'Although the effects of drugs averaged over large groups were small, some patients did benefit markedly …'

editorial

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Difficult times for Alzheimer's treatments

A diagnosis of Alzheimer's disease (AD) is never good news. Some of the gloom has been dispelled over the past few years, first with dramatic increases in our understanding of the disease processes and then with a series of clinical studies, indicating that particular classes of drugs could either improve patients' conditions or slow the onset or progression of the disease.

Several hypotheses try to explain what happens to the brain in AD and each one opens up a potential means of treatment. Some strategies are focused mainly on treating symptoms, such as memory loss or the psychotic features of the disease, whereas others focus their attack on their biological causes and offer the hope of halting or slowing disease progression. Other strategies are based on the ever-growing understanding of the biology of AD, whereas others have been suggested by epidemiological studies that indicate possible benefits of treatments, such as cholesterol-lowering or anti-inflammatory drugs. Recently, all of these strategies have encountered some difficult times, threatening to leave the Alzheimer's medicine cabinet looking very bare.

Antipsychotics

For many years, typical and more recently atypical antipsychotics, such as olanzapine and risperidol, have been used to treat the behavioral and psychotic aspects of AD [1]. Concerns about the safety of these compounds in the elderly led to a review by regulatory authorities in the USA and the EU. The FDA analysis of 17 randomized clinical trials using a range of atypical antipsychotics in AD patients showed an increase in mortality rates of up to 1.7 times compared with placebo. No single cause of this increased mortality, as well as increased incidence of cardiovascular events and pneumonia, were identified in the studies examined. A Public Health Advisory was issued by the FDA in April 2005. The compounds affected were AstraZeneca's Seroquel (quetiapine), Bristol-Myers Squibb's Abilify (aripiprazole), Eli Lilly's Zyprexa (olanzapine) and Symbyax (fluoxetine plus olanzapine), Johnson and Johnson's Risperdal (risperidone), Novartis' Clozaril (clozapine) and Pfizer's Geodon (ziprasidone). The use of older typical agents is under review.

Amyloid vaccination

The difficulties that have been encountered by β-amyloid vaccine treatments have been extensively discussed elsewhere. The early excitement surrounding the potential of anti-amyloid immunotherapy, such as AN-1792 to prevent plaque formation or to remove plaques, has been tempered by the serious

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adverse events including meningoencephalitis early trials. Even worse is that, as the studies have progressed with the patients who were immunized, the vaccinated patients have fared no better than the control patients on tests of memory and cognitive function. This setback does not represent an end to immunotheraphy, as passive immunization with antibodies that do not evoke a T-cell response offers a viable alternative strategy. Thus, although this approach might prove more difficult and take longer to establish than originally hoped, much has been learned and this strategy still offers realistic, if somewhat longer-term, hope of treatment [2].

Prophylactic treatments

Oxidative damage caused by free radicals might be one of the underlying processes that induces neuronal death in AD [3]. Chronic administration of vitamin E has been proposed as a possible neuroprotective strategy to prevent disease progression. A recent prospective controlled study in patients with mild cognitive impairment, which could be a prodromal phase of AD, has suggested that there is little or no benefit to vitamin E treatment in these patients [4]. Safety concerns about long-term treatment with vitamin E raised in by a recent meta-analytical study [5] have compounded the case against this particular strategy.

The findings from epidemiological studies that suggested lower prevalence of AD in patients taking statin drugs to lower cholesterol do not appear to be well supported in prospective studies [6]. Although the decreased prevalence (the number of people in any given cohort or population with the condition) of AD was corroborated, incidence (the number of new cases emerging) did not change with treatment. This suggests that results from the cross-sectional studies can be subject to confounding factors. Physicians might be less likely to prescribe statins to patients who have early signs of AD, for example.

