Table 4.

Over the entire course of the study, 320 subjects with AD (37.6%) withdrew because of adverse events; all 320 were exposed to physostigmine. Of these, 109 subjects withdrew because of adverse events other than those considered typical cholinergic symptoms, although these subjects may also have reported symptoms of nausea and/or vomiting. None of these 109 subjects discontinued because of adverse events related to liver function abnormalities.

No clinically significant abnormalities were observed in the results of biochemistry or hematologic studies of the physostigmine or placebo groups. In particular, liver function abnormalities occurred in only 1 (0.1%) of 847 physostigmine-treated subjects during all phases of the study. There appeared to be no clinically important changes in vital signs, electrocardiography, or physical examinations related to physostigmine treatment.

Table 1. Subject Characteristics at Screening by Treatment Group for Responders Entering Double-blind Phase*

Variable	Physostigmine Salicylate 12 mg bid (n = 46)	Physostigmine Salicylate 15 mg bid (n = 37)	Physostigmine (n = 83)	Placebo (n = 93)
Demographics				
Age, y				
Mean ± SD	71.2 ± 9.4	71.8 ± 8.4	71.5 ± 8.9	71.4 ± 8.0
Range	50-88	48-87	48-88	50-87
Sex, No. (%) male	26 (57)	22 (59)	48 (58)	62 (67)
Race, No. (%)				
White	45 (98)	34 (92)	79 (95)	89 (96)
African American	1 (2)	2 (5)	3 (4)	4 (4)
Hispanic	0	1 (3)	1 (1)	0
Weight, kg				
Mean ± SD	71.0 ± 14.5	71.8 ± 12.9	71.3 ± 13.7	72.1 ± 13.0
Range	43-108	40-102	40-108	46-111
Neuropsychological tests, mean ± SD score				
ADAS-Cog	29.8 ± 11.9	27.8 ± 11.9	28.9 ± 11.9	29.0 ± 11.3
MMSE	18.5 ± 4.6	18.5 ± 5.1	18.5 ± 4.8	18.4 ± 4.5
Modified Hachinski, mean ± SD score	0.5 ± 0.8	0.4 ± 0.5	0.4 ± 0.7	0.6 ± 0.9

**ADAS-Cog indicates Alzheimer's Disease Assessment Scale, cognitive subscale (range, 0-70; lower score better); MMSE, Mini-Mental State Examination (range, 0-30; higher score better); Modified Hachinski, modified Hachinski Ischemia Scale; and bid, twice daily. No statistically significant differences were observed between physostigmine and placebo for any variable.*

Table 2. Adjusted Mean Difference Scores of Physostigmine Salicylate vs Placebo for Double-blind Phase, ITT LOCF Analysis*

Efficacy Measures	Physostigmine No. of Subjects	Physostigmine Score	Placebo No. of Subjects	Placebo Score	Treatment Difference	Test	*P*
Primary measures							
ADAS-Cog	80	−0.96 ± 5.22	90	1.06 ± 5.17	−2.02	$F_{1,167}$ = 6.42†	.01
CIBIC+	70	0.00 ± 0.88	82	−0.33 ± 0.82	0.33	$F_{1,150}$ = 5.68; χ^2_1 = 5.51‡	.02; .02
CGIC	82	−0.12 ± 0.87	90	−0.30 ± 0.84	0.18	$F_{1,170}$ = 1.87; χ^2_1 = 1.86‡	.17; .17
Secondary measures							
MMSE	75	−0.25 ± 2.98	84	−0.87 ± 3.20	0.62	$F_{1,156}$ = 1.55†	.22
IADL	78	1.28 ± 12.48	85	3.51 ± 12.54	−2.23	$F_{1,160}$ = 1.31†	.25

**Values are given as mean ± SD unless otherwise indicated. ITT indicates intent-to-treat; LOCF, last observation carried forward; ADAS-Cog, Alzheimer's Disease Assessment Scale, cognitive subscale (range, 0-70; negative change indicates improvement); CIBIC+, Clinician Interview-Based Impression of Change-Plus (range, −3 to 3; positive change indicates improvement); CGIC, Clinical Global Impression of Change (range, −3 to 3; positive change indicates improvement); MMSE, Mini-Mental State Examination (range, 0-30; positive change indicates improvement); and IADL, Instrumental Activities of Daily Living (range, 4-32; negative change indicates improvement).*

†Least-squares adjusted mean difference scores during 12 weeks of treatment, analysis of covariance.

