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ABSTRACT

Several therapeutic strategies have been followed for Alzheimer's disease (AD). The 'cholinergic hypothesis' for AD, formulated in the late 1970s, directed therapy research towards causal therapies based on curing the cholinergic deficit. This strategy has yielded equivocal results.

We will first review the various attempts that have been made in treating AD with cholinergic and non-cholinergic therapies. We propose that it may be more wise to pursue symptomatic treatment. In addition, postponing further decline or slowing decline may also be valuable goals. Future therapeutic interventions should focus more on treatment of affective and emotional disturbances (anxiety, fear), than on memory alone. The former disturbances have a greater impact on quality of life than the latter.

We conclude that it may be more advantageous to use more than one treatment strategy. Interventions directed at non-biological aims or at non-cognitive domains may be more relevant than interventions directed at cognitive c.q. memory dysfunctions.

INTRODUCTION

Decreases in cognitive functions are regarded as an inevitable consequence of increasing age. Most elderly people complain about forgetting and decreased concentration and this compromises their quality of life (1). Pathological disorders of memory and other cognitive functions are present in the dementia syndrome, notably Alzheimer's disease (AD). In cases of dementia, the cognitive disturbances are frequently accompanied by affective and behavioural symptoms, that eventually require a complete and perpetual institutional care of the patient. Apart from the patient, the partner and other direct relatives also experience reduced quality of life because of the heavy burden that is placed on them. Besides, dementia has a great impact on the society because of the financial and organisational consequences for both family and society.

Because of the heavy burden for patient primary care and society, the search for treatments of dementing conditions, especially AD has

been amplified in the preceding 15 years. Unfortunately, although great progress has been made in our understanding of basal mechanisms of drug action in the brain and in our understanding of particular brain changes in Alzheimer patients, a breakthrough in treatment does not seem near.

The present paper reviews the state-of-the-art of therapy with an emphasis on the rationale for each treatment. The reader is referred to excellent reviews for further references and a more in-depth evaluation of clinical trials (2,3). We believe that original claims to a possible curative therapy are not realistic. A less ambitious goal is symptomatic treatment. In addition, retarding or postponing a rapid deterioration are also important aims. We will first address the progress in cholinergic therapy and then describe other treatment strategies.

THE CHOLINERGIC HYPOTHESIS

At the beginning of the 1980s, the cholinergic hypothesis of geriatric memory dysfunction was formulated by Bartus and coworkers (4). The rationale behind the treatment with cholinergic compounds is:
1. The most consistently reported change in AD is a change in the activity of cholineacetyl transferase in the cortex; 2. There is a substantial decrease of cholinergic neurons in the forebrain, and there is a relation between cholinergic changes and the severity of dementia and histopathological changes; 3. Studies in healthy volunteers show memory disturbances after treatment with an agent which blocks postsynaptic acetylcholine (ACh) receptors. The ACh-esterase inhibitor physostigmine antagonises this process.

These findings underlie the hypothesis that AD treatment with cholinergic compounds (cholinomimetics) could show positive effects on the disease in a way similar to the dopaminergic therapy in Parkinson's disease. Many clinical trials have investigated the cholinergic hypothesis. Most of the studies that used the ACh precursor choline or lecithin alone were not effective, despite preliminary positive reports. Also, some recent studies with receptor agonists have not been successful.

With respect to inhibitors of ACh degradation, the beneficial effects that have been published in renowned scientific papers, have led to a strong lobby by Alzheimer associations. Many years of clinical research with ACh-esterase inhibitors such as physostigmine had not given any impressive results. In 1986, Summers and coworkers published an influential paper in the New England Journal of Medicine (5). The authors treated a group of 17 patients with AD. There were 14 subjects who completed the blinded phase II, and 12 patients entered a third phase involving long term administration of tetrahydroaminoacridine (THA).

The results indicated a clear-cut effect of treatment in most subjects. Various tests and assessment scales showed substantial improvement in the performance with THA. Summers even mentioned that one subject was able to resume most of her homemaking tasks; another was able to resume employment on a part-time basis; a third was able to resume playing golf daily. Immediately after publication of Summer's paper questions arose about the methodology of the study and also about the generalisibility of the results. For instance, Tyrell, Hardy and Rossor (6) drew attention to the fact that cholinergic defects are not the unique feature in AD. AD is a multiple neurotransmitter disease, involving various monoamine neurotransmitters, glutamate, GABA and several peptides. Treatment of only one transmitter deficit cannot be expected to be of great therapeutic value in AD. Heterogeneity of AD would explain why occasionally a patient clearly benefits from THA, but overall the enthusiasm about THA needed to be tempered.

