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A DOUBLE-BLIND, PLACEBO-CONTROLLED MULTICENTER STUDY OF TACRINE FOR ALZHEIMER'S DISEASE

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Abstract Background. In Alzheimer's disease, there is a marked decline in the function of cholinergic neurons in the brain. However, studies of treatment with cholinesterase inhibitors have produced conflicting results. We conducted a multicenter trial to evaluate whether the cholinesterase inhibitor tacrine (1,2,3,4-tetrahydro-9-acridinamine monohydrochloride monohydrate) could improve cognition in patients with Alzheimer's disease.

Methods. Of 632 eligible patients with probable Alzheimer's disease, 215 improved while receiving tacrine during a preliminary crossover phase to determine responsiveness and the best dose. The 215 patients were randomly assigned to receive either placebo or their best dose of tacrine (10 or 20 mg four times a day) in a six-week, double-blind trial. The primary measures of efficacy were the cognitive subscale of the Alzheimer's Disease Assessment Scale and the Clinical Global Impression of Change scale; the secondary measures included the Mini-Mental State Examination and the assessment of the activities of daily living.

Results. At the end of the six-week trial, the patients receiving tacrine had a mean adjusted cognitive-subscale

score of 30.3 (Alzheimer's Disease Assessment Scale) as compared with 32.7 in patients receiving placebo. This represents a smaller decline (by 2.4 points) in cognitive performance in the tacrine group ($P < 0.001$). There were no differences between the groups in their global-rating scores. The tacrine group had a significantly smaller decline in the activities of daily living. The results of the Mini-Mental State Examination favored tacrine, but the differences were small and not statistically significant (a score of 16.0 with tacrine vs. 15.3 with placebo; $P = 0.08$). Gastrointestinal symptoms, elevation of aminotransferase levels, and headache were the most frequent side effects; all could be reversed by reducing the dose or discontinuing treatment.

Conclusions. In this short-term study in patients with Alzheimer's disease who were selected for apparent responsiveness to tacrine, treatment with tacrine resulted in a statistically significant reduction in the decline of cognitive function, although this reduction was not large enough to be detected by the study physicians' global assessments of the patients. (N Engl J Med 1992;327:1253-9.)

IN Alzheimer's disease the brain has a variety of neurotransmitter deficits, and the most striking and consistent change is a marked decrease in the activity of choline acetyltransferase, a marker for cholinergic neurons. Although there are other changes in neurotransmitters, the reduction in choline acetyltransferase activity correlates best with the degree of memory impairment.¹ Drugs that inhibit central cholinergic function also induce memory deficits² — a finding further supporting the role of the cholinergic

system in normal cognitive function. A possible therapeutic approach to Alzheimer's disease may be to compensate for the loss of central cholinergic neurons by potentiating the activity of the remaining intact cells with acetylcholinesterase inhibitors.³⁻⁵

1,2,3,4-Tetrahydro-9-acridinamine monohydrochloride monohydrate (tacrine hydrochloride) is a centrally active, reversible cholinesterase inhibitor.^{6,7} The results of two pilot studies of tacrine in patients with presumptive Alzheimer's disease suggested that they had moderate improvement in their performance on psychometric tests and in global assessments after they were treated with tacrine alone or in combination with lecithin.^{8,9} In 1986, Summers et al.¹⁰ reported significant improvement in global status and the performance of psychometric tests in 16 patients treated with tacrine. These results, although widely criticized,¹¹ were promising enough to justify a large-scale, multicenter, controlled study to determine whether tacrine could improve cognition in Alzheimer's disease. An "enriched-population" design (i.e., study of

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*The investigators and institutions of the Tacrine Collaborative Study Group are listed in the Appendix.

patients selected for their potential to respond) was chosen because the clinical, biochemical, and pathological heterogeneity of the disease and clinical experience suggested that not all patients would respond to any single treatment, and that those who did respond might do so only within a limited dose range.

