Alzheimer Disease and Associated Disorders
Vol. 13, No. 3, pp. 124–129

Clinical Trials in Alzheimer Disease: Debate on the Use of Placebo Controls

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Summary: During the past 10 years, there has been a rapidly growing number of pharmaceutical industry-sponsored drug trials for treatment of Alzheimer disease (AD) and other neurodegenerative diseases. As public awareness and concerns about AD have grown, so has interest in developing drug therapies for retarding symptom progression, delaying onset, and ultimately curing the disease. Ethical debate on the use of placebo control trials in AD research has come of age in the United States with the availability of treatments approved by the Food and Drug Administration. The experts and the public agree that more effective therapies are necessary, and new therapeutic options are being developed as rapidly as possible. The arguments on each side of the debate are provocative and important but do not provide unequivocal justification for either the abandonment or the maintenance of placebo-controlled trials in all AD research. Clinical trials differ with respect to scientific and practical goals, and these factors inherently affect the ethical priorities of each study. We present these contrasting points of view to delineate some of the issues rather than to make specific recommendations other than to urge that all clinical trials in AD should be designed with careful consideration of the ethical issues surrounding the use of placebo controls. As new and more effective treatments emerge, the ethical framework for placebo use in AD studies will require frequent re-examination. To make wise choices, patients, caregivers, physicians, and ethicists (among others) must have a voice in this continuing discussion. **Key Words:** Placebo—Clinical trials—Ethics—Alzheimer disease.

Received December 23, 1998. Accepted January 6, 1999.

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During the past 10 years, there has been a rapidly growing number of pharmaceutical industry-sponsored drug trials for treatment of Alzheimer disease (AD) and other neurodegenerative diseases. As public awareness and concerns about AD have grown, so has interest in developing drug therapies for retarding symptom progression, delaying onset, and ultimately curing the disease. In 1993, the United States Food and Drug Administration (FDA) approved the use of tacrine (Cognex®, Parke-Davis/Warner Lambert), a cholinesterase inhibitor, for treatment of symptoms in patients with mild to moderate AD. More recently, in November 1996, the drug donepezil (Aricept®, Eisai/Pfizer), another cholinesterase inhibitor, received FDA approval for treatment of symptoms in AD. Other drugs are currently in various stages of study and development, and it is likely that some of these may receive FDA approval in the next few years.

The FDA approval of tacrine and donepezil as therapeutic agents in AD has implications for how future clinical trials in AD will be conducted in the United States. Specifically, the availability of these new medications raises ethical concerns for the continued use of placebo-controlled clinical trials in AD. Placebo-controlled scientific studies remain the gold standard for demonstrating the efficacy of an experimental drug (Growdon, 1993). Although in clinical trials tacrine and donepezil have shown only modest treatment efficacy, these drugs now present a viable and potentially attractive treatment alternative to patients and families considering participation in a long-term clinical trial with an unproven experimental drug and a placebo arm. In addition, some experts believe that widespread prescription use of donepezil and tacrine and growing public awareness of the drugs have made these medications a de facto standard of care for treatment of AD. Thus, the question has arisen as to whether, in the era of donepezil and tacrine, conducting placebo-controlled AD drug trials continues to be ethical.

Such a question is both a marker of scientific progress in the field, and a clarion call for ethical inquiry and discussion. In 1998, the Alzheimer Association and the Internal Ethics Committee of the Alzheimer Disease Cooperative Study (ADCS) co-sponsored a conference in Minneapolis on placebo-controlled drug trials in AD (Cassel and Alzheimer's Association Ethics Panel, 1998). At that conference, a number of experts in ethics and AD addressed the many different aspects of the placebo problem. In the present article, we review the types of placebo controls and address this topic in AD research with spirited pro and con position statements by leading participants at the conference. We conclude with a summary statement concerning the current status of the placebo question in AD, and the likely evolution, if not resolution, of this question for the field.