An investigation by the Food and Drug Administration revealed serious shortcomings in Summers' study. Many claims could not be controlled for and several mysteries remained (7). Further studies with THA or THA-like drugs have been undertaken since. A recent study by Eagger et al. (8) was positive with respect to a treatment effect of tacrine. These authors investigated 89 patients and assessed efficacy by the mini mental state examination (MMSE). There are several problems with this study. Only a selected group of 65 patients could be analysed, because there were many drop-outs with side effects, mainly liver dysfunctions. Because of the high incidence of these side effects, it can be questioned whether the study was properly blinded. Also, drug effects were only found in the domain of cognitive functions as measured with MMSE. This is a diagnostic instrument that gives information only on one aspect of the difficulties which the AD patient experiences. Thus, apart from the cognitive dysfunctions that are prominent in the early stages of AD, behavioural changes, changes in personality, and activities of daily living are also prominent in AD, as well as depression and changes in quality of life or social network. A change in only one of these aspects may be scientifically interesting and rewarding but not clinically relevant when, for instance a cognitive change is not paralleled by changes in the other variables.

Further difficulties result from the first very large THA trial involving several hundreds of patients. Serious abnormalities of liver enzymes appeared in several subjects. The trial was stopped (9), and this became a serious drawback in developing a possible anti-dementia agent. Eventually, several more papers on THA were published (10-12). Gauthier et al. (11) showed only a slight but statistically significant effect on the MMSE but not in any clinical measure. There are also methodological

questions over this study, but it is clear that these points do not compromise a possible treatment effect. More recently, Davis et al. (12) reported a multi-centered study in which AD patients were treated for six weeks with tacrine. Only patients that seemed responsive to tacrine in an enrichment phase were included (215 out of 632). Treatment with tacrine resulted in a statistically significant reduction of cognitive decline, but this reduction was not large enough to be detected in global clinical measures.

These studies have taught investigators much about clinical trials in AD. It is now known that the expectations as to the possible positive effects were exaggerated, and that clinical researchers should be more cautious in transmitting their results to the general public, especially when the methodology has not been optimal. Higher standards must be used in the design of such studies. In this respect, it is quite revealing to cite from the editorial in the New England Journal of Medicine that accompagnied Summer's report. Here, Davis and Mohs (13) discussed some aspects of the cholinergic hypothesis and especially Summers' trial. They end their editorial by stating:

> *Only recently has the development of neuropsychiatric agents, used in the treatment of disease, followed a rational path. From this perspective, the finding of Summers et al., represents a triumph for the scientific method.(...) The logical process that led to the administration of the THA to patients with AD was a positive reflection of our nation's investment in science.*

This statement is clearly far too optimistic for the results that were described by the researchers, indicating that in view of what we know from Summers' study we should be more cautious in our appraisal of findings reported in clinical trials.

NON-CHOLINERGIC DRUGS IN AD

There are other pitfalls in clinical trials on AD. The controversy as to the effect of drugs in AD has been illustrated nicely with the issue of intracerebro-ventricular bethanechol. Whitehouse (14), in an editorial in Neurology, reviewed existing data and concluded that the findings were controversial. Studies with this drug were again characterised by many methodological problems. Recent studies found some small benefits that were not outweighed by the risks of administrating the drug via an intracerebro-ventricular cannula with pump. Again, like THA, a drug and a drug-delivery procedure were unmasked that have been suggested by the media to lead to a breakthrough in AD treatment.

According to Whitehouse, thousands of families of AD patients have been led to believe in a breakthrough that did not come. He suggests that the process of drug development and performance of clinical trials should proceed more carefully so as not to create false hopes for those with the disease.

One drug already on the market for alleviation of symptoms associated with dementia is hydergine. There is already about 10 years of controversy as to whether this drug has more than a non-specific activating effect. Some years ago, a meta-analysis revealed that hydergine had no direct effect on cognitive functioning. The positive effect which was sometimes found should be ascribed to a general activating or a mild antidepressive action. Recently, Thompson et al.(15) set out to measure the potential efficacy of hydergine in a well controlled trial in 80 AD patients. It seemed that the hydergine group was not better than placebo on any test, and there were even two measures on which the hydergine group was worse. These authors concluded that hydergine was ineffective as a treatment for AD. Many clinicians may regard the substance as a kind of comforting placebo to be given since there is nothing else to give.