METHODS

Patients

Outpatients of both sexes, each of whom had a care giver to ensure compliance with the protocol, were selected according to the following criteria: age of at least 50 years, a diagnosis of probable Alzheimer's disease as defined by the National Institute of Neurological Disorders and Stroke Work Group,¹² a score of 10 to 26 (inclusive) on the Mini-Mental State Examination (MMSE),¹³ and a score of 4 or less on the modified Hachinski Ischemia Scale.¹⁴ Patients were excluded if they required concurrent medications known to affect the central nervous system. Informed consent was obtained from the patient (or his or her legal representative) and the care giver. The institutional review board of each of the 16 study centers approved the study.

Study Design

The study consisted of an "enrichment" phase, a placebo base-line phase, a double-blind phase, and a sustained active phase (Fig. 1). During the enrichment phase, patients were randomly assigned to one of three titration sequences; in each sequence, placebo or tacrine was given in a dose of 40 or 80 mg a day (in four equal doses) for two weeks each. Doses were expressed in terms of active substance; therefore, a daily dose of 80 mg was equivalent to 100 mg of the hydrochloride salt. These treatment regimens reflected an amended protocol; the original protocol had included doses of 120 and 160 mg of tacrine a day, but because of marked elevations of aminotransferase levels, these doses were eliminated. The potential therapeutic response was assessed at the completion of each two-week period of the enrichment phase. During the following two-week placebo base-line phase, base-line data on safety and efficacy were collected and the data from the enrichment phase were evaluated to determine whether each patient had a "best-dose" response to tacrine, defined as the dose of tacrine (40 or 80 mg a day) that resulted in a total score on the Alzheimer's Disease Assessment Scale (ADAS)¹⁵ that was at least 4 points lower (a lower score indicates a better outcome) than the score obtained during the enrichment phase, without intolerable side effects. Patients with a reduction of at least 4 points on the ADAS during the enrichment (dose-titration) phase entered the subsequent six-week parallel-group, double-blind, placebo-con-

trolled phase and were randomly assigned to treatment with either their best dose of tacrine or placebo. Patients completing the double-blind phase entered a six-week, sustained active (treatment) phase.

Outcome Measures

Efficacy was assessed according to two primary and six secondary measures.

Primary Measures

The ADAS assesses the patient's core cognitive and noncognitive deficits.^{15,16} The cognitive subscale includes assessment of word recall, naming of common objects and fingers, the ability to follow simple commands, constructional (copying figures) and ideational (addressing a letter) praxis, orientation, word-recognition memory, spoken language, comprehension of spoken language, word finding, and recall of test instructions. The noncognitive component includes assessment of tearfulness, depression, concentration, cooperation, delusions, pacing (gait), increased motor activity, tremors, and change in appetite. Assessment was carried out at screening, at the completion of each two-week treatment period during the dose-titration phase, at the completion of the two-week placebo base-line phase, after two, four, and six weeks of treatment in the double-blind phase, and at the end of the six-week sustained active phase. Equivalent parallel versions of word lists were developed for the word-recall and word-recognition tasks. The cognitive-function subscale was used as a primary outcome measure.

The Clinical Global Impression of Change (CGIC), which has a 7-point scale, was used by the study physician to rate each patient along a continuum from "very much worse" to "very much improved."¹⁷ Assessments were made in relation to the appropriate base line — i.e., the screening for the dose-titration phase, and the placebo base line for the double-blind and sustained active phases. A study physician completed the CGIC by interviewing the patient and family, without consulting any other test results.

Secondary Measures

Secondary outcome measures included the ADAS total score, the score on the ADAS noncognitive subscale, and the score on the MMSE.¹³ The quality of life was measured with the Progressive Deterioration Scale (PDS),¹⁸ the Instrumental Activities of Daily Living (IADL) assessment,¹⁹ and the Physical Self-Maintenance Scale (PSMS).¹⁹ These assessments were carried out at placebo base line in patients in whom a best dose had been determined and at the end of the double-blind and sustained active phases.

