Cholinesterase Inhibition for Alzheimer Disease

A Meta-analysis of the Tacrine Trials

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Objectives.—To determine the effects of cholinesterase inhibition with tacrine hydrochloride for the symptoms of Alzheimer disease in terms of cognitive performance, clinical global impression, behavior, and functional autonomy.

Data Sources.—The Cochrane Dementia Group registry of trials.

Study Selection.—Unconfounded, randomized, double-blind, placebo-controlled trials in which tacrine had been given for more than 1 day and that were completed before January 1, 1996.

Data Extraction.—Two reviewers independently selected trials for inclusion and individual patient data were sought.

Data Synthesis.—Data were analyzed from 12 trials that included 1984 patients with Alzheimer disease. At 12 weeks, cognitive performance, as measured by the Mini-Mental State Examination (score range, 0-30), was better in patients receiving tacrine than in patients receiving placebo by 0.62 points (95% confidence interval [CI], 0.23-1.00; $P = .002$). Compared with similar untreated patients who would be expected to deteriorate by 0.50 to 1.00 points on the Mini-Mental State Examination during 12 weeks, the progress of patients receiving tacrine would be expected to range between an improvement of 0.12 and a deterioration of 0.38 points. The odds ratio for improvement on the Clinical Global Impression of Change scale (range, 1-7) for patients receiving tacrine compared with those receiving placebo was 1.58 (95% CI, 1.18-2.11; $P = .002$). The behavioral noncognitive subscale of the Alzheimer's Disease Assessment Scale (range, 0-50) showed a difference in favor of tacrine of 0.58 points (95% CI, 0.17-1.00; $P = .006$). Improvement on the Progressive Deterioration Scale, largely an index of functional activities, was not significant (0.75; 95% CI, −0.43 to 1.93; $P = .21$). Age, severity of dementia, and exposure to tacrine prior to randomization had no clear influence on the treatment effect. There was a nonsignificant trend toward increasing effect with increasing dose for cognitive function and the Clinical Global Impression of Change. For patients without prior exposure to tacrine, the odds of patients' withdrawing during the study while they were receiving tacrine compared with placebo was 3.63 (95% CI, 2.80- 4.71; $P < .001$). Eleven (95% CI, 7-31) patients would need to be treated to achieve any improvement on the Clinical Global Impression scale, and 42 (95% CI, 23-125) to achieve a moderate or marked improvement. One patient would be expected to withdraw for every 4 (95% CI, 3-5) patients treated.

Conclusions.—Cholinesterase inhibition with tacrine appears to reduce deterioration in cognitive performance during the first 3 months and increase the odds of global clinical improvement. Effects observed on measures of behavioral disturbance were of questionable clinical significance, and functional autonomy was not significantly affected. The clinical relevance of the benefits of cholinesterase inhibition remains controversial, and long-term trials with clinically relevant end points are required.

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CHOLINESTERASE inhibition has been the dominant therapeutic strategy to treat the symptoms of Alzheimer disease. Tacrine hydrochloride, a cholinesterase inhibitor, was the first drug to be widely marketed for the symptomatic treatment of Alzheimer disease. Despite being licensed in several countries, the efficacy of tacrine in treating the symptoms of Alzheimer disease remains controversial, and governmental approval for its use has been refused in several countries. The use of crossover designs that harbor methodological problems, different outcome measures in different studies, an enrichment phase in some

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trials, confounding by lecithin, and the overall modest treatment effects observed in the positive studies have all contributed to the uncertainty and lack of consistency between trials. Individual trials are often too small to detect modest treatment effects reliably. To characterize better the effects of cholinesterase inhibition, we performed a systematic review of the trials of tacrine in Alzheimer disease with central analysis of individual patient data.

METHODS

Identification of Studies and Collection of Data

Trials were included only if they were randomized, double blind, placebo controlled, and involved more than 1 day of treatment for Alzheimer disease, irrespective of having been published. Only trials that had unconfounded treatment comparisons of tacrine vs placebo or tacrine plus lecithin vs lecithin were considered. For inclusion, the trial had to have been completed before January 1, 1996. Studies were identified from the Cochrane Dementia Group database of trials by searching the terms *tacrine*, *tetrahydroaminoacridine*, and *THA*: the extensive and detailed search strategy can be found elsewhere.[1] Additional sources of data were participating investigators of these trials and Parke-Davis Pharmaceuticals, Morris Plains, NJ. A single reviewer discarded irrelevant citations, based on the title of the publication and its abstract. If a suggestion was made that an article could possibly be relevant, it was retrieved for further assessment. Two reviewers independently selected the trials for inclusion in the meta-analysis from the culled citation list. There were no disagreements about the selection of trials.

