ORIGINAL ARTICLE

Improving Drug Trials for Mild to Moderate Alzheimer's Disease

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ABSTRACT: Over the last two decades, numerous studies have been conducted on subjects with mild to moderate Alzheimer's disease. The objective of this paper was to review concerns raised in the literature about the design and methodology of these clinical trials and to make recommendations to deal with the limitations identified. Concerns raised in the literature include the following: undue focus on statistical rather than clinical significance; the need for further pharmacoeconomic evaluations; the non-representativeness of the study populations; perceived inadequacies in the direct-comparison studies conducted to date; the limitations of open-label extension studies; the inability of standard psychometric tools to document all the relevant treatment effects; the ethics of placebo-controlled trials; and, problems caused by the actions of the regulatory authorities. Recommendations are made to deal with the issues raised.

RÉSUMÉ: Améliorer les essais thérapeutiques sur la maladie d'Alzheimer de légère à modérée. Au cours des vingt dernières années plusieurs études ont été faites chez des sujets atteints de la maladie d'Alzheimer de légère à modérée. L'objectif de cet article était de revoir la littérature concernant les problèmes relatifs au plan d'étude et à la méthodologie de ces essais cliniques et de faire des recommandations pour pallier ces problèmes. Les problèmes suivants ont été relevés dans la littérature : l'accent est mis sur la signification statistique plutôt que sur la signification clinique; la nécessité d'évaluations pharmaco-économiques plus poussées; la non-représentativité des populations étudiées; les imperfections relevées dans les études de comparaison directe effectuées jusqu'à maintenant; les limites des prolongations d'essais ouverts; l'incapacité des outils psychométriques standards à documenter les effets thérapeutiques pertinents; l'éthique des essais contrôlés par placebo et les problèmes engendrés par les dispositions adoptées par les autorités chargées de la réglementation. Nous faisons des recommandations pour résoudre les problèmes décelés.

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The goal of the 2nd Canadian Conference on Antidementia Guidelines was to build on the 1995 paper by Mohr et al.[1] In comparison to some of the other topics (e.g., Mild Cognitive Impairment), numerous studies dealing with the treatment of mild to moderate Alzheimer's disease (AD) have been published. In this paper, I will review the concerns raised about these clinical trials. Recommendations for future drug trials of mild to moderate AD will be made to deal with the identified limitations.

Methods

Data for this review were initially derived from literature in the possession of the author. Additional papers for review were identified in a series of Medline searches (limited to the terms "clinical trials", "English" and humans) with the keywords "Alzheimer," "Alzheimer's", "dementia", "effect size", "responder", "endpoints", "end points", "pharmacoeconomics", "outcome measures", "global measures" and "treatment effect," used individually and in various combinations. Other reports were selected from the references of the papers identified. Articles selected for inclusion in this paper were chosen by the author based on their representativeness of the most relevant work.

Results

Criticisms raised in the literature about the clinical trials done to date include the following:

Statistical Versus Clinical Significance

Undue emphasis has been placed on statistical tests of significance rather than "more socially relevant outcomes"

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and/or "practical effectiveness".[2,3] Even trivial therapeutic effects can become statistically significant if a large enough sample is used. This has led to a questioning of the practical value of the drugs available for AD, such as the cholinesterase inhibitors (ChEIs). In the effort to ensure the clinical significance of the benefits seen in AD trials, a number of approaches have been recommended.