Statistical Analysis

Statistical analyses were performed by the Warner-Lambert Company and independently verified by the University of Iowa. Analyses of the results of the double-blind phase included data collected at the end of the placebo base-line phase and during the double-blind phase. The analyses included all patients with efficacy measurements for a particular test both at the placebo base line and at the end of the double-blind phase, and all patients who had both a placebo-base-line observation and at least one double-blind observation (i.e., the last) or who were included in an intention-to-treat analysis.

Both parametric and nonparametric methods were used to analyze the scores on the ADAS and its subscales and those on the PDS, MMSE, PSMS, and IADL. Analysis of covariance was used to compare the two treatment groups, with the value from the double-blind phase as the dependent variable. For each of the dependent variables, the model included the effects of the study center, treatment group, and the placebo-base-line value as covariates. Since six centers had fewer than 10 patients who were eligible for efficacy analysis, these centers were combined in pairs per protocol (i.e., the center with the most patients combined with the center with the least) to form three centers. Additional models including the interaction between the study center and treatment confirmed the generalizability of results across centers.

Nonparametric analyses using Cochran-Mantel-Haenszel mean-

Figure 1. Study Design.

Alzheimer's disease was diagnosed according to the criteria of the National Institute of Neurological Disorders and Stroke.¹² P denotes placebo administration for two weeks; T40, administration of 40 mg of tacrine a day for two weeks; and T80, administration of 80 mg of tacrine a day for two weeks. For the definition of "best dose," see the Methods section.

score statistics were used to compare the placebo and tacrine groups with respect to the center-adjusted change from base line to the end of the double-blind phase. The nonparametric Friedman test was also performed. The score for the CGIC from the double-blind phase was analyzed by means of center-adjusted Cochran–Mantel–Haenszel statistics. Since this variable was ordinal, both integer scores and modified ridit scores²⁰ were used.

RESULTS

Enrichment Phase

The characteristics of the 632 patients who entered the study were similar during all three titration sequences of the enrichment phase (data not shown). Data that would allow the best dose of tacrine to be determined were available for 563 of these patients (89 percent), for 231 of whom (41 percent) a best dose was calculated. For 90 of the 231 patients, the best dose was 40 mg of tacrine a day, and for 141 it was 80 mg a day. The distribution of best doses was similar among the men and women and among the patients less than 65 years of age and those 65 or older.

The first two weeks of treatment during the dose-titration phase can be viewed as a simple, parallel-group study of placebo and tacrine in a dose of 40 mg a day. Analysis of covariance in 609 patients revealed a mean decrease of 2.5 points in the tacrine group and 1.0 point in the placebo group, after the effect of the study center and the ADAS total score obtained at screening had been controlled for. The difference between the groups of 1.5 points in favor of tacrine was significant ($P = 0.002$). The difference between the groups was over and above any possible in-study or learning effect. A significant in-study improvement in the ADAS score was also recorded in the placebo group two weeks after screening ($P = 0.004$).

Placebo Base-Line Phase

This phase was designed to serve as a washout period followed by the true base-line measurement for the main, double-blind (drug versus placebo) phase. However, the patients did not fully return to their pretreatment status at the end of this period. The ADAS scores at the placebo base line were almost 1.5 points higher than at screening, and the subsequent greater-than-expected decline in the placebo group indicated an in-study or carry-over effect.

Double-Blind Phase

Of the 231 patients with a best dose, 215 entered the double-blind phase, 112 of whom were randomly assigned to placebo (mean age, 70.5 years) and 103 to treatment with their best dose of tacrine (mean age, 70.3 years). Data on 187 to 195 patients were included in the sample used for the analyses at the end of the double-blind phase, and data on 198 to 209 pa-

tients were included in the intention-to-treat analyses. The demographic characteristics and scores on the ADAS and MMSE were similar in both groups during the double-blind phase and in the patients whose best dose could not be determined (data not shown).