All patients in these trials were diagnosed as having "probable" Alzheimer disease according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria.[2]

Outcome measures in these trials included assessments of neuropsychological function, global clinical measures of change, behavioral disturbance, activities of daily living, and quality of life. The scales most commonly used were the Mini-Mental State Examination[3] (range, 0-30) as a measure of cognition; Clinical Global Impression of Change[4] (range, 1-7) and Clinical Interview-Based Impression[5] as overall measures of clinical usefulness; the noncognitive scale of the Alzheimer Disease Assessment Scale[6] (range, 0-50) as a measure of behavioral disturbance; and the Progressive Deterioration Scale[7] to assess change in functional autonomy.

Individual data on all randomized patients were sought for the above outcome measures and for age, sex, severity of disease at baseline, treatment assignment, dose, duration of treatment, and withdrawal from the study. The first treatment period only of crossover trials was considered. Data from any enrichment (dose titration) phase prior to the main efficacy phase were excluded.

Statistical Analysis

A high proportion of patients did not complete their course of study medication, particularly in the tacrine arm of studies in which patients had not been exposed to tacrine prior to randomization. To be conservative, the main analyses performed were on the intention-to-treat populations. Treatment duration and times of assessment varied among the studies. For each measure of cognition and behavior the summary measure for each patient was the rate of change (least squares slope) calculated from all assessment times and the results expressed in terms of the effect of 12 weeks of tacrine compared with placebo. Patients who dropped out early from a study had a final value calculated by extrapolation using the mean placebo slope within that trial from their time of dropout. This extrapolation compared well with values obtained on dropouts who returned for a final study assessment. The rate of change was then calculated from this final value and the baseline value. For each study, the standardized difference was calculated by dividing the difference in the mean tacrine and the mean placebo slopes by the study pooled SD. The 12-week end point was chosen because there was a sharp drop in the number of patients with planned assessments after this point. The 6- and 24-week estimates from the model can be reached by multiplying the 12-week values by 0.5 and 2, respectively. For comparison with the intention-to-treat analyses, on-treatment analyses were performed at weeks 6, 12, and 24 using recorded data from patients still receiving treatment at those times. The on-treatment analyses at weeks 6, 12, and 24 were performed on the change from baseline. For studies lasting less than 6 weeks, the last assessment time was used in week 6 analysis. Because of the limited amount of data, only on-treatment results are presented for the measure of functional autonomy. Both the standardized differences and the changes from baseline were analyzed using meta-analysis techniques for normally distributed data.[8] For the Global Clinical Impression scale the last observation recorded for a patient was analyzed. Patients' conditions were categorized as "improved," "no change," or "worsened." A proportional odds model was fitted to each study to provide an odds ratio (OR) for improvement with tacrine compared with placebo, and techniques for pooling these values were used.[9] The number needed to treat was calculated from the OR and from the overall proportion of patients improving while taking placebo. Based on the number of randomized patients, an OR for early withdrawal from tacrine compared with placebo was calculated for each study, together with a pooled estimate[8] for studies without an enrichment (dose titration) phase. The number needed for 1 withdrawal was calculated from the OR and the overall proportion of patients receiving placebo who withdrew early.

Study estimates of treatment effect and pooled estimates[8,9] are presented together with their 95% confidence interval (CI). In studies with more than 1 tacrine arm, the data for all doses were combined to provide 1 tacrine group. Tests for heterogeneity between studies were performed. Random effect pooled estimates are presented. Regression analyses were performed to assess relationships between treatment effects and age, sex, severity of disease (based on the Mini-Mental State Examination scale) at baseline, dose of tacrine, and exposure to tacrine prior to randomization.

RESULTS

There were 15[10-24] eligible trials of which 3,[10-12] involving a total of 37 patients, were excluded because of the unavailability of suitable data (eg, lack of a common outcome measure or individual patient data). This resulted in available data on 1984 (98%) of a total of 2021 patients. The characteristics of the included studies are described in the Table. Six were crossover studies, of which 4 involved exposure to tacrine prior to randomization (enrichment). Six studies were of a parallel group design, of which 3 involved exposure to tacrine prior to randomization. The trials involved dosages varying from 20 to 160 mg/d, varying duration of treatment (3-36 weeks), and varying times and frequencies of assessment.

Two of the studies[18,20] contained more than 1 tacrine group with fixed dosage regimens. Details are given in the Table. In 3[17,23,24] of the remaining 10 studies, patients were given their "best dose" based on the prerandomization dose titration phase and in the other 7 studies patients were titrated to their best dose by the clinician after randomization, giving possible maximum dosages between 80 and 120 mg/d. Therefore, it is difficult to assess whether there is a dose-response relationship. The average final daily dose of all patients randomized to tacrine is presented with the treatment effects