Findings showing prophylactic effects of anti-inflammatory treatments have been challenged by more recent studies. It is notable that the majority of the controlled trials for non-steroidal anti-inflammatory drugs (NSAIDs) do not support their preventative role in AD. A meta-analysis of case-control and cohort studies [7] found that the negative association between NSAID use and AD was reduced when incidence rather than prevalence was measured, and the association disappeared completely when cognitive decline was taken as the endpoint. The authors concluded that much of the association could be caused by several biasing factors, such as recall or prescription bias, as in the case of the statins mentioned above. The safety issues that have arisen around some NSAID compounds might have clouded further this issue.

Not so NICE for AChE inhibitors and memantine

Three acetylcholinesterase (AChE) inhibitor compounds have been licensed for the treatment of AD, donepezil (Aricept®, Pfizer), galanthamine (Reminyl®, Shire, Janssen) and rivastigmine (Exelon®, Novartis). In 2004, the UK Government's National Institute for Clinical Excellence (NICE) performed a Health Technology Assessment of these compounds and the low-affinity uncompetitive N-methyl D-aspartate (NMDA) antagonist memantine (Axura®, Ebixa®, Lundbeck) [8]. All compounds showed modest efficacy in patients in randomized controlled trials for periods up to one year. The NICE report assessed the efficacy and cost effectiveness of the compounds over periods of up to several years after diagnosis.

The draft report was published in March 2005 and caused some dismay in the pharmaceutical industry and nothing short of outrage in patients' groups (www.alzheimers-research.org.uk/site/fullnews.asp?id=82). The NICE experts concluded that the compounds had only limited efficacy over the extended period of evaluation of years (rather than months) and did not justify the cost of treatment. The next step would have been to issue guidelines that do not recommend the use of the compounds for treatment in new cases of AD. This was due in July, but has since been put back to October.

The sponsoring companies have always agreed that the effects are modest. They argue however, with patient and caregiver support, that this was better than nothing. Furthermore, although the effects of drugs averaged over large groups were small, some patients did benefit markedly from the drugs. Pharmaceutical company economists propose that the money saved by keeping patients out of full-time care offsets the cost of treatment. If you add enhanced quality of life for patients and for those who care for them, the average £2.50 a day ($4.00) seems a very small price to pay. NICE, forced to look at the bigger picture, argue that the benefit only pertains for the early phases of treatment. Continued treatment, while exposing patients to potential side effects of the drugs for little or no benefit, shifts the balance against the drugs. Furthermore, even such a modest daily expenditure, multiplied by the full duration of the AD and across the ever-increasing number of people falling victim to the disease, represents an enormous cost burden on the health service.

The logical interim solution would be to allow physicians to start patients on their drug of choice and review progress at regular intervals. It might be possible or even desirable to discontinue treatment after six months or a year, when no further benefits are likely to accrue. Not to offer treatment at all when the drugs can show some benefit would seem to be more than parsimonious.

Reasons to be cheerful?

It might appear that after a very long journey we are pretty much back where we started with AD, before AChE compounds were available. We are, however, much further on in our knowledge of the biology of the disease and valuable lessons have been learned from some of the failures [9]. Other treatment strategies, either symptomatic

(e.g. nicotinic agonists, AMPA potentiators, histamine H3 antagonists or serotonin 5-HT6 antagonists [10]) or disease process modifiers (metal-chelating agents e.g. clioquinol), still offer varying degrees of hope.

The negative findings for NSAIDs and statins might highlight the need for better-controlled studies with earlier intervention rather than abandoning these hypotheses altogether.

Pharmacogenomics could provide vital clues as to which patients might benefit from individual treatments, helping to direct clinicians to the best treatments, and helping pharmaceutical companies focus clinical trials on the patients most likely to derive benefits. The study on vitamin E [4] noted that apoliprotein E ε4 carriers accounted for most of the positive effect of donepezil in their cohort. As this marker was the best predictor of those progressing from mild cognitive impairment to more-severe forms of AD, this could be the most important long-term finding from that study.

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