Efficacy Analysis

The unadjusted mean score on the ADAS subscale for cognitive function increased (from placebo base line to the end of the double-blind phase [six weeks]) by 3.0 points in the placebo group and by 0.5 point in the tacrine group, indicating that the decline in the tacrine group was smaller (Table 1). The least-squares-adjusted mean score on the ADAS cognitive subscale was 30.3 in the tacrine group and 32.7 in the placebo group; the difference of 2.4 points, favoring tacrine ($P < 0.001$), was supported by the results of nonparametric analysis ($P = 0.001$) (Table 2). The consistency of the difference was supported by the range of the P values ($P < 0.001$ for all comparisons) when each center was dropped in turn from the analysis. The overall result of the study was not determined by the results at any one center alone.

Data from the CGIC were analyzed with the original, 7-point scale as well as categorical ratings of the patients as "improved" or "unchanged" as compared with "worse." At the end of the double-blind phase, there was no significant difference between the tacrine and placebo groups in the mean scores or the dichotomized ratings (Table 2).

In the patients studied, the score on the ADAS cognitive subscale accounted for approximately 85 percent of the ADAS total score. Thus, the total scores (Table 2) were similar to those on the cognitive subscale, with significant differences between the tacrine and placebo groups according to both the parametric ($P < 0.001$) and nonparametric ($P = 0.003$) analyses. The significant difference between the groups was due

Table 1. Mean Scores (Unadjusted) at Placebo Base Line and the End of the Double-Blind Phase.

EFFICACY MEASURE (POSSIBLE SCORES*)	PLACEBO†			TACRINE†		
	PLACEBO BASE LINE	DOUBLE BLIND	CHANGE	PLACEBO BASE LINE	DOUBLE BLIND	CHANGE
Primary measures						
ADAS, cognitive (0–70)	29.2	32.2	3.0	30.7	31.1	0.5
CGIC (1–7)						
Mean score	NA	4.0	NA	NA	3.9	NA
Patients improved or unchanged/patients worse	NA	75/26	NA	NA	67/22	NA
Secondary measures						
ADAS, total (0–115)	33.9	37.7	3.8	35.5	36.2	0.7
ADAS, noncognitive (0–45)	4.7	5.5	0.8	5.1	5.3	0.2
PDS (0–100)	46.6	44.1	–2.5	46.8	46.7	–0.1
IADL (4–32)	17.6	18.1	0.5	17.5	17.5	0.0
PSMS (6–30)	8.3	8.2	–0.1	8.5	8.8	0.3
MMSE (0–30)	16.3	15.3	–0.9	16.1	16.0	–0.1

*A lower score indicated improvement on all tests except the PDS and MMSE, on which a higher score indicated improvement. ADAS denotes the Alzheimer's Disease Assessment Scale, CGIC the Clinical Global Impression of Change, PDS the Progressive Deterioration Scale, IADL the Instrumental Activities of Daily Living, PSMS the Physical Self-Maintenance Scale, and MMSE the Mini-Mental State Examination.

†NA denotes value not available. Values for changes reflect calculations with unrounded base-line values.

to a much greater decline in function in the placebo group (ADAS total score, 3.8 points) than in the tacrine group (0.7 point) (Table 1 and Fig. 2). Although this decline was apparently due in part to loss of a positive drug effect from the dose-titration phase, and in part to the estimated advance of Alzheimer's disease, some of the decline cannot be accounted for by these two phenomena, suggesting a rebound-withdrawal effect. During the double-blind phase, 26 percent of the patients given tacrine and 9 percent of those given placebo had a decline of at least 4 points in the ADAS total score ($P = 0.002$ by chi-square test) (Fig. 3). The mean score on the ADAS subscale for noncognitive function changed little in either group (Table 1).