Study Characteristics of Randomized Controlled Trials of Tacrine*

Trials	Design	Enriched Population	Treatment Comparisons	Total No. of Patients Randomized	Duration of Treatment, wk	Median Age, y (Interquartile Range)	Females, %	Mean Baseline MMSE Score
Chatellier and Lacomblez,[13] 1990	CO	No	T + L vs P + L	67	4	66 (61-73)	64	13.4
Gauthier et al,[14] 1990	CO	Yes	T + L vs P + L	46	8	67 (61-71)	50	17.2
Åhlin et al,[15] 1991	CO	Yes	T vs P	15	4	62 (56-65)	53	19.1
Molloy et al,[16] 1991	CO	Yes	T + L vs P + L	27	3	69 (64-71)	45	16.1
Davis et al,[17] 1992	PG	Yes	T vs P	215	6	71 (66-75)	53	16.3
Farlow et al,[18] 1992†	PG	No	T vs P	468	12	72 (67-77)	52	18.5
Wilcock et al,[19] 1993	CO	No	T vs P	85	12	69 (64-76)	53	15.7
Knapp et al,[20] 1994‡	PG	No	T vs P	663	30	74 (68-78)	52	18.4
Maltby et al,[21] 1994	PG	Yes	T + L vs P + L	41	36	69 (64-75)	49	16.8
Wood and Castleden,[22] 1994	PG	No	T vs P	154	12	77 (69-81)	60	17.0
Forette et al,[23] 1995	PG	Yes	T vs P	122	6	67 (62-75)	61	19.9
Foster et al,[24] 1996	CO	Yes	T + L vs P + L	81	4	69 (64-76)	54	17.7

*CO indicates crossover; PG, parallel group; T, tacrine; L, lecithin; P, placebo; and MMSE, Mini-Mental State Examination.

†During the initial 6 weeks, patients received placebo or 20 mg/d or 40 mg/d of tacrine hydrochloride. During the second 6 weeks, half of the patients in each group continued on the same treatment. Half received an increased tacrine dosage. Those receiving placebo began taking tacrine hydrochloride at 20 mg/d, those receiving 20 mg/d increased to 40 mg/d, and those receiving 40 mg/d increased to 80 mg/d.

‡Group 1 received placebo; group 2 received 40 mg/d of tacrine hydrochloride for 6 weeks, then 80 mg/d for 24 weeks; groups 3 and 4 received 40 mg/d of tacrine hydrochloride for 6 weeks, 80 mg/d for 6 weeks, and 120 mg/d for 6 weeks. Group 3 remained taking a dosage of 120 mg/d for a total of 18 weeks; after 6 weeks at 120 mg/d, group 4 titrated to 160 mg/d for the last 12 weeks.[20]

to provide a broad indication of any possible dose-response relationship.

More than 40 different outcome measures were used in the 12 trials. Only the Mini-Mental State Examination scale was common to all trials. The Clinical Global Impressions of Change were used in 5 studies, the noncognitive portion of the Alzheimer Disease Assessment Scale was used in 7, and the Progressive Deterioration Scale was used in 4.

Cognition

The intention-to-treat analysis showed that for Mini-Mental State Examination scores at 12 weeks there was a 0.62 (95% CI, 0.23-1.00; $P = .002$) point difference in favor of tacrine relative to placebo (Figure 1). The on-treatment analysis at 6 weeks, based on 11 studies, revealed a difference of 0.58 points (95% CI, 0.22-0.94; $P = .002$) and at 12 weeks, based on 5 studies, a difference of 0.77 points (95% CI, 0.35-1.20; $P < .001$). In a further subset of patients providing observations at both 6 and 12 weeks, the tacrine effect was estimated to be 0.29 points and 0.65 at 6 and 12 weeks, respectively. Two trials[20,21] providing data at 24 weeks showed a difference of 1.41 points (95% CI, 0.67-2.15; $P < .001$). There was no significant evidence of heterogeneity between the studies ($P = .6$). The average final daily dose from each study showed no significant evidence of a greater treatment effect with increasing dose ($P = .6$). Figure 2 shows the relatively few data that are available from direct randomized trials to assess the relationship between effect and dose. In addition, it should be remembered that since these results are based on the on-treatment analysis and larger numbers of dropouts occurred in the higher dose groups, the treatment effects may have been inflated. The intention-to-treat analysis showed that age and prior exposure to tacrine had little influence on the treatment effect. Men appeared to benefit more from tacrine than women by an average of 0.44 points (95% CI, 0.02-0.84; $P = .04$) on the Mini-Mental State Examination after 12 weeks of treatment, and this differential effect was independent of age.

The cognitive subscale of the Alzheimer Disease Assessment Scale[6] (range, 0-70) was used in 5 of the 12 trials, and the intention-to-treat analysis showed a 2.07 (95% CI, 1.36-2.78; $P < .001$) difference in favor of tacrine at 12 weeks.

Clinical Global Impression of Change

The Clinical Global Impression of Change and Clinical Interview-Based Impression scales, used to provide an overview by the clinician of whether a patient is getting better or worse, revealed an OR for improvement for tacrine compared with placebo of 1.58 (95% CI, 1.18-2.11; $P = .002$ (Figure 3). There was no significant evidence of heterogeneity between the studies ($P = .2$). Relating the treatment effect to average final daily doses gave some evidence for an increasing effect with increasing dose, although the effect was not statistically significant ($P = .09$). Age, sex, severity of dementia, and prior exposure to tacrine had no clear influence on the treatment effect. This was also the case when considering patients who had marked or moderate improvement. The number of patients who need to be treated for 1 patient to benefit was estimated to be 42 (95% CI, 23-125) when considering marked or moderate improvement and 11 (95% CI, 7-31) when considering any level of improvement.