Apart from cholinergic strategies, other classes of drugs have also been investigated. Generally, these trials have not yielded any drug that is revolutionary. Interest in catecholaminergic drugs is supported by the finding of catecholaminergic deficiencies in AD. Noradrenaline is also involved in aspects of memory and depression. The use of serotonergic drugs was based on the finding that postmortem AD brain has reduced concentrations of serotonin. There are also some clinical observations that behavioural symptoms can be substantially relieved by antidepressants (16). Recent interest in GABA-ergic compounds is based on the hypothesis that GABA-ergic systems could modulate cortical ACh turnover and that GABA antagonism might facilitate cholinergic neurotransmission, thus improving memory. Other strategies include antiviral agents, antihypertensive agents, opioids, and metals. Peptidergic strategies are based on the finding that many peptide neurotransmitters coexist with chemical neurotransmitters and have some modulating action on brain processes. In addition, several brain peptides seem to be reduced in AD. Unfortunately, peptides related to pituitary adrenocorticotrophic hormone (ACTH) and vasopressin have not been found to lead to clinically significant treatment effects (1). In a recent study, in collaboration with the Rudolf Magnus Institute for Pharmacology in Utrecht, a double-blind cross-over trial was completed with 12 subjects. Several neuropsychiatric tests served as measures of evaluation. There were no significant treatment effects (17). A similar picture emerges in a study from the Maastricht Memory Clinic by Verhey and Jolles. 18 patients with mild AD were treated with acetylcarnitine (Alcar) in a similar design. Neuropsycho-

logical and neuropsychiatric measures were used to evaluate the treatment. Alcar occurs naturally in the body and has a role in energy metabolism. Again, the results did not show a beneficial drug effect (Jolles and Verhey, unpublished data). Other investigations completed at the Mario Negri Institute, Italy did indicate some effect of Alcar, in long-term treatment for one year. Alcar seemed to retard development of dementia. These investigations found that the placebo group deteriorated more than the Alcar group (18). Several other tests showed that the progressive deterioration in the drug group was not as strong as in the placebo group. This kind of study is of interest because it draws attention to the fact that drugs which slow the dementing process are at present as urgently needed as drugs which reverse the process.

LEARNING FROM THE PHARMACOLOGICAL TREATMENT STUDIES

The first major difficulty is the nature of AD. Many drug trials seem to follow an implicit theory namely that AD is a disorder of memory. There is a rapidly increasing literature that this is not the case (19). The neuropathology of AD shows us that various brain regions are affected and that associated behaviours range from memory via language and attention to problem solving ability.

A second important question is whether AD is a one-neurotransmitter disease. Again the answer is no. Various neurotransmitters are affected and these are related to a variety of cognitive behaviours, again from memory to problem solving (6,19).

A third point: memory loss is not the most invalidating deficit in AD. Apart from deficits in the cognitive domain - memory, disorientation, language, praxis - there are very serious problems in both affect and behaviour. These behavioural problems, restlessness, wandering, psychosis, aggression and anxiety require treatment as much as the cognitive problems do (20,21). And there has also been a disproportionate interest by drug developing institutions and researchers in the cognitive symptomatology. Yet, memory is not a unitary function and consists of various sub-processes that are dependent on other neurotransmitters and centres in the brain. Drugs for treatment of memory disorders can be of many classes (22).

Fourth, there are other problems in AD trials: groups are often too heterogeneous, especially in older studies (table 1).

The optimum study design is a parallel-group controlled study, but most studies were characterised by methodological flaws. Furthermore, statistically significant results on some psychometric measures are, in most cases, not reflected by clinically relevant findings. For instance, a score on a memory test which is somewhat better without concomitant

Table 1. Problems in AD clinical trials

Heterogeneity of groups
Poor study designs
Lack of sensitive and reliable evaluation measures
Side effects and toxicity
Statistical effects but marginal clinical effect
Drugs focused on only one symptom
Drugs focused on one neurotransmitter
Predementing stages are not a nosological entity and thus 'not interesting' for pharmaceutical industry

improvement in activities of daily living is not interesting from a clinical point of view.

The final point is that we lack effective interventions in the very early stages of AD. There have been few clinical trials on possible dementia prodromes, i.e. at a time when the subject is not yet demented (23). It has been argued that this is the moment for treatment with agents that can halt or slow deterioration, but industries and researchers have been somewhat reluctant to go deeper into this matter. One reason for this reluctance is that the predementing stages are not regarded as a nosological or disease entity (3).