Two of the three quality-of-life scales showed a significant difference between the groups in favor of tacrine. The differences were due primarily to a larger decline in performance in the placebo group than in the tacrine group. The mean PDS score at the end of the double-blind phase decreased 2.5 points from the placebo base line in the placebo group and changed little (0.1 point) in the tacrine group (Table 1) — a difference significant according to both parametric ($P = 0.04$) and nonparametric ($P = 0.01$) analyses (Table 2). Similarly, the mean IADL score increased 0.5 point from placebo base line in the placebo group but did not change in the tacrine group — another difference significant according to the parametric ($P = 0.03$) and nonparametric ($P = 0.04$) analyses. A difference in the PSMS score favored placebo, but this difference was not statistically significant (Table 2).

The mean MMSE score decreased by 0.9 point in the placebo group and 0.1 point in the tacrine group from placebo base line to the end of the double-blind phase (Table 1). This difference in favor of tacrine did not reach statistical significance (Table 2). An analy-

Figure 2. Mean Change in ADAS Total Score during the Phases of the Study.

ADAS denotes the Alzheimer's Disease Assessment Scale. All patients received tacrine and placebo during the dose-titration phase and placebo during the placebo base-line phase. Patients who received placebo during the double-blind phase were switched to tacrine therapy during the sustained active phase.

sis of the last available observations from the double-blind phase confirmed the results of the parametric and nonparametric analyses, except that the difference in the decline in the MMSE scores (0.9) was significant and favored tacrine ($P = 0.03$).

Sustained Active Phase

One hundred ninety-nine patients entered the sustained active phase and continued or began treatment with their best dose of tacrine; 187 patients completed this phase. Patients assigned to double-blind tacrine treatment received it continuously for 12 weeks and were referred to as the tacrine-tacrine group; those assigned to placebo received tacrine for 6 weeks and were referred to as the placebo-tacrine group.

During the sustained active phase, the patients and clinicians were aware that all patients were receiving tacrine, but did not know the dose or the agent to which the patients had previously been assigned. In the placebo-tacrine group, the crossover to tacrine during this phase resulted in an improvement of 3.3 points in the mean score on the ADAS, which occurred between the end of the double-blind phase and the end of the sustained active phase (Fig. 2). At the end of 12 weeks, with both groups receiving tacrine, there was no significant difference in the ADAS total score. During the sustained active phase, the score declined 0.5 point in the tacrine-tacrine group.

Safety Analysis

Forty-two percent of the patients given tacrine had at least one serum alanine aminotransferase value above the upper limit of normal,

Table 2. Results of Efficacy Analyses.

EFFICACY MEASURE*	POINT DIFFERENCE BETWEEN GROUPS†			PARAMETRIC ANALYSIS‡		NONPARAMETRIC ANALYSIS‡	
	PLACEBO BASE LINE	DOUBLE BLIND	95% CI	P VALUE	AGENT FAVORED	P VALUE	AGENT FAVORED
Primary measures							
ADAS, cognitive	1.1	-2.4	-3.49 to -1.31	<0.001	Tacrine	0.001	Tacrine
CGIC							
Mean score				0.30§	Tacrine	NA	NA
Patients improved or unchanged vs. patients worse				0.76	Tacrine	NA	NA
Secondary measures							
ADAS, total	1.0	-3.0	-4.41 to -1.58	<0.001	Tacrine	0.003	Tacrine
ADAS, noncognitive	0.1	-0.6	-1.29 to 0.12	0.17	Tacrine	0.31	Tacrine
IADL	-0.2	-0.5	-0.92 to -0.14	0.03	Tacrine	0.04	Tacrine
PDS	0.5	2.8	0.59 to 5.07	0.04	Tacrine	0.01	Tacrine
PSMS	0.1	0.3	-0.01 to 0.65	0.12	Placebo	0.36	Placebo
MMSE	-0.2	0.7	0.05 to 1.39	0.08	Tacrine	0.08	Tacrine

*For explanation of abbreviations of tests, see the first footnote to Table 1.

†Difference in least-squares mean scores. CI denotes confidence interval.

‡The level of significance in the analysis was $P < 0.05$. NA denotes value not available.