Types of Controls

There are three types of placebo controls. *Historical controls* compare the outcome of subjects treated with an agent to the outcome expected from the "known history of the disease," typically based on data gathered from the literature. Although this type of study has the ethical advantage that all subjects can be treated, there are several disadvantages. First, the outcome from a disease may change over time. For example, in the United States, dietary changes and treatment of hypertension have reduced the incidence of stroke over the past 30 years. Therefore, a primary prevention trial carried out today to compare the effects of an agent on the incidence of stroke with use of an historical control group would find an ineffective agent to be successful in reducing the incidence of stroke, because of the natural decrease in incidence over time. Second, detailed demographic and clinical information on the subjects is often not included in published reports, and the controls may not have comparable key characteristics. Third, historical controls are also particularly vulnerable to selection bias in which individuals with nonrandom outcomes are compared with the experimental treatment group.

Nonrandomized concurrent controls have been used in some studies, particularly in surgical trials, in which a clinician decides to subject some patients to surgery, but not others, and to compare the outcome of the two groups. Such studies are problematic, in that groups may not be comparable in important characteristics and again are subject to selection biases.

Randomized control studies are the standard against which all other designs must be compared. In these studies, all subjects are equally likely to be assigned to either the intervention or the control group, thereby reducing bias from unknown confounders. Randomization is also important for the validity of statistical tests of significance. If randomization is not used, assumptions concerning the comparability of the groups and statistical

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models must be assured before valid comparisons can be made. A review of the use of anticoagulation therapy in acute myocardial infarction revealed that of 32 studies, 15/18 with historical controls and 5/8 nonrandomized concurrent controls trials showed statistically significant results favoring anticoagulation therapy. In contrast, only 1 of the 6 studies using randomized controls showed statistical results in support of this therapy (Chalmers et al., 1977).

CASE FOR ELIMINATING PLACEBO CONTROLS IN AD RESEARCH (DAVID KNOPMAN AND JOHN MORRIS)

AD now is a treatable disorder (Knopman and Morris, 1997). Two cholinesterase inhibitors (ChEIs), tacrine hydrochloride and donepezil hydrochloride, have been approved by the FDA for the symptomatic treatment of mild to moderate AD. Although the magnitude of the benefit is modest, the efficacy of ChEIs for cognitive, behavioral, and global function has been demonstrated amply in multiple studies (Davis et al., 1992; Farlow et al., 1992; Knapp et al., 1994; Thal et al., 1996; Wilcock and Wilkinson, 1996; Corey-Bloom et al., 1998; Morris et al., 1998). ChEIs have become the first-line agents for the treatment of AD (Doraiswamy and Steffens, 1998); other than newer ChEIs, no antidementia drugs are likely to receive FDA approval in the next few years. Donepezil in particular has been widely used. Since its release in January 1997, more than 500,000 patients have been treated with this drug (information courtesy of National Data Corporation Health Information Services, Phoenix, AZ, U.S.A.). These data suggest that a substantial proportion of the estimated 2.5 million Americans with AD (Graves and Kukull, 1994) already have been exposed to ChEI therapy.

Scientific Concerns in Placebo-Controlled Trials

The emergence of ChEIs for the treatment of AD has several important practical implications for current and future clinical trials of antidementia drugs. Before tacrine was approved in 1993, the options for AD patients seeking therapy were limited almost exclusively to experimental drugs in clinical trials or hydergine and herbal remedies. Now there are other choices and the pool of treatment-free patients eligible for clinical trials has been reduced substantially by the number of patients using tacrine or donepezil. Patients who are ChEI-naive are more difficult to recruit for participation in clinical trials, because they often elect to try FDA-approved ChEIs before enrolling in a trial with unproven agents and with the risk of randomization to an inactive (placebo) treatment arm. These factors suggest that patients who volunteer for placebo-controlled clinical trials may be "ChEI failures" or are otherwise different from AD patients choosing ChEI therapy. The generalizability of findings from such studies to the AD population at large may be thus limited.