In this respect, it is interesting to follow the profile of scores of AD patients on various scales, such as the Alzheimer Disease Assessment Scale and the Sandoz Geriatric Scale. In a study in the Maastricht Cognition and Dementia Research and Clinical Centre, the Netherlands, 18 patients were followed over 18 months, and there was evidently a decline over this time because of generally increasing scores (+30%) on these scales. A decline in cognitive performance in these patients was found with respect to word list learning: a 35% of decrease within 10 months. A drug that would slow this process or postpone it would be of great importance. Researchers in The Netherlands calculated that a drug which would postpone later stages of dementia for 5 years would result in a decrease in the number of demented patients in nursing homes by 25% in the year 2000.

It may be helpful to summarise the various aims that are explicitly and implicitly present in drug treatment studies. Many have hoped to find a treatment for the cause of AD. This is something else than symptomatic or palliative therapies that are now the norm. As mentioned above, most studies have focused on cognitive symptoms. Now there is a difference in aims when the clinical psychopharmacological researcher sets out to reverse the course, to postpone further decline, or to slow further decline. The prevention of dementia by treatment in a very early stage is a specific example of postponing or slowing the decline.

However, much research is still to be done to improve the methodology of early identification of AD.

CONCLUSION

A final point that must be made in this paper refers to the nature of the pharmacological treatment itself. It is astonishing to find that there is no lack of enterprise in the scientific community in the search for new and better drugs, but that virtually nothing exists with respect to well-controlled studies with non-biological strategies. We all agree that AD is a brain disease. However, most of the symptoms of this disease are on the behavioural, psychological, and social level. Depression is an important symptom especially in the early phases of dementia. Loss of control by the subject may be more important for him or her than deterioration of memory functions. Clinical researchers in the Maastricht Centre have therefore started with the development of non-biological intervention strategies. It was the aim to be able to offer the patient and his or her family more than drugs because what they seem to need is help for their worries, support for their wish to cope with environmental demands, and wish to reduce the burden to care for a patient with functional deficits. A controlled intervention study has been performed in patients with serious memory disorders who are not demented: two groups of subjects were compared, each consisting of 12 individuals (24). Patients had been individually matched with subjects in the other group. Group 1 received a selective memory training in a 5-week-period. Group 2 received what has been called function-oriented guidance, consisting especially of psycho-education, strategy training and training of coping strategies in daily life (25). Patients were middle-aged and older. They were characterized by objective memory disorder and memory complaints but they were not demented. Their selection was based on extensive neuropsychological testing. The results of this investigation showed that the training group had better performance in several cognitive tests. However, the striking thing was that the guidance group which did *not* perform better on cognitive tests, was characterised by increased feeling of control over their dysfunctions. They were less depressed, their knowledge about their condition was increased, and this treatment effect generalised to normal life situations. This was not the case in the training group (24).

The findings are of relevance since they indicate that non-biological treatments are able to change aspects of the cognition and behaviour of subjects who complain of memory disturbances and that the result can be an increased quality of life. This is an example of a treatment strategy that aims at compensating for deficits rather than restoring the

original functions. There are also indications that it can be similarly important to treat patients in early phases of Alzheimer dementia with antidepressants: the mood problems may be more relevant for patient and care givers than the reduced memory functions. The same may apply for behavioural functions, but there is up till now no accepted treatment for this aspect. Possibly, strategies derived from the field of neuropsychological rehabilitation may prove relevant in that respect (table 2).

Table 2. Future intervention strategies

Causal pharmacological treatment ('cure')
Pharmacological treatment for one or more symptoms (cure or postponing or slowing the process)
Prevention of dementia by pharmacological treatment in predementing stage (AAMI or related condition)
Pharmacological treatment of depression, aggression, anxiety etc.
Psychological treatment of dementing patient, e.g. function oriented guidance
Psychological treatment of primary caregiver
Hometraining of primary caregivers

In summary, future interventions should be directed at both biological and nonbiological strategies. Of course, there should be an active search for a possible cure for the disease. But treatment of one or more symptoms remains of major importance. In addition, more impetus should be given to drug treatment in predementing phases because it is reasonable to expect that a possible prevention of further brain degeneration might most effectively be performed in a stage that the brain is not yet grossly and structurally lesioned. Better methods for early diagnosis should therefore also be developed. Of major importance is the development of drug treatment for conditions which are of major concern for primary care-givers, in later stages like restlessness, anxiety, and psychotic symptoms in the very old. Finally, psychological interventions seem warranted of both the patient, the health-care giver and the social support system in both early and later stages of the disease.

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