Behavior

The noncognitive portion of the Alzheimer Disease Assessment Scale, used as a measure of behavioral disturbance, showed a 0.58 (95% CI, 0.17-1.00; $P = .006$) difference in favor of tacrine at 12 weeks (Figure 4). The on-treatment analysis at 6 weeks, based on 6 studies, revealed a difference of 0.37 (95% CI, −0.01 to 0.74; $P = .06$) and at 12 weeks, based on 4 studies, a difference of 0.49 (95% CI, −0.06 to 1.05; $P = .08$); neither of these reached statistical significance. The only study[20] with data at 24 weeks showed a difference of −0.47 (95% CI, −1.53 to 0.60; $P = .4$), in other words, a difference in favor of placebo that was not statistically significant. There was no significant evidence of heterogeneity among the studies ($P = .8$). There were no significant effects of dose, age, sex, prior exposure to tacrine, or disease severity on the treatment comparison.

Functional Autonomy

The Progressive Deterioration Scale was used in 4 studies (Figure 5). At 6 weeks, there was a nonsignificant difference of 0.75 (95% CI, −0.43 to 1.93; $P = .21$). Two studies[18,20] had follow-up periods that were longer than 6 weeks; one study[20] suggested benefit, and the other did not.[18]

Withdrawals

In 5 studies, there was no enrichment (dose titration) phase prior to the main efficacy phase. In these studies, patients receiving tacrine were significantly more likely to withdraw (OR for withdrawal from tacrine compared with placebo was 3.63 [95% CI, 2.80-4.71; $P < .001$]). No significant evidence of heterogeneity existed between the studies ($P = .5$). The reason for withdrawal was not available for all patients, but in the studies by Farlow et al[18] and Knapp et al,[20] elevated transaminase levels was given as the main reason. The number of patients needed for 1 withdrawal was estimated to be 4 (95% CI, 3-5).

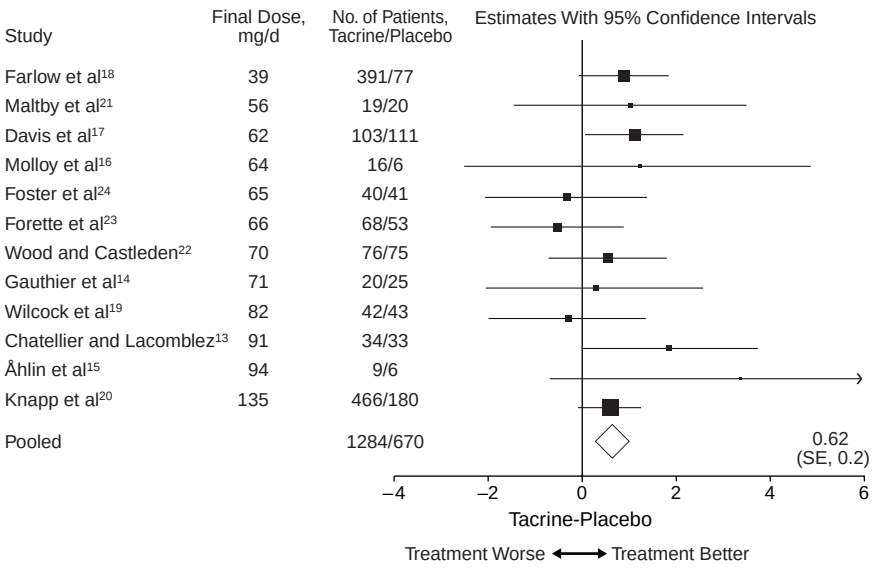

Figure 1.—Change in Mini-Mental State Examination cognitive score for tacrine compared with placebo during 12 weeks. Results are based on standardized rates of change. The final dose is the average final daily dosage of all patients randomized to tacrine in each study.