§Value was derived from ridit analysis.

and 21 percent had values at least three times the upper limit of normal. Elevations above the upper limit of normal were more common among women (67 percent) than men (32 percent). The mean time from the first dose of tacrine to the first alanine aminotransferase value above the normal range was 7 weeks, and the time from the first dose to the maximal elevation was 10 weeks. In all cases, alanine aminotransferase levels returned to normal after a mean of five weeks. None of the patients with elevated levels had any symptoms or any evidence of a classic hypersensitivity reaction.

The incidence of side effects among patients given tacrine remained relatively constant throughout the study. Except for elevated alanine aminotransferase levels, the most frequent side effects of either placebo or tacrine (i.e., those occurring in at least 7 percent of the patients during any phase) were nausea, vomiting, headache, diarrhea, and abdominal pain (Table 3).

One hundred thirteen patients (18 percent) were permanently withdrawn from the study because of side effects; 66 of all patients (10 percent) were withdrawn because of alanine aminotransferase elevations. Eighty of the 113 patients withdrew during the dose-titration phase, 11 during the placebo phase, 12 during the double-blind phase, and 10 during the sustained active phase.

DISCUSSION

This study used an enrichment design to test the efficacy of a cholinesterase inhibitor in a group considered more likely to respond to direct manipulation of cholinergic function than an unselected population of patients with probable Alzheimer's disease. Such an approach attempts to target treatment for patients who may have an underlying neurochemical disorder that is responsive to cholinergic manipulation.

Figure 3. Cumulative Percentage of Patients According to the Change in ADAS Total Score from the Placebo Base-Line Phase to the End of the Double-Blind Phase. A decrease of 4 points was considered to denote a "best-dose response" to tacrine.

Table 3. Adverse Events Occurring in ≥ 7 Percent of Patients in the Dose-Titration, Double-Blind, or Sustained Active Phase.

ADVERSE EVENT	DOSE TITRATION		DOUBLE BLIND		SUSTAINED ACTIVE
	PLACEBO (N = 612)	TACRINE (N = 630)	PLACEBO (N = 112)	TACRINE (N = 103)	TACRINE (N = 199)
	number of patients (percent)				
Nausea or vomiting	15 (3)	85 (14)	4 (4)	13 (13)	15 (8)
Headache	34 (6)	67 (11)	11 (10)	13 (13)	23 (12)
Alanine aminotransferase ≥ 100 IU/liter	36 (6)	59 (10)	2 (2)	15 (15)	16 (8)
Diarrhea	12 (2)	47 (8)	4 (4)	4 (4)	10 (5)
Abdominal pain	3 (1)	19 (3)	1 (1)	8 (8)	6 (3)

The placebo base-line phase of the study was designed as a washout period after the initial trial of tacrine, to allow patients to return to base-line state before the six-week double-blind treatment phase. This interval was insufficient, as demonstrated by the initial improvement in the ADAS scores in both groups at placebo base line and by the subsequent excessive decline in the ADAS scores in the placebo group during the double-blind phase. This carry-over effect complicates interpretation of the study.

At the completion of the six-week double-blind phase, the tacrine group had a significantly smaller decline in cognitive function ($P < 0.001$) than the placebo group, as assessed on the ADAS cognitive subscale. When the variables of the ADAS were analyzed individually, word-recognition memory alone showed a significant difference ($P = 0.002$). Supporting data for a positive response to tacrine were obtained during the dose-titration phase. The first two weeks of dose titration represent a randomized, double-blind, parallel-group study. Here, too, tacrine in a dose of 40 mg a day produced improvement in the ADAS total score as compared with placebo.

Patients improved between screening and the placebo base-line phase, presumably because of a combination of in-study or learning effects and the residuum of a positive response to tacrine during dose titration. During the double-blind phase, function declined moderately in the tacrine group; it declined rapidly in the placebo group, to a level below that recorded at screening. This relatively large decline in the latter group appears to have been due to the loss of a positive drug effect, a moderate decline due to the progression of Alzheimer's disease, and possibly an additional loss, suggesting a withdrawal effect. This decline in the placebo group is the basis of the statistically significant advantage of tacrine.