In 1990, the US Food and Drug Administration proposed guidelines for the clinical evaluation of antidementia drugs.[4,5] To receive approval, significant benefits had to be demonstrated on both a cognitive measure and a global evaluation. The latter was to ensure that the treatment effect was not "trivial".[5] The Clinician's Interview-based Impression of Change (CIBIC) and the CIBIC-plus (which includes input from a caregiver) have been the most widely used global measures in AD trials.[4] Problems with the CIBIC/ CIBIC-plus include the potential for rater bias, inconsistencies in format and content, inconsistencies in defining a treatment effect, poor inter-rater reliability, uncertainty about responsiveness to change and relative insensitivity in detecting improvement.[4,6-8]

The Committee for Proprietary Medicinal Products of the European Agency for the Evaluation of Medicinal Products in 1997 issued their own guidelines on medicinal products in the treatment of AD.[4] Improvements in symptoms should be sought in three domains: cognition as measured by objective tests (cognitive endpoint); activities of daily living (functional endpoint); and, overall clinical response as reflected by a global assessment (global endpoint). In studies, two primary variables are to be stipulated - one must be cognitive while the other is to ensure the clinical relevance of any improvements seen in cognition. There is a requirement to examine overall benefit at the level of individual patients (responder analysis). A responder was typically defined as a patient who, at six months, showed improvement to a pre-specified degree on the cognitive measure and had not worsened in the other two domains.[4] Responder analyses were to verify the clinical relevance of the observed effect size by determining a response rate.[9] Concerns about responder analyses include the arbitrariness of the definition of a responder and loss of information by dichotomizing what is continuous or ordinal data.[9]

A Minimal Important Difference (MID) was initially defined as the smallest difference in the score of a domain of interest that patients perceived as beneficial and which would lead, in the absence of troublesome side effects and/or excessive cost, to a change in management.[10] From the standpoint of a physician, a MID has been described as the smallest effect size that would lead a practitioner to recommend therapy for a patient.[11] There was a published attempt to determine a MID for dementia studies. As part of a survey about vascular dementia, Canadian geriatricians and neurologists were asked: "From your experience following demented patients, what are the smallest changes in the Folstein Mini-Mental State Examination scores that are compatible with a noticeable change in the patient's overall condition?"[12] The mean value obtained from the respondents (n = 161) was 3.72. This was proposed as a MID for dementia studies.

There were a number of problems with this study. The ambiguous question asked oversimplified the issue. Defining a clinical trial as "positive" solely on whether the mean difference (between the intervention and control arms) on the Mini-Mental State Examination was 3.72 or greater, could marginalize other legitimate outcomes and trivialize issues such as cost and/ or the resources required to produce the specified change. The perspective of the patient and/ or their caregiver was not sought. A MID obtained from a survey can vary greatly depending on who is asked and how.[11] Achieving consensus on a MID[13] for AD trials seems as likely as finding either "the holy grail"[13] or "the pot of gold at the end of the rainbow".[14]

Goal Attainment Scaling represents another attempt at assessing the clinical significance of the impact of therapy at the level of the individual. It is a clinimetric outcome measure that captures individualized treatment effects and incorporates patient preferences.[15] It begins by the selection of dementia-related problem areas for the individual patient. Each of the identified problems is described in an observable manner. Possible outcomes with treatment are then described, ranging from getting a lot better (assigned a score of +2), showing no change (score = 0) to getting a lot worse (score = -2). When the patient is seen in follow-up, their outcome status with regards to the identified problems is determined and scored. Goal Attainment Scaling represents a potentially practical way of measuring meaningful outcomes for patients and caregivers in AD trials.[16]

Another attempt to assess whether treatment leads to meaningful improvements is by using statistical survival techniques.[17-20] Endpoints are selected that are presumably objective, clinically meaningful, frequent, representative of true progression and relatively rare at the beginning of the study.[18] The intervention group is then compared to the control group on the time required to attain one of these endpoints. Unfortunately, there is no consensus on which endpoints should be used. Some may be inappropriate for assessing the effectiveness of a medication for AD. Institutionalization is an endpoint often suggested,[17-20] but this typically arises from a complex mix of clinical, environmental, social, financial and/or health service factors.[3] Drug therapy would have a direct impact on only clinical factors.