Ethical Concerns

There also are important ethical implications. Although not all clinicians necessarily accept ChEI therapy as "standard of care," the proven (albeit modest) efficacy of these compounds and the lack of alternative approved therapies have combined to create a demand for this treatment (as reflected by the increasing volume of prescriptions for donepezil). For many, ChEIs have or will become "standard" clinical practice. The Declaration of Helsinski states clearly that every patient, including those of a control group, should be assured that they will receive the best proven diagnostic and therapeutic method (Rothman and Michels, 1994). The interpretation of what constitutes "proven" or "effective" treatment depends on the point of view of the observer, but the interpretation does not require that the treatment will cure or even modify the disease effect. The United States agency responsible for drug evaluation (FDA) has determined that both tacrine and donepezil are effective in the treatment of mild to moderate AD.

New and potentially more effective drugs for AD must continue to be evaluated, however, because ChEIs are far from ideal drugs. Efficacy is modest and, at this point, the only proven treatment effect is symptomatic rather than disease modifying. Moreover, not all patients respond to ChEI therapy and quality of life may not be enhanced, even among responders (Post and Whitehouse, 1998). Nonetheless, currently available ChEIs offer palliation of symptoms for many AD patients. The withdrawal or withholding of benefits from proven therapy, as occurs when patients are randomized to inactive treatment in placebo-controlled clinical trials, is unacceptable from our ethical perspective (Knopman et al., 1998). With the availability of effective treatment, we suggest that placebo-controlled trials for the evaluation of drug therapies for AD are no longer justified ethically.

Although placebo-controlled study designs are preferred when appropriate because they are easier to interpret, alternative designs are also suitable for the evaluation of new drugs. These designs still include a control group, but instead of a placebo, the controls receive an approved drug at appropriate doses for the illness being treated. This *add-on study* design compares the effect of an approved drug together with a new compound versus the approved drug alone. Such a design has been used for years to evaluate new compounds in conditions (e.g., epilepsy) in which established therapies are available. An *active control design* represents a second alternative in which the subjects in one limb of the study receive an

approved drug and those in the other limb receive the new drug to determine whether the new treatment is superior to the available treatment, rather than simply whether it is more effective than nothing (placebo).

Concerns About Informed Consent

Advocates of placebo-controlled trials in AD argue that the risk of withholding modestly effective ChEI therapy for short durations (<24 weeks) is presented adequately in the informed consent process so that patients may choose reasonably to accept that risk. The informed consent process, which optimally provides sufficient medical information to allow the patient to make an intelligent decision about treatment choice, comprises three elements: (1) information; (2) voluntary choice; and (3) competency (Marson et al., 1995). Although many investigators take the responsibility for providing information seriously, the process may be flawed by unintended bias if, for example, patients are being recruited for a trial that the investigator believes to be important or from which the investigator perhaps stands to benefit financially (e.g., as the recipient of a research grant or contract to conduct the study; Morris, 1994). Enthusiastic investigators might minimize the risks of withholding active treatment even for a short duration in attempts to encourage subjects to participate in placebo-controlled studies.

The impaired capacity of demented patients to understand information also limits truly informed decision making. Assessing capacity to consent is difficult and physician judgment about competency in AD varies greatly (Marson et al., 1997). The risks of placebo-controlled studies, no matter how trivial, may not be fully appreciated by even mildly demented patients with impaired reasoning abilities. The practice of obtaining proxy consent from the patient's surrogate (often the spouse or adult child) does not satisfactorily resolve the quandary, as the surrogate's decisions usually reflect their choice rather than a substituted judgment (i.e., what the patient would decide; Muncie et al., 1997). Thus it is problematic to rely on the informed consent process to protect vulnerable AD subjects who are being asked to participate in placebo-controlled studies (Karlawish and Whitehouse, 1998).

The case for abandoning placebo-controlled studies in AD is compelling. AD patients are taking standard ChEI therapy (e.g., donepezil) in large numbers. Placebo-controlled clinical trials in AD may suffer substantially from poor recruitment and unrepresentative samples. It makes sense to compare directly the effects of new agents (or combinations of agents) for the treatment of AD with the effects of ChEIs, so that superior treatments can be identified (Knopman et al., 1998). The elimination of placebo controls in favor of active controls in AD clinical trials is ethically appropriate. We believe strongly, therefore, that placebo controls should no longer be used in the evaluation of new drugs for the treatment of AD.