When the patients given placebo received tacrine during the

sustained active phase, they regained most of the ground lost (improvement, 3.5 points) during the 6 weeks of placebo administration, nearly returning to their placebo base-line level after 12 weeks (Fig. 2). The blinding for the double-blind phase was not broken, and thus the expectation of a response during the sustained active phase was equal in both groups. The response during the sustained active phase supports the finding of a positive response to tacrine.

Both the placebo-tacrine group and the tacrine-tacrine group had an improvement of approximately 1 point in the ADAS total score during the 22 weeks from screening to the end of the sustained active phase (Fig. 2). It is likely that this improvement represents both a beneficial drug effect and residual improvement due to an in-study effect.

Ninety-five percent of the patients were assigned one of the three ratings of the CGIC, indicating that physicians evaluating patients according to this scale were unable to recognize changes resulting from tacrine or placebo administration. An alternative explanation is that the size of the effect may not have been large enough in the majority of patients to be recognized. Significant differences favoring tacrine were noted in the secondary measures of efficacy in the analysis of the double-blind phase (the PDS and the IADL) and in the intention-to-treat analysis (the PDS, the IADL, and the MMSE), indicating that care givers noted a smaller decline in the activities of daily living in the patients given tacrine than in those given placebo.

The results of this study differ from previously reported results.^{10,21-23} The effects of tacrine are clearly not as large as reported earlier,¹⁰ nor as large as the effect represented by the 2.5-point decrease on the MMSE reported in a recent English study²³; however, the current study used different methods and a substantially lower maximal dose of tacrine (80 mg a day). On the other hand, our results lead to somewhat different conclusions from the negative results reported in French and Canadian studies.^{21,22} Both these studies had fewer patients (67 and 52, respectively) and a crossover design. The Canadian study had a four-week washout period between treatment periods and demonstrated a statistically significant improvement on the MMSE of about 1 point after four weeks of tacrine administration, but not after eight weeks.²² The French study did not have a washout period and failed to demonstrate improvement on the MMSE.²¹ The present study demonstrated greater benefit than the French and Canadian studies, but less benefit than the English study.

The central questions regarding the effectiveness of tacrine in the treatment of probable Alzheimer's disease are, What is the magnitude of the effect? and How is it defined clinically? Our study did not enable us to determine with certainty the magnitude of the improvement resulting from the use of tacrine. The failure to restore base-line conditions fully at the

end of the washout period after dose titration made it impossible to calculate the size of the drug effect with certainty. Interactions between the drug effect, the practice effect, loss of the drug effect, drug withdrawal, the carry-over effect, and worsening of the underlying Alzheimer's disease may all have occurred. Clearly, the size of the drug effect at the doses tested is not as large as that in the most favorable study.¹⁰

A rough estimate of the size of the drug effect can be derived from an analysis of the ADAS scores at the end of the sustained active phase of the study. The mean score was 0.7 point higher 22 weeks after screening. If the expected decline is estimated to be 3 points on the basis of a reported 7-point decline per year,¹⁶ the patients had ADAS total scores nearly 3 points higher than those expected without treatment. This is the equivalent of about five months' gain in performance, nearly 3 more words remembered from a list of 10, or nearly three more simple commands followed.

Adverse events, most of which were gastrointestinal disturbances, were relatively minor. The most common adverse event was nausea or vomiting. Tacrine-induced increases in alanine aminotransferase values limited the dose to 80 mg a day in this study and resulted in the withdrawal of a substantial number of patients (10 percent). When treatment was stopped or the dose reduced, alanine aminotransferase levels returned to normal in all patients, with no long-term sequelae. Thus, with frequent monitoring and a conservative upper limit on the dose, adverse events involving the liver were safely managed. The experience in this study, in a population of relatively healthy patients with probable Alzheimer's disease, however, may not lend itself to generalization to all patients with this disorder.