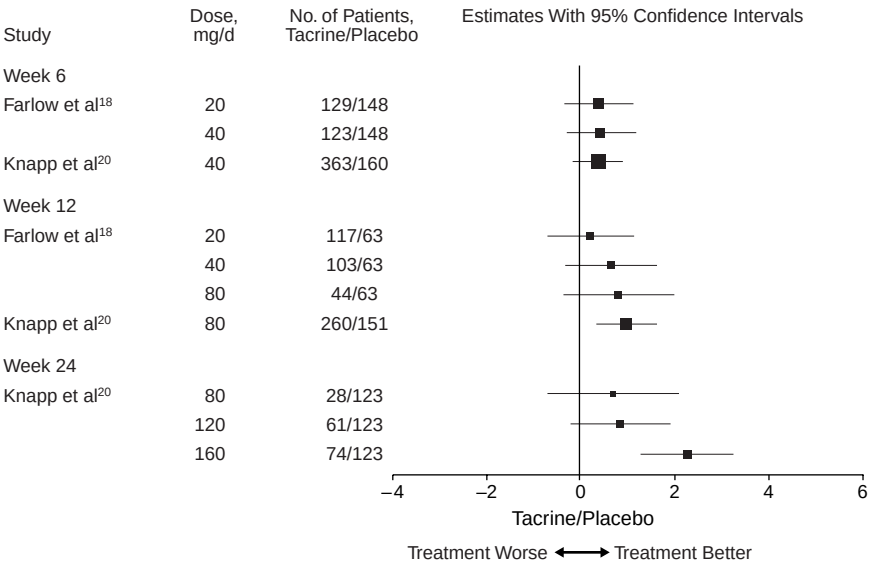

Figure 2.—Change in Mini-Mental State Examination cognitive score for tacrine relative to placebo at 6, 12, and 24 weeks for studies with fixed dosage regimens. Results are based on raw means at each time point. The dosage is that given at the time of the assessment.

COMMENT

This meta-analysis provides evidence that tacrine has an overall beneficial, but small, effect on cognitive function and the clinician's Global Impression of Change in patients with probable Alzheimer disease who had been recruited in several countries. There is a statistically significant positive effect on cognition as measured by the Mini-Mental State Examination (and the cognitive portion of the Alzheimer Disease Assessment Scale). How this effect should be interpreted for patients with Alzheimer disease is debatable. It should be noted that the trial patients were not representative of the general population of patients with Alzheimer disease.[25] In particular, they were younger than the average patient but similar in age to patients in trials of other cholinesterase inhibitors.[26,27] One method of interpretation is to relate the treatment effect to the natural history of untreated patients who are similar. Annual deterioration of about 4.2 points on the Mini-Mental State Examination has been reported for a population of untreated patients with Alzheimer disease, similar to those who entered some of the trials of tacrine, with baseline Mini-Mental State Examination scores of 10 to 21.[28] This finding is in keeping with trials of other cholinesterase inhibitors in which the placebo groups deteriorated by 1 to 2 points on the Mini-Mental State Examination over 6 months.[26,27] Assuming a linear rate of disease progression over time, we would expect untreated patients to deteriorate by between 0.50 and 1.00 points in 12 weeks. In the meta-analysis, tacrine was found to reduce the 12-week deterioration by 0.62 points compared with placebo. Therefore, the corresponding range of responses to tacrine would be expected to lie between an improvement of 0.12 points and a deterioration of 0.38 points. The results of the meta-analysis should not be extrapolated beyond the 12-week period nor to patients who are very different from those entered in the trials. There is no controlled evidence that tacrine delays the long-term course of symptoms.

The effect on Clinical Global Impressions of Change suggests that tacrine can produce clinically observable differences in overall conduct, behavior, and function. The odds of improving when taking tacrine compared with placebo increased by about 50%, and the number of patients needed to treat to show any improvement was 11, while the number needed to treat for a "moderate" or "marked" improvement was 42. What this clinically observable effect means in practice and which symptoms of Alzheimer disease are involved in producing this change is unclear. In some studies the global score included information from both patient and informant, whereas in others it was reported from just the patient.

The effect of tacrine on the behavioral symptoms, as assessed by the noncognitive portion of the Alzheimer Disease Assessment Scale with an effect of 0.58 on a scale of 1 to 50, is of questionable clinical significance. It may be that tacrine has little effect on behavior. Alternatively, it may be that there is too much variability in this measure and that it is insensitive in assessing behavioral abnormalities. Another consideration is that since behavioral symptoms were exclusion criteria for entry into these studies, a longer time interval may be necessary for behavioral symptoms to become prominent and, hence, affected by tacrine.

The assessment of the effect of tacrine on functional autonomy was limited by the availability of only 4 studies using the Progressive Deterioration Scale and the small number of assessment times. There was a nonsignificant trend for some effect of tacrine, particularly at the higher dose levels. Again, there is much variability with the use of this instrument (a visual

analog scale composed of 100-mm lines for each question completed by the caregiver) and the test may be insensitive.

Previous suggestions that tacrine is more effective in patients with mild disease,[29] moderate disease,[30] and in older patients[31] were not supported by this meta-analysis. Nor was there support for prior exposure to tacrine influencing the treatment response.[32] Why women should respond less favorably to tacrine is unknown, especially because plasma levels of tacrine are higher in women. Determining demographic or disease characteristics as predictors of response is difficult when the size of the treatment difference between tacrine and placebo treatment is modest, the combined sample size is still relatively small at 1984 patients, and the dosing regimen and study design vary considerably among trials. Analysis of subgroups in these situations may easily give rise to spurious findings purely because of chance, and the finding may easily be attributed to the multiple statistical tests performed for each characteristic. Therefore, the chief emphasis should be on the overall results rather than on any of the subgroup findings.

