Clinical trials in Alzheimer’s disease

A report from the Medical Research Council Alzheimer’s Disease Clinical Trials Committee

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Abstract
Recent advances in Alzheimer’s disease imply a need for adequate clinical trials of new treatments which require careful design. The disorder is progressive and shows clinical heterogeneity. While large-scale trials of elderly subjects are appropriate in relation to assessment of drugs or other treatments designed to prevent progression of the disorder, the outcome measurements in such biological treatment trials require careful planning. Studies of individual patients are relevant for answering certain specific questions. Relatively short cross-over trial designs may be appropriate to some pharmacological studies. The choice of neuropsychological instruments for measuring change is critically important, particularly in excluding test/retest artefact and in avoiding floor and ceiling effects. Test scales designed for assessment of specific neuropsychological deficits, or forming part of standard IQ assessments are unlikely to prove robust. Tests can be selected and developed for individual patients, but generalisation of the results of such experiments to the disease as a whole is not inevitable. There is a need to develop psychological instruments for measuring change that are robust and relevant to the clinical problem of progressive dementia.

New neuropathological and neurochemical knowledge concerning Alzheimer’s disease has led to an increasing interest in the possibility of treatment. Current concepts suggest two main avenues of treatment. First, a symptomatic modification of the mental defect might be feasible, for example, by drug treatment and, secondly, it may prove possible to modify the natural history of the disease by directly approaching the causative abnormality, when this is better understood. We shall refer to these as symptomatic and biological treatments, respectively.

The cholinergic hypothesis has been particularly fruitful in generating research.1-3 This hypothesis suggested that the defect of learning and memory which is characteristic of the disease is due to defective synthesis of acetylcholine, a neurotransmitter involved in neural activity in the hypothalamus and in the neurons of the isodendritic core that project widely to the cortex.4 This concept has been tested in a number of short trials of choline, lecithin and physostigmine.5-6 These trials, however, lacked uniformity in diagnostic criteria, in staging the clinical deficit, and in recognition of the importance of previous intellectual and educational level. Further, the instruments used in these studies for psychometric assessment were neither uniform nor readily comparable. Indeed, these investigations exposed the lack of validated test schedules suitable for assessment of patients and of agreed research protocols for clinical studies in the dementias.

These problems were addressed by the Medical Research Council (MRC) in a workshop held at New College, Oxford, in September 1986 at which minimum guidelines for data collection in clinical and pathological studies of the dementias were agreed.7 These guidelines are intended to allow data collected in different research projects in the United Kingdom to be compared more readily, and to allow testing of basic hypotheses when data collected in different research projects apparently conflict. These guidelines were not devised with clinical trials in mind and therefore are not necessarily intended to be used as measures of change. The guidelines recommend test schedules that are suitable for use by investigators of widely differing academic backgrounds, but which have not yet been validated in test/retest trials in dementia.

To facilitate well-designed clinical trials of new treatments in Alzheimer’s disease the MRC decided to explore the minimal framework necessary for testing new symptomatic and biological treatments. In considering this it was recognised that any suggestion that an effective treatment might be under development would place great pressure on the manufacturer, investigator and physician, since there might be a demand from patients and their families for the treatment to be made available, perhaps before adequate trials were completed. Thus it is of fundamental importance that even initial trials of new treatments should be scientifically rigorous.8 Inadequately planned pilot trials might make it impossible to conduct a full and adequate trial at a later date.

SOURCE OF NEW TREATMENTS
Putative treatments for Alzheimer’s disease have begun to emerge from current research into neurochemical and neurotransmitter
abnormalities in the disease. As in any disease of unknown cause, possible treatments may also emerge from patient interest groups, from epidemiological studies, from treatments currently applied to other disorders, or from other sources. As has been the case in multiple sclerosis and motor neuron disease, adequate trials of these treatments are required to assess their potential benefits properly within the usual framework of toxicological, preclinical and clinical evaluation. So far, compounds used to test the cholinergic hypothesis have been naturally occurring foodstuffs, for example, choline and lecithin, or other compounds, such as physostigmine and tetrahydroacridine, that are no longer subject to patent agreements and therefore of less potential interest to the pharmaceutical industry.