‡Determined using analysis of variance (F) and Cochran-Mantel-Haenszel statistic (χ^2).

COMMENT

In this dose-enrichment study, physostigmine salicylate was efficacious in the treatment of the cognitive deficits of AD in doses of 12 or 15 mg bid. Physostigmine was statistically superior to placebo for the ADAS-Cog and the CIBIC+ by means of traditional ITT LOCF or completers analysis. No significant differences were observed for the CGIC or the secondary outcome measures. The beneficial effects of physostigmine treatment were modest and came with substantial adverse effects that may limit the clinical usefulness of this drug.

The mean treatment difference of −2.02 points on the ADAS-Cog in the ITT LOCF analysis accrued from a −0.96-point improvement in physostigmine-treated subjects and a 1.06-point worsening in placebo-treated subjects. Based on an average annual rate of worsening on the ADAS-Cog of 6 to 8 points per year,[29] this translates into an approximate 3- to 4-month delay in the progression of cognitive decline for the group receiving physostigmine. This treatment effect size is larger than that previously reported in a 6-week study of physostigmine with dose enrichment (−1.75 points)[18] but smaller than that reported in a 24-week study of physostigmine without dose enrichment (−2.9 points).[30] These differences are most likely secondary to the varying treatment periods of the 3 studies, the different dosing regimens used, and the variable use of dose enrichment. The treatment effect size with the CIBIC+ in the ITT LOCF analysis in our study (0.33 points) is actually slightly larger than that observed in the 24-week study without dose enrichment (0.26 points).[30]

Direct comparison of treatment effects between physostigmine and other AChEIs is limited by considerable methodological differences among studies. The mean treatment difference of –2.02 points on the ADAS-Cog in the ITT LOCF analysis (or –2.31 for the completers analysis) is somewhat lower than the values of –2.5 to –3.8 reported in other 12-week trials of AChEIs.[12,15,31] However, these studies did not use dose enrichment, which may be associated with smaller treatment effects. Nonetheless, the mean treatment difference of 0.33 points for the CIBIC+ in the ITT LOCF analysis (or 0.31 for the completers analysis) in our study is comparable to that reported (0.35 points) in the only other 12-week trial that used this instrument.[15] The treatment effect sizes in a 24-week study of physostigmine without dose enrichment (–2.9 points for ADAS-Cog; 0.26-0.31 points for CIBIC+)[30] are also similar to those reported for AChEI trials of equivalent duration.[13,14,32,33]

Puzzling in our results is the divergence of the 2 global ratings, ie, the CIBIC+ demonstrated significant treatment effects, whereas the similar CGIC rating did not. Two possible explanations for this discrepancy are that the CIBIC+ possessed greater sensitivity, since it was based on a dedicated structured interview, whereas the CGIC was usually rated using information obtained routinely by the study clinician during the visit, and that the CGIC was not blinded to adverse events, and so may have been unfavorably biased by the presence of adverse effects. As in other reports with this agent[18,30] and other AChEIs,[13,15] our study found no changes in the IADL scale.[25] This particular scale may lack sufficient sensitivity to change in patients with mild to moderate AD. By contrast, other AChEIs[13,16] have demonstrated IADL improvement as measured by the Progressive Deterioration Scale,[34] a scale developed specifically for measuring functional change in AD.

The dose-enrichment design warrants additional comment. This design was used to preselect potential phy-