Early withdrawal from studies was much higher for patients receiving tacrine compared with placebo. Elevated transaminase levels were given as the main reason for this in the 2 largest studies.[18,20] The use of tacrine, therefore, is limited for this reason.

The intention-to-treat analysis was an attempt to combine data from studies that had different treatment periods and different assessment times. It assumed linear rates of symptom progression over time in each treatment group and of increasing tacrine effect over time. The limited amount of data on patients completing assessments at both 6 and 12 weeks supported this. Differences between the results of the intention-to-treat and on-treatment analyses may have been due to different patients in the 2 sets of analyses. Because of the large number of dropouts in some trials, especially at higher doses, these analyses may have been biased. Uncontrolled long-term follow-up of the treatment group from 1 trial[33] showed that tacrine therapy appeared to delay nursing home placement, but also that the pattern of decline is consistent with the drug having a limited symptomatic effect that does not increase linearly with time. Only 2 of the 12 trials had assessments after 12 weeks; therefore, it is not possible to make reliable estimates of the effects of tacrine beyond then. However, the limited data from the larger of these 2 trials support the observation of linear disease progression, at least for 30 weeks.[34]

Important issues remain in the use of tacrine that this meta-analysis could not

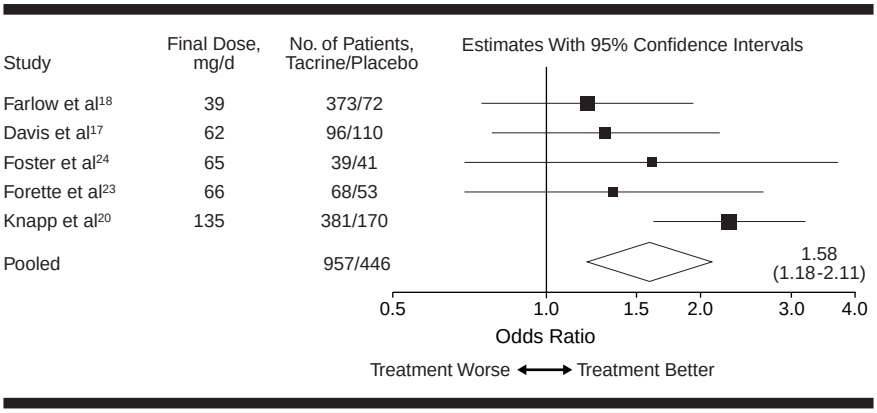

Figure 3.—Clinical Global Impression of Change. Odds of improvement on tacrine compared with placebo.

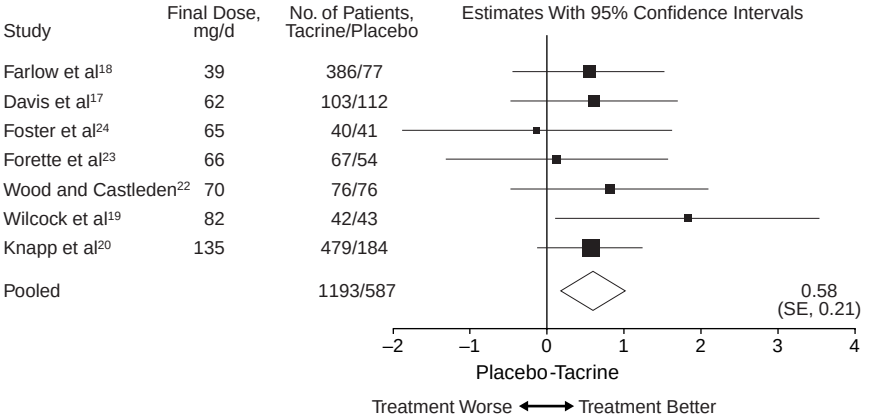

Figure 4.—Change in Alzheimer's Disease Assessment Scale noncognitive score for tacrine compared with placebo during 12 weeks. Results are based on standardized rates of change.