This study has limitations. The patients had mild-to-moderate impairment; therefore, it is not known whether the results of the efficacy analysis would apply to a population with greater impairment. A relatively large number of patients were dropped from the study because a best dose could not be determined for them or because alanine aminotransferase levels were elevated, leaving the responsiveness of this group in question. In addition, the duration of the controlled portion of the study was limited to six weeks.

These results demonstrate a statistically significant difference in favor of tacrine as compared with placebo in their effects on the cognitive performance of patients with probable Alzheimer's disease, although the improvement was not detected by clinicians' global evaluations. It is not possible to determine the exact magnitude of the treatment effect; nonetheless, some patients may receive clinically meaningful benefit from treatment with tacrine. Additional potentially useful clinical steps might emerge from alternative therapeutic approaches. For example, attempts to generate more central cholinergic activity than that

produced in the current study could prove useful. Similarly, it would seem worthwhile to pursue alternative strategies designed to augment cholinergic function as well as to reverse other neurotransmitter deficits prominent in the illness.

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APPENDIX

The following investigators and institutions participated in the Tacrine Collaborative Study: *Joseph and Kathleen Bryan Alzheimer's Disease Research Center, Duke University Medical Center, Durham, N.C.*: N.L. Earl, S.V. Taylor, E.A. Hinman-Smith, and C. Clark; *University of Southern California School of Medicine, Los Angeles*: L.S. Schneider, V. Henderson, H.C. Chui, S. Pawluczyk, R. Gleason, and M.F. Zemansky; *University of Washington, Seattle*: M.A. Raskind, E.R. Peskind, and R.F. Barnes; *Washington University School of Medicine, St. Louis*: J.C. Morris and M.A. Coats; *University of Massachusetts, Worcester*: D.A. Drachman, J. Swearer, D. Pollen, A. Mitchell, C. Lippa, A. Maloon, and M. Moonis; *Neuro/Medical Research Associates, Miami Beach, Fla.*: B.S. Baumel, L.S. Eisner, M. Karukin, and S. Coiffman; *Southern Illinois University, Springfield*: V. Kumar, R.F. Zec, and C. Womack; *University of Minnesota Medical School, Minneapolis*: D. Knopman and S. Deinard; *Burke Medical Research Institute, Cornell University Medical College, White Plains, N.Y.*: J. Blass, R.S. Black, and K. Nolan; *Rush-Presbyterian-St. Luke's Medical Center, Chicago*: J.H. Fox, D.A. Bennett, J. Heyworth, B. Bernard, R.S. Wilson, and C. Schneider; *University of California, Los Angeles*: L. Jarvik, E. Lavretsky, A. Bystrysky, R. Kahn-Rose, J. Sherman, E.J. Wiseman, B. Dickson, and M. Miller; *University Hospitals of Cleveland, Cleveland*: P.J. Whitehouse, J. Kennedy, R.H. Civil, M.F. Sanders, and A.H. Schnell; *Baylor College of Medicine, Houston*: R.S. Doody, N.D. Nelson, and E. Lipscomb; *Johns Hopkins University School of Medicine, Baltimore*: C.H. Kavas, A. Morrison, and L. Remchuck; *Mount Sinai Medical Center, New York*: K.L. Davis, R.C. Mohs, M. Davidson, T.M. Ryan, R.E. Markofsky, L. Bierer, C. Herman, R. Kahn, M. Serby, B. Lawlor, R. Stern, P.A. Farrel, P. Knott, and R.K. Yang; *University of California, San Diego*: L.J. Thal, D. Bower, and D. Salmon; *Cambridge Neuroscience, Inc., Cambridge, Mass.*: E.R. Gamzu; *Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, Ann Arbor, Mich.*: S.I. Gracon, T. Hoover, J.D. Wallace, M.K. Srirama, K.W. Lewis, W.G. Berghoff, and B.A. Baron; *University of Iowa, Iowa City*: C.S. Davis, R.F. Woolson, and P.A. Wasek.

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