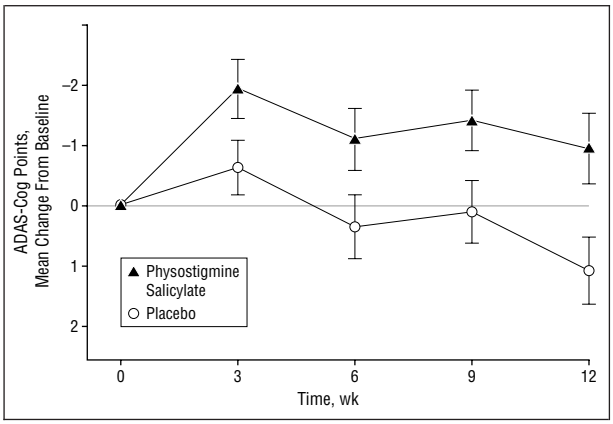

Figure 3. *Comparison of mean change in the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog) from baseline between the physostigmine salicylate (12- and 15-mg twice daily doses pooled [n = 80]) and placebo (n = 90) groups in the double-blind phase. The SEM is used instead of SD for legibility. A strong trend toward a drug-placebo difference emerged by 3 weeks ($F_{1,164}$ = 3.84 [P = .052]) and continued to increase at 6 weeks ($F_{1,167}$ = 3.85 [P = .051]), 9 weeks ($F_{1,167}$ = 4.38 [P = .04]), and 12 weeks ($F_{1,167}$ = 6.42 [P = .01]).*

Table 4. Significant Adverse Events Reported by at Least 5% of Subjects During Double-blind Phase*

Adverse Event	Physostigmine Salicylate–Treated 12 mg bid (n = 46)	15 mg bid (n = 37)	All Doses (n = 83)	Placebo-Treated (n = 93)
Any	39 (85)	31 (84)	70 (84)	93 (100)
Nausea	20 (43)	19 (51)	39 (47)	1 (1)
Vomiting	21 (46)	18 (49)	39 (47)	3 (3)
Dizziness†	8 (17)	14 (38)	22 (27)	4 (4)
Diarrhea	9 (20)	7 (19)	16 (19)	2 (2)
Sweating†	5 (11)	6 (16)	11 (13)	2 (2)
Abdominal pain	4 (9)	5 (14)	9 (11)	1 (1)
Anorexia	6 (13)	2 (5)	8 (10)	2 (2)
Asthenia†	0	7 (19)	7 (8)	0
Eructation	6 (13)	1 (3)	7 (8)	1 (1)
Dyspepsia	4 (9)	2 (5)	6 (7)	2 (2)
Headache	3 (7)	3 (8)	6 (7)	2 (2)
Confusion†	0	5 (14)	5 (6)	3 (3)
Weight loss†	1 (2)	3 (8)	4 (5)	0
Tremor†	1 (2)	3 (8)	4 (5)	0
Nervousness	1 (2)	3 (8)	4 (5)	1 (1)
Hallucinations	2 (4)	2 (5)	4 (5)	1 (1)
Malaise†	1 (2)	2 (5)	3 (4)	0
Insomnia	1 (2)	2 (5)	3 (4)	3 (3)
Chest pain	1 (2)	2 (5)	3 (4)	3 (3)
Agitation	1 (2)	2 (5)	3 (4)	6 (6)
Chills†	0	2 (5)	2 (2)	0
Pallor†	0	2 (5)	2 (2)	0
Dyspnea†	0	2 (5)	2 (2)	1 (1)
Accidental injury	0	2 (5)	2 (2)	4 (4)
Arthritis	0	2 (5)	2 (2)	3 (3)
Pain	0	1 (3)	1 (1)	6 (6)

*Data are given as number (percentage) of subjects. Bid indicates twice daily.
†Denotes a dose-related adverse event (occurring in at least 5% of the 15-mg group, twice that of placebo group, and greater than the 12-mg group).

Table 3. Adjusted Mean Difference Scores of Physostigmine vs Placebo for Double-blind Phase, Completers Analysis*

Primary Efficacy Measures	Physostigmine Salicylate No. of Subjects	Physostigmine Salicylate Score	Placebo No. of Subjects	Placebo Score	Treatment Difference	Test	P
ADAS-Cog	64	–1.05 ± 5.30	80	1.26 ± 5.04	–2.31	$F_{1,141}$ = 7.10†	.009
CIBIC+	61	0.02 ± 0.90	78	–0.29 ± 0.79	0.31	$F_{1,137}$ = 4.67; χ^2_1 = 4.55‡	.03; .03
CGIC	66	–0.08 ± 0.86	80	–0.33 ± 0.84	0.25	$F_{1,144}$ = 3.11; χ^2_1 = 3.06‡	.08; .08