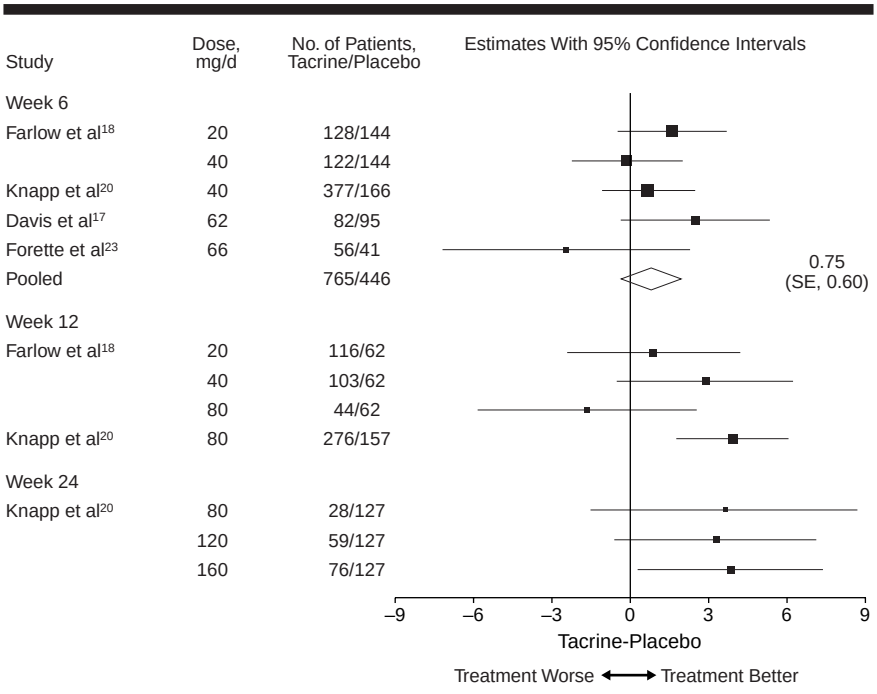

Figure 5.—Change in the Progressive Deterioration Scale scores for tacrine compared with placebo at 6, 12, and 24 weeks.

address. First, the relationship between treatment effect and dose was difficult to assess because in most studies the dose for each patient was titrated to or selected to be the patient's "best" dose. Second, there is a lack of controlled data on clinically important end points such as dependence and institutionalization. Third, the lack of long-term studies also means that we cannot assess whether the beneficial effects of continuous therapy reach a plateau, how long they endure, or when it is best to withdraw treatment.

How generalizable are these results to other cholinesterase inhibitors? The types of controlled study carried out for other cholinesterase inhibitors have also been short-term, ranging from 12 weeks to 6 months using similar kinds of outcome measures. Again, no long-term controlled studies beyond 1 year have been conducted. Results from the controlled trials suggest that although the newer cholinesterase inhibitors have fewer adverse effects and withdrawals from protocol, their efficacy is consistent with that found for tacrine.[26,27] The effects on cognition, Clinical Global Impression scales, functional scales, and behavioral scales for donepezil, rivastigmine, and trichlorfon (metrifonate) are broadly similar to that found in this analysis.[26,27] An independent meta-analysis of all the relevant controlled data for each agent would aid in an assessment of overall efficacy, particularly for functional and behavioral measures, and identify potential responders.

Efforts should continue to be directed toward further defining the types of patients and the circumstances in which they may benefit from newer cholinesterase inhibitors, prospectively defining subgroups to assess response and using better measures of important functional and behavioral outcomes. Addressing these issues reliably requires much larger trials, ideally all using a common core set of assessments of behavior and function, as well as cognition and Clinical Global Impression of Change. Furthermore, none of the cholinesterase inhibitors have reliable controlled data on meaningful outcomes such as dependency and institutionalization or other aspects of long-term efficacy; such trials are urgently needed.