**Table Criteria for clinical diagnosis of Alzheimer’s disease (modified from McKhann et al. 1984)**

<table>
<thead>
<tr>
<th>Criteria for clinical diagnosis of Alzheimer’s disease</th>
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<tr>
<td>1 Probable Alzheimer’s Disease</td>
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<tr>
<td>a) Dementia, established clinically, by dementia scale</td>
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<tr>
<td>b) Appropriate deterioration of memory and other cognitive functions</td>
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<td>c) Onset after the age of 60, most commonly after the age of 65 years</td>
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<tr>
<td>d) No disturbance of consciousness.</td>
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<td>e) No other disease that could account for impairment of memory or cognition.</td>
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<tr>
<td>2 Other features of Alzheimer’s disease</td>
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<tr>
<td>a) Progressive deterioration of specific cognitive abilities, for example, language, motor skills and perception.</td>
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<tr>
<td>b) Appropriate, progressive impairment of everyday behaviour.</td>
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<td>c) A family history may be present.</td>
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<td>d) Abnormal investigations are frequent, for example EEG and CT scan (atrophy of brain).</td>
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<tr>
<td>e) Depression, sleeplessness, incontinence, weight loss, myoclonus and gait disorder are common. Seizures occur in the advanced stage.</td>
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<tr>
<td>3 Clinical features to exclude a diagnosis of Alzheimer’s disease</td>
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<tr>
<td>a) Sudden onset.</td>
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<td>b) Presence of focal neurological disturbance.</td>
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<tr>
<td>c) Seizures of gait disturbance early in the natural history of the disease.</td>
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<tr>
<td>d) Presence of other neurological diseases, for example Parkinson’s disease, stroke or tumour.</td>
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**DIAGNOSTIC CRITERIA AND SELECTION OF PATIENTS**

Since no specific diagnostic test is available, the diagnosis of Alzheimer’s disease remains a matter of clinical decision-making. This problem has been addressed by a working group which suggested criteria for definite, probable and possible Alzheimer’s disease.

These criteria (table) represent a consensus view. Similar criteria have been validated by clinical and pathological studies, yielding a sensitivity for clinical diagnosis of greater than 80% and a specificity of 78%.

There is continuing controversy concerning the nosological status of early and late onset cases, familial cases, and the coexistence of typical Alzheimer-type dementia with marked extrapyramidal features, particularly in patients with Parkinson’s disease. Finally, Alzheimer’s disease and cerebral vascular disease may coexist, since both disorders are common in the elderly.

Patients with this combination of disorders are generally not suitable for research studies of Alzheimer’s disease itself. For research studies the clinical diagnosis of Alzheimer’s disease should be supported by quantitative assessments of the abnormality in intellectual function, for example by application of the Mini-Mental State Examination, the Blessed Dementia Scale, the Cambridge Cognitive Examination, the Geriatric Mental State Test, or by neuropsychological and other tests, for example, the National Adult Reading Test, as a measure of pre-morbid intellect.

**CONSENT**

The issue of informed consent for research investigations in patients with impaired mental abilities must be addressed by the investigators, the Ethical Committee, and the patient’s family. Clearly, research into the cause and treatment of Alzheimer’s disease, and of other dementias, is necessary and important. It is justified when the proposed research addresses questions that are relevant, uses appropriate methods, and seeks a defined outcome. It is for the Ethical Committee to consider these factors. The research must involve no undue physical or emotional risk for the patient, and must be clearly understood by the patient’s family and, as far as possible, by the patient.

**STAGE OF THE DISEASE**

Patients may be entered into a therapeutic trial at any stage of the disease. In the earliest stages, however, diagnosis is difficult, and depression may complicate the clinical picture.

At this stage the placebo effect of intervention must also be considered. On the other hand, if diagnosis is delayed until the later stages of the disorder so much degeneration may have occurred in the brain that the capacity for functional improvement in mental state, or arrest of the biological process may be limited.

Treatments intended to have a neurobiological effect on the natural history of Alzheimer’s disease imply knowledge of the rate of progression of the untreated disease, and of the sequence of development of particular clinical and neuropsychological features. Detailed longitudinal studies of the natural history of Alzheimer’s disease are therefore required to fully assess clinical variability in the course of the disease. Sufficient detailed information for this purpose is not currently available and, as a result, it is difficult to estimate sample size in studies of biological treatments.

**LOGISTICS**

Early cases of Alzheimer’s disease are likely to be found in family practices, since such patients will be living at home. Collecting such cases is difficult, since many will not be aware of their mental impairment and will not have presented to their general practitioners. Hospital patients are likely to exhibit a relatively
late stage of the disease and although they are available for study, a major beneficial effect of treatment might not be expected in such patients. Short-term studies of three months to one year are more likely to be achievable than long-term studies. Short-term studies also offer the advantage that a cross-over trial design can be used to investigate the effects of a symptomatic treatment in individual patients, using assessment schedules previously determined in relation to the patient's cognitive deficit on the basis of detailed neuropsychological testing. In studies of larger groups of patients, parallel and cross-over designs may be applied. In the latter design an adequate wash-out period must be allowed and the problems of deterioration during the course of the trial should be addressed. Studies of this type imply the selection of patients at an intermediate grade of functional severity, who are accessible to repeated testing. Experience with such trials suggests that to demonstrate a treatment effect, periods of therapy of one to three months may be appropriate. A biological treatment might result in arrest of progressive deterioration rather than improvement in mental performance. Assessment of such an effect probably requires an extended period of treatment and measurement that implies a long-term commitment. Generally, symptomatic pharmacological effects should be seen, by improved performance, after much shorter treatment periods than those required to note a biological effect.