Reporting on effect size is probably the most commonly used strategy to address concerns about the relevance of clinical trial findings. Effect size is an indicator of the importance of the results of a study regardless of the sample size.[21] It focuses on signal to noise as indexed by the ratio of differences to variance.[13] In AD trials, ChEIs (high dose effect size = 0.25-0.47) and memantine (0.32-0.62) produce small to moderate effect sizes on cognitive and global measures.[22,23]

Another statistical approach is the reporting of the Number Needed to Treat (NNT). This is the number of patients who need to receive the treatment in question, compared to another treatment (often placebo), for one patient to gain a "specified benefit". The NNT in order to see improvements on study measures for ChEIs and memantine range from three to eight.[23,24] The relevance of the "specified benefit" examined in these analyses remains debatable. The NNT approach can be combined with responder analyses.

Need for High Quality Pharmacoeconomic Studies

There is no consensus about the cost implications of the therapies available for the treatment of AD. At one end of the

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spectrum, the authors of the AD2000 study have said that ChEIs are over-priced considering their minimal benefits.[17,25] At the other end, industry-sponsored pharmacoeconomic evaluations show models where significant cost savings arise from delays in the progression to more severe stages of dementia. Drug costs are more than offset by anticipated lower caregiver and non-drug related health care costs. A number of methodological concerns about these studies have been raised.[26,27] The models presented are problematic because they are based on a number of assumptions, rely on the results of short-term trials to estimate long-term costs and may not be generalizable to other settings and regions.

Concerns about the Representativeness of the Subjects Studied

It has been claimed that subjects recruited into the AD drug trials are not representative of all patients with AD.[2,3,28,29] For example, younger patients are over-represented in clinical studies.[28] The majority of patients in Ontario prescribed donepezil during 2001-2002 would have been ineligible for the clinical trials that led to its approval.[29] Selection criteria for two industry-sponsored AD trials excluded 92.1-95.6% of 3,470 subjects with AD attending one of nine AD Diagnostic and Treatment Centers in California.[30] Subjects who were provisionally eligible were younger, more likely male, better educated, wealthier and more likely to be white than ineligible subjects.[30] An Israeli dementia clinic participating in a number of drug studies found that only 13% of their patients with AD could be recruited into one or more AD drug trials.[31] Cohen-Mansfield[32] reported recruitment rates of 1% and 14% for two dementia drug trials. Until recently drug manufacturers were under no obligation to ensure that those enrolled in drug studies were representative of the total population of individuals with the condition of interest. Studies were conducted primarily to provide proof that the drug has a beneficial therapeutic effect in at least some patients. Regulatory bodies are now encouraging sponsors to test their medication on the full range of patients who will eventually be using their drug if it is approved for marketing.

A specific issue has been the decision to restrict entry for most AD trials to those with probable AD. This leads to an attempt to recruit patients with a single cause for their dementia. It has been argued that homogeneous study populations would be more likely to show drug effects because the agent would be targeted to subjects without confounders. For many patients, though, dementia has a complicated etiology. In the ACCORD study, 36.8% of patients diagnosed with AD were felt to have a second condition contributing to their dementia.[33] A number of autopsy series have shown a high rate of concomitant pathology.[34-36] For example, Barker et al[36] found that only 54.3% (159/293) of AD cases had "pure AD" with concomitant central nervous system pathologies found in the remaining 45.7%. Comorbidities and atypical features in one report did not substantially affect AD outcomes.[37] The authors of this paper argued that subjects with possible AD can be considered for inclusion in AD drug trials to improve the generalizability of the findings obtained.