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References

1. Qizilbash N, Lopez Arrieta J, Lewington S. The efficacy of tacrine in Alzheimer's disease. In: Beppu H, van Dongen M, Huppert F, Kaye J, Qizilbash N, Schneider L, eds. *Dementia Module of the Cochrane Database of Systematic Reviews 1997* [book on CD-ROM and online]. Oxford, England: Update Software Cochrane Library; 1997:3.
2. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;4:939-944.
3. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-198.
4. Guy W. *Clinical Global Impressions: ECDEU Assessment Manual for Psychopharmacology*. Rev ed. Rockville, Md: Dept of Health, Education and Welfare; 1976:218-222. Publication ADM 76-338.
5. Knopman DS, Knapp MJ, Gracon SI, Davis CS. The Clinician Interview-Based Impression (CIBI): a clinician's global change rating scale in Alzheimer's disease. *Neurology*. 1994;44:2315-2321.
6. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry*. 1984;141:1356-1364.
7. DeJong R, Osterlund OW, Roy GW. Measurement of quality of life changes in patients with Alzheimer's disease. *Clin Ther*. 1989;11:545-554.
8. Whitehead A, Whitehead JA. General parametric approach to the meta-analysis of randomised clinical trials. *Stat Med*. 1991;10:1665-1677.
9. Whitehead A, Jones NMB. A meta-analysis of clinical trials involving different classifications of response into ordered categories. *Stat Med*. 1994; 13:2503-2515.
10. Davies B, Andrews D, Stargatt R, et al. Tetrahydroaminoacridine in Alzheimer's disease. *Int J Geriatr Psychiatry*. 1990;5:317-321.
11. Fitten LJ, Perryman KM, Gross PL, et al. Treatment of Alzheimer's disease with short- and long-term oral THA and lecithin: a double-blind study. *Am J Psychiatry*. 1990;147:239-242.
12. Minthon L, Gustafson L, Dalfelt G, et al. Oral tetrahydroaminoacridine treatment of Alzheimer's disease evaluated clinically and by regional cerebral blood flow and EEG. *Dementia*. 1993;4:32-42.
13. Chatellier G, Lacomblez L. Tacrine (tetrahydroaminoacridine; THA) and lecithin in senile dementia of the Alzheimer type: a multicentre trial. *BMJ*. 1990;300:495-499.
14. Gauthier S, Bouchard R, Lamontagne A, et al. Tetrahydroaminoacridine-lecithin combination treatment in patients with intermediate-stage Alzheimer's disease. *N Engl J Med*. 1990;322:1272-1276.
15. Åhlin A, Nyback H, Junthe T, et al. THA in Alzheimer's dementia: clinical, biochemical and pharmacokinetic findings. In: Iqbal K, McLachlan DCR, Winblad B, Wisniewski HM, eds. *Alzheimer's Disease: Basic Mechanisms, Diagnosis and Therapeutic Strategies*. New York, NY: John Wiley & Sons Inc; 1991:522-532.
16. Molloy DW, Guyatt GH, Wilson DB, et al. Effects of tetrahydroaminoacridine on cognition, function and behaviour in Alzheimer's disease. *CMAJ*. 1991;144:29-34.
17. Davis KL, Thal LJ, Gamzu E, et al. Tacrine in patients with Alzheimer's disease: a double-blind, placebo-controlled multicenter study. *N Engl J Med*. 1992;327:1253-1259.
18. Farlow M, Gracon SI, Hershey LA, et al. A 12-week, double-blind, placebo-controlled, parallel-group study of tacrine in patients with probable Alzheimer's disease. *JAMA*. 1992;268:2523-2529.
19. Wilcock GK, Surmon DJ, Scott M, Boyle M, Mulligan K, Neubauer KA. An evaluation of the efficacy and safety of tetrahydroaminoacridine (THA) without lecithin in the treatment of Alzheimer's disease. *Age Ageing*. 1993;22:316-324.
20. Knapp MJ, Knopman DS, Solomon PR, Pendlebury WW, Davis CS, Gracon SI, for the Tacrine Study Group. Controlled trials of high-dose tacrine in patients with Alzheimer's disease. *JAMA*. 1994; 271:985-991.
21. Maltby N, Broe GA, Creasy H, Jorm AF, Christensen H, Brooks WS. Efficacy of tacrine and lecithin in mild to moderate Alzheimer's disease: double blind trial. *BMJ*. 1994;308:879-883.
22. Wood PC, Castleden CM. A double-blind, placebo-controlled, multicentre study of tacrine for Alzheimer's disease. *Int J Geriatr Psychiatry*. 1994;9: 649-654.
23. Forette F, Hoover T, Gracon S, et al. A double-blind, placebo-controlled, enriched population study of tacrine in patients with Alzheimer's disease. *Eur J Neurol*. 1995;2:1-10.
24. Foster NL, Peterson RC, Gracon SI, Lewis K, for the Tacrine 970-6 Study Group. An enriched population, double-blind, placebo-controlled, crossover study of tacrine and lecithin in Alzheimer's disease. *Dementia*. 1996;7:260-266.
25. Schneider LS, Olin JT, Lyness SA, Chui HC. Eligibility of Alzheimer's disease clinic patients for clinical trials. *J Am Geriatr Soc*. 1997;45:923-928.
26. Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT, and the Donepezil Study Group. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology*. 1998;50:136-145.
27. Morris JC, Cyrus PA, Orazem J, et al. Metrifonate benefits cognitive, behavioral, and global function in Alzheimer's disease patients. *Neurology*. In press.
28. Ferris SH, Mackel JA, Mohs R, et al. A multicenter evaluation of new treatment efficacy instruments for AD clinical trials. *Alzheimer Dis Assoc Disord*. 1997;11(suppl 2):S1-S12.
29. Nordberg A, Lilja A, Lundquist H, et al. Tacrine restores cholinergic nicotinic receptors and glucose metabolism in Alzheimer patients as visualized by positron emission tomography. *Neurobiol Aging*. 1992;13:747-758.
30. Farlow MR, Brashear A, Hui S, Schneider L, Unverzagt F, and the Tacrine Study Group. The effects of tacrine in patients with mild versus moderate stage Alzheimer's disease. In: Iqbal K, Mortimer JA, Winblad B, Wisniewski HM, eds. *Research Advances in Alzheimer's Disease and Related Disorders*. New York, NY: John Wiley & Sons Inc; 1995:283-292.
31. Eagger S, Levy R. Serum levels of tacrine in relation to clinical response in Alzheimer's disease. *Int J Geriatr Psychiatry*. 1992;7:115-119.
32. Davis KL, Powchik P. Tacrine. *Lancet*. 1995; 345:625-630.
33. Knopman D, Schneider L, Davis K, et al, and the Tacrine Study Group. Long-term tacrine treatment: effects of nursing home placement and mortality. *Neurology*. 1996;47:166-177.
34. Smith F. Mixed-model analysis of incomplete longitudinal data from a high-dose trial of tacrine (Cognex) in Alzheimer's patients. *J Biopharm Stat*. 1996;6:59-67.