MEASUREMENT

Scales of functional improvement may include behavioural and cognitive tests, assessments of the quality of life achievable by the patient, and scales of activities of daily living and functional competence. Longer-term investigations might include hospital admission rates, and some quantitative determination of the use of social resources, such as district nurses, social workers, day-care centres, calls for help on neighbours, and on other agencies such as the local police. Secondary effects related to the amount of attention given by the investigators and other staff, can be obviated by the use of a randomised placebo treatment arm. Depressive features may similarly be controlled in this way. The choice of the measurement instrument used is influenced by trial size and design. Small trials have some advantages. For example, patients can be selected in such a way that particular variables may be studied. The result of such a study, however, may not be generally applicable to other patients. Larger trials are likely to include patients with different combinations of clinical and neuropsychological deficits, implying the necessity for robust, and generally agreed multiple measures of outcome. Cross-over studies of individual patients are particularly useful in assessing such variables as dose-response curves, and in pilot studies of particular neuropsychological deficits, or even of new drugs. Trials of this type can be used to identify responders in a patient population, and to determine the best dose of the compound studied. However, cross-over studies of individual patients will not address the question of the overall usefulness of a treatment in the generality of patients with Alzheimer's disease. Thus an attempt to establish both the effectiveness of a treatment and its optimum dosage in one trial is probably over-ambitious.

Sensitivity to change is an important aspect of any assessment procedure. The semi-quantitative methods of assessing mental state in current use were designed not for use in determining change or rate of change, but in quantifying the degree of mental abnormality. These scales are empirical and non-linear, and it is by no means appropriate to compare an individual's performance from one time to another in relation to any possible effect of a treatment. Thus these scales are not necessarily well-suited to longitudinal studies. Neuropsychological studies using the WAIS are more readily quantifiable but are intended more for diagnostic or educational assessment in patients with focal brain lesions than for clinical trials in a diffuse disorder in which testing will be necessary at multiple points in a relatively short period of time. The WAIS was specifically designed not to be sensitive to short-term fluctuations in performance. Although some neuropsychological test profiles include alternative test schedules, most have not been validated in longitudinal studies of drugs on mental state. Specific measures of verbal and non-verbal memory, immediate recall of random word lists and the effect of delay and distraction procedures are useful test procedures. Semantic memory tasks are also reliable in testing cognition, but there is no evidence that these tests are relevant to the experience of daily living.

Floor and ceiling effects are common problems in studies of dementia. Many demen-ted patients achieve zero scores on standard tests but, if the tests that are chosen are too easy then some less severely disabled patients will achieve maximum scores. These problems emphasise the value of single case studies using appropriately designed measurement instruments. Direct indices of the effect of a compound are useful in confirming that it has pharmacological actions, for example, salivation or change in ocular accommodation are features of cholinergic effect outside the central nervous system. The ultimate measure of outcome must be better functioning in tasks of daily living, despite the initial concentration on more easily measured variables, such as learning and recall. New, properly validated scales of daily living abilities and performance are needed to cover the range of deficits encountered in patients with dementia, especially in patients with less severe cognitive defects.

SAMPLE SIZE AND POWER CONSIDERATIONS

Several factors will influence study duration and size. These include the chosen outcome of the study, the assessment instruments used,
Clinical trials in Alzheimer's disease

with their inherent variability, and the criteria for entry of subjects into the trial. Death is an unambiguous outcome of a progressive disorder, but will be less frequent than other outcomes and is a poor measure of benefit in a dementia. Outcomes based on the rate of deterioration of mental ability are dependent on the availability of sensitive measures of cognitive change. Currently, the variance of these measures is large and this is therefore an important factor in determining sample size. Preliminary studies to estimate this variability in the patient population to be studied may well be necessary to assure an adequate sample size. The heterogeneity of the patients studied will also influence power and sample size calculations. Separate analyses within homogeneous patient strata may be appropriate, but should be considered at the stage of trial design, rather than at the completion of the study.

12 Bellinger, Overall, Swan AG. Efficacy of oral physostigmine in primary degenerative dementia; a double-blind study of responses to different dose levels. Psychopharmacology 1985;91:147–51.