Weakness of the Comparison Trials

In Canada three ChEIs and memantine are being marketed for the treatment of AD. The issue of which drug to use as initial therapy, especially those with moderate AD, is contentious. Comparison of relative efficacy and tolerability across clinical trials is not appropriate because of inter-study differences in the baseline characteristics of the populations enrolled, the efficacy measures used and/ or how safety evaluations were done. Randomized controlled trials (RCTs) that directly compare one agent with another would be the preferred way of making drug comparisons - if they are done in a scientifically sound manner. No RCTs comparing memantine with a ChEI have been published. There are four RCTs, all supported by one of the pharmaceutical firms, contrasting one ChEI with another.[38-41] There were methodological limitations and/ or no significant differences found on the primary outcome measures in these studies. [42,43] None of the ChEIs has been shown to offer an efficacy advantage.

The Need for Better Outcome Measures

There are three challenges here. First, the results from the measures used in AD drug trials can be difficult for patients, caregivers, practitioners and funders to translate into something that is meaningful to them. What does an average 3.4 point benefit on the ADAS-Cog mean? To most it is just a number. Second, many of the scales used require training and take too much time to be practical in a primary medical care practice. This complicates translating research findings to the clinical setting. Finally, the scales used in evaluating treatment efficacy do not capture all the relevant treatment effects. A survey of physicians' opinions about the manifestations of AD that benefit the most from available therapies found that many (e.g., alertness, ability to keep attention, participating in leisure activities, repetition) are not captured in a systematic fashion by the standardized measures currently used in AD trials.[44]

Doubts about Open-Label Extension Studies

Open-label extensions of RCT are commonly conducted. While a way to obtain access to promising agents before they are approved for marketing, they are also justified on scientific grounds. It is felt that these studies can provide information on long term efficacy, safety and tolerability.

A number of ethical and scientific reservations about open-label extension trials have been raised.[45] Their validity in the determination of safety and tolerability has been questioned. A proportion of subjects entered into open-label extension studies will have taken the agent during the RCT portion of their participation. If intolerant of the agent during this portion, they likely would not enroll in the extension. By screening out at least some of those who developed significant adverse effects to the drug, an exaggerated sense of the tolerability of the new agent will arise. As well the likelihood of observing rare adverse events will be low in these trials.[46]

It has been argued that these studies can demonstrate continued efficacy of the drug over a longer period of time. This is a dubious assertion. For one thing, assessments of outcomes are not blinded in open-label extensions. A second issue is

deciding on what comparator to use. For a progressive condition like AD, deterioration over time with symptomatic therapy is expected. To demonstrate efficacy the investigator will likely have to come up with a comparison group to show differences between observed and expected changes over time. A variety of approaches have been proposed but none is considered standard.[47] In these studies a declining proportion of subjects remain available for data collection. The published results of a 144-week open-label extension study of two RCTs of donepezil is a particularly egregious example of the fall-off in the number of subjects remaining as time goes on. A total of 941 subjects entered the RCTs. Only 56 (6% of the initial group) were still enrolled at week 144. The authors of the report still stated that based on their study they felt donepezil was "an effective and safe drug for long-term symptomatic treatment of mild to moderately severe AD for up to 144 weeks."[48]

Observational and randomized, double-blind trials can reach quite divergent conclusions. An industry sponsored observational follow-up study[49] reported that highly compliant AD patients treated with donepezil delayed on average their first dementia-related nursing home placement by over 21 months. This study was criticized on a number of fronts in subsequent letters to the editor.[50-52] In contrast, the AD2000 study found no apparent effect of donepezil on nursing home placement. The relative risk of entering institutional care among those treated with donepezil compared to those assigned to placebo group was 0.97 (95% CI 0.72-1.30).[3,17] While it is possible that ChEIs might be associated with a modest delay in nursing home placement, it is highly unlikely that they can postpone placement by two years.

Ethics

There has been an ongoing debate about the ethics of placebo-controlled trials.[3,53,54] The major concern with the continued use of placebos is the availability of beneficial symptomatic therapy (e.g., ChEIs) in our country. Even if this hurdle can be dealt with (by arguing that the available agents for AD likely do not provide meaningful improvements),[3] there is uncertainty about the ability of a subject with AD to give informed consent to waive arguably effective forms of therapy. Consent forms have been described as being as difficult to read and understand as political commentaries in The New Yorker.[53] Misconceptions by non-demented participants of clinical trials are common,[55] let alone among individuals with executive dysfunction on the basis of AD.