CASE FOR RETAINING PLACEBO CONTROLS IN AD RESEARCH (MARTIN FARLOW AND LEON THAL)

Scientific clinical investigations virtually always demand that a control group be used to compare the responses of treated patients with those of untreated patients. Before the 1950s, many studies did not include control groups. When Pasteur developed the vaccine for rabies or penicillin was given for pneumococcal pneumonia, the outcome in treated patients was so different from that in untreated patients that no control group was needed. However, for treatment trials in which differences are more subtle and the course of the disease variable, a control group is clearly required.

Placebo-Controlled Trials in Other Illnesses

It is true that placebo-controlled trials have been abandoned in some neurological illnesses such as epilepsy, for which add-on designs are now the norm. The magnitude of the effect in epilepsy trials (reduction in seizure frequency and severity), however, is usually much greater than the small treatment effect observed in AD clinical trials. In contrast, investigational trials of antidepressants still commonly use placebo controls (American Psychiatric Association, 1993). Many of the justifications for use of placebo in these trials are directly analogous to the current therapeutic situation in AD: new drugs with equivalent efficacy but with fewer side effects are still needed and new second-line drugs for nonresponders need to be developed. High rates of placebo response for existing drugs could lead to a false conclusion of therapeutic equivalency if they were used as active comparators. In addition, there is difficulty in determining rates of side effects against active comparators that also potentially cause significant side effects.

Symptomatic and Disease-Modifying Trial Designs

Concerns have been expressed that it is not ethical to deny AD patients the proven benefits of currently established therapies, a situation that would occur for control patients in trials in which a placebo is used. In addressing these concerns, it is helpful to consider trials of symptomatic therapy (typically of a shorter duration of 6 months or less) separately from trials of putative disease-modifying agents (typically of longer duration, from 1 to 2 years).

Trials for Symptomatic Therapy

ChEIs have been demonstrated to provide mild improvement in cognition in AD patients (Knapp et al., 1994; Thal et al., 1996; Wilcock and Wilkinson, 1996; Morris et al., 1997, 1998; Corey-Bloom et al., 1998; Rogers et al., 1998). Use of these drugs for palliative therapy continues to increase. These drugs are not without side effects and cause anorexia, dyspepsia, nausea, and vomiting.

Benefit from these compounds is relatively small. The Mini-Mental State Examinations (Folstein et al., 1975) from several trials have shown less than a 1-point difference between patients treated with placebo and those treated with ChEIs. The magnitude of the treatment effect has typically been about 40% of the size of the standard deviation. Thus, overlap between placebo and drug treatment groups has been large.

Studies with "active agent" controls, therefore, would not be able to detect small effect size without large numbers of subjects. Previous clinical trials in AD patients have also shown high rates of placebo response, further complicating the situation. Given these limitations, there is still a clear need for more effective symptomatic drugs with fewer side effects. The power of active comparator trials is insufficient to identify these drugs in a reasonably timely and efficient manner. Abandoning placebos for active comparators raises another concern: such trials might show therapeutic equivalence of an ineffective new drug to the active comparator by chance, whereas the placebo comparator would have demonstrated the lack of effect. Active control trials clearly assume that an established therapy is effective. In treatment trials for AD, currently established therapies have only minor degrees of efficacy, such that even drugs found to be effective in AD may have negative studies (two tacrine trials had negative results: Chatellier and Lacomblez, 1990; Gauthier et al, 1990).