*Values are given as mean ± SD unless otherwise indicated. ADAS-Cog indicates Alzheimer's Disease Assessment Scale, cognitive subscale (range, 0-70, negative change indicates improvement); CIBIC+, Clinician Interview-Based Impression of Change-Plus (range, –3 to 3, positive change indicates improvement); and CGIC, Clinical Global Impression of Change (range, –3 to 3, positive change indicates improvement).
†Least-squares adjusted mean difference scores during 12 weeks of treatment, analysis of covariance.
‡Determined using analysis of variance (F) and Cochran-Mantel-Haenszel statistic (χ^2).

sostigmine responders and their optimal dose. Our study was not constructed to test the value of dose enrichment in predicting therapeutic response during an extended therapeutic trial; such a goal would require that nonresponders also enroll in the double-blind phase. One previous study[18] adopted such a design and demonstrated that the cohort of nonresponders during dose enrichment once again failed to respond to physostigmine during an extended treatment phase. By contrast, a simple comparison of therapeutic response in enriched[11,18] vs unenriched[12,13,30] populations studied with physostigmine or tacrine suggests that the enriched populations show no greater treatment effect and, if anything, a slightly weaker effect. Reasons for this paradoxical finding are unclear, but may include carryover effects from the dose-enrichment to the extended-treatment phase as well as an undefined refractoriness of subjects previously exposed to AChEIs. Our study appears to demonstrate a true enrichment for tolerability if not for efficacy: 32.5% of subjects discontinued due to adverse events during the dose-enrichment phase, compared with 10.2% during the double-blind phase. The major limitation of the dose-enrichment design involves the large number of subjects dropped from the study because of adverse events or the absence of a best dose, leaving the responsiveness of this group in question.

The 4-week placebo-washout phase appeared to be of adequate duration, as there was no evidence of a carryover effect from the dose-enrichment phase into the double-blind phase. For those subjects with AD who entered the double-blind phase, the mean ADAS-Cog at screening was 28.96 compared with 28.76 at the start of the double-blind phase. Similarly, mean MMSE at screening was 18.45 compared with 18.27 at the start of the double-blind phase. By contrast, in previous studies of physostigmine[18] or tacrine[11] that used only 2-week washout periods between dose-enrichment and double-blind phases, subjects did not fully return to their pretreatment status at the end of this washout period. The ADAS-Cog scores were 1.4[18] or 1.5[11] points lower (ie, better) at entry into the double-blind phase than at screening.

In our study, the most commonly reported adverse effects were nausea and vomiting, which each occurred in 47.0% of physostigmine-treated subjects during the double-blind phase. These numbers are in agreement with those of the previous 6-week trial of similar design[18] as well as those of previous smaller trials.[9,10,17] They are also higher than those reported in trials of both AChEIs approved by the Food and Drug Administration, although direct comparisons are limited by differences in reporting methods and dosing regimens. Among subjects with AD receiving tacrine hydrochloride, 80 to 160 mg/d in a 30-week trial, 35% experienced nausea and/or vomiting[13]; whereas of subjects receiving donepezil hydrochloride, 10 mg/d in a 24-week trial, 10% and 7% experienced nausea and vomiting, respectively.[14] The high adverse event profile for physostigmine in our study may result in part from the use of a fixed-dose regimen. In clinical practice, the use of a lower starting dose and a gradual and flexible dosing regimen may well reduce the incidence of adverse effects. The apparent dose relatedness of several adverse events (Table 4), with the slightly greater number of responders to the 12- than the 15-mg bid dose regimen in the dose-enrichment phase, suggests that the lower dose should be tried first in clinical practice.

Given the rather high incidence of gastrointestinal cholinergic side effects compared with other AChEIs, the role of physostigmine in the clinical arena remains to be determined. The literature contains multiple demonstrations of the efficacy of AChEIs in AD, and the magnitude of treatment effect has been remarkably similar across agents.[11-16,18,30-33] This uniformity of efficacy has been observed despite significant differences among these drugs in clinical pharmacology and in patient tolerability. In clinical practice, the use of physostigmine will likely be restricted to those patients who experience negligible adverse effects or who have responded poorly to other treatments. To our knowledge, the possibility that individual patients with AD may show preferential treatment responses to specific AChEIs has not yet been investigated.

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