Issues with the Regulatory Authorities

Regulatory authorities have been criticized for the inconsistency in their requirements for drug development and approval.[56] Issues related to product labeling have also been raised.[56]

Recommendations

The following recommendations for studies of mild to moderate AD are made to deal with a number of the criticisms found in the literature.

1) In the reporting of clinical trials for mild to moderate AD, an attempt should be made to address the issue of the practical importance of the results obtained. This might be done, for example, by reporting effect sizes. While this may seem self-evident, it still is not routinely done. For example, the recently published trial of donepezil for patients with severe AD[57] did not deal in a satisfactory manner with the question, "Is the difference between groups large enough to be worth achieving?"[58] The authors did not report on effect sizes or the NNT in order to achieve a "specified benefit." Their sample size calculations were based on the differences seen on their primary outcome measures in prior studies of patients with moderate-to-severe AD. They worked out how many subjects had to be enrolled in order to achieve a 90% power with an α level of 0.05. Later the authors referred to these differences as being of "clinical significance" but no justification for this assertion was presented.[58]

2) Rigorous pharmacoeconomic studies of the agents available for the treatment of AD are required. Detailed guidelines for authors and peer reviewers of these studies have been published.[59]

3) Efforts should be made to improve the generalizability of clinical trials for mild to moderate AD. Exclusion criteria (e.g., comorbid conditions, medications) should be kept to a minimum. In future clinical trials, subjects with possible, as well as probable, AD should generally be eligible. It should also be permissible to recruit subjects with a concomitant condition suspected of contributing to the dementia, unless there is some clear and specific rationale for not allowing this. The need for homogenous, precisely defined patient groupings is less pressing in this relatively mature research area, where we already have abundant data on "pure" disease. One way to deal with the resultant diversity would be to recruit a sufficient number of patients with and without the factor(s) of interest in order to permit either stratification and/or pre-planned subgroup analyses that would, in turn, allow statistically valid conclusions to be drawn.

4) Direct-comparison clinical trials should be done in a rigorous manner. Attention should be paid to study size, duration, threats to internal validity, comparator bias and the interpretation of results.[42] Sponsorship of these trials by a manufacturer of one of the drugs being studied raises particular concerns. An examination of drug company sponsored trials indicates that they are more likely to show results favouring the product produced by the funder.[60] This observation might be explained by pharmaceutical firms selectively funding studies where they are confident their agent is superior, doing poor quality research, selecting a comparator that favours the company's agent and/ or by not publishing trials with unfavourable results. While it would be preferable if comparison trials were conducted by independent parties, these studies may not be of sufficient scientific interest to attract funding from agencies other than pharmaceutical firms (e.g., government). To decrease the possibility of bias, industry-sponsored comparison trials must be carefully scrutinized by investigators, regulatory agencies and ethics committees.[61]

5) There remains a need to develop valid, reliable, sensitive (to change), comprehensive, practical (for the clinical setting) and relevant measures to capture treatment effects. The standard measures used in AD trials would be rated better on the first three attributes than the latter three. There is a very real danger that those designing, funding, approving and/ or reviewing studies

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will stick with what has been used and not consider alternatives. As an investigator who has participated in a number of AD trials over 15 years I've been struck by the mind-numbing similarity in the outcome measures selected.

6) For mild to moderate AD, placebo-controlled trials are ethically unacceptable. This does not include add-on to standard therapy study designs where a placebo control remains ethically acceptable.

Declaration

Dr. Hogan has participated in Dementia drug studies sponsored by the following companies: Janssen-Ortho, Neurochem, Novartis and Pfizer. He has also given presentations sponsored by Merck, Novartis and Pfizer.

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