Trials for Disease-Modifying Agents

Examining the longer duration trials, the evidence that specific medications may delay disease progression in AD patients is limited at best. The most convincing study is a recent double-blind, placebo-controlled, 2-year duration trial of vitamin E and/or selegiline in patients with moderate to severe AD (Sano et al., 1997). The vitamin E-treated group in this trial progressed 25% less rapidly to a mixed criteria endpoint. Unfortunately, there were baseline differences in severity of disease between the groups and only after adjusting for these group differences were statistically significant beneficial effects observed for vitamin E. No differences in cognitive functioning were observed between any of the groups. The results of this trial have not been replicated. No other agents have been shown to delay the underlying biological disease process of AD. Thus, for trials that examine disease progression, the scientific and ethical rationales for continuing the use of placebo controls as the standard of comparison remain intact.

Practical and Ethical Rationales for Continuing Placebo-Controlled Trials

Numerous patients with AD have already been exposed to symptomatic therapy with ChEIs. Future clinical trials will therefore include large numbers of nonresponders to this form of therapy. This will result in a selection bias so that the result may not be generalizable to the population at large. Nevertheless, it can be argued that these patients are exactly the ones for whom new, more effective therapies are needed.

Concerns have been expressed that patients with AD are mentally impaired and thus incapable of giving true informed consent. In such circumstances, current guidelines suggest that if effective therapies for a disease or condition are available, every patient should be entitled to "effective" therapy. The argument here is whether available remedies for AD constitute truly effective therapies. The magnitude of the therapeutic effect from ChEIs is small as measured by cognitive tests and it is generally difficult to assess in terms of practical clinical benefit. No drug has been demonstrated conclusively to slow disease progression. Because the magnitude and probability of clinical benefit from existing therapies is limited, it is premature to abandon placebo-controlled trials.

In summary, ChEIs are being used increasingly as symptomatic therapy for AD. Vitamin E is also being prescribed for its reported disease-delaying effects as well as possible general benefits to health, thus making it more difficult to recruit patients with AD for placebo-controlled clinical trials. In our view, this shift in community practices does not constitute a new "standard of care" and thus does not mean that conducting placebo-controlled studies is unethical, nor does it change the reality that these trials are inherently more efficient and effective in evaluating treatment effects in AD. The notion of standard of care involves not only widespread use, but also a conviction on the part of all interested parties that the therapy has obvious and tangible benefits. Donepezil and vitamin E seem to fall short in that aspect despite their quantitative demonstrations of efficacy.

Under some circumstances, adaptation rather than abandonment of past trial designs may be necessary. Some strategies to consider include: increasing the numbers of patients on active drug versus placebo, limiting

study duration for symptomatic drugs to 6 months, and permitting concomitant use of symptomatic medications such as ChEIs in disease-modifying trials. Blanket abandonment of placebo controls in AD treatment would be detrimental to the rapid development of newer, more successful treatments for this devastating illness.

CONCLUDING REMARKS

Ethical debate on the use of placebo control trials in AD research has come of age in the United States with the availability of FDA-approved treatments. Evidence of effectiveness has been shown for ChEIs such as tacrine and donepezil, and other compounds are likely to be available soon. It is not ethical to withhold "effective" treatment from a patient, but the efficacy of these compounds is modest and does not extend to all patients. Moreover, these treatments do not appear to change the overall course of the disease. The experts and the public agree that more effective therapies are necessary, and new therapeutic options are being developed as rapidly as possible. Clinical trials will determine their "effectiveness."

The arguments on each side of the debate, at present, are provocative and important but, at this point, do not provide unequivocal justification for either the abandonment or the maintenance of placebo-controlled trials in all AD research. Clinical trials differ with respect to their scientific and practical goals, and these factors inherently affect the ethical priorities of each study. We present these contrasting points of view to delineate some of the issues rather than to make specific recommendations other than to urge that all clinical trials in AD should be designed with careful consideration of the ethical issues surrounding the use of placebo controls. As new and more effective treatments emerge, the ethical framework for placebo use in AD studies will require frequent re-examination. To make wise choices, patients, caregivers, physicians, and ethicists (among others) will all need to have a voice in this continuing discussion.

Acknowledgments. This study was supported by the National Institute on Aging, Alzheimer's Disease Cooperative Study, AG010483.

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