Are drugs targeted at Alzheimer's disease useful?

1 Useful for what?

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Whether drugs aimed specifically at Alzheimer's disease are useful is best approached by considering the various possible expectations about drugs used in this devastating condition.

Reversal or arrest of underlying neurobiological process

The characteristic neuropathological changes in this condition were first described by Alois Alzheimer in 1906—that is, the senile plaques and neurofibrillary tangles which accumulate in various parts of the brain of affected subjects.¹ Until we understand the process by which these structures are formed it seems unrealistic to expect any definitive treatment. Nevertheless, it should be pointed out that the relation between these structures and the equally characteristic changes in cholinergic and other neurotransmitters² is not known. Common sense suggests that plaques and tangles must come first and neurotransmitter changes second, but common sense is not always good science and alternative mechanisms have been suggested whereby cholinesterases, which are also proteases, might lead to the formation of plaques and tangles.²

Symptomatic improvement

Even though we may be unable to alter the underlying process, it may nevertheless be possible to achieve some symptomatic improvement in memory and orientation and in the ability to cope with the demands of everyday life that might be both socially and economically useful. Many agents with claims to effectiveness are currently marketed for this condition. Most have been developed on faulty premises and are of doubtful efficacy. For the sake of brevity I will confine myself to those based on the "cholinergic hypothesis"³ as these have been evolved with a clear rationale and have been most widely tested experimentally. In 1976 the enzyme choline acetyltransferase was shown to be deficient in the brains of patients dying from Alzheimer's disease.^{4,5} Choline acetyltransferase catalyses the reaction which leads to the production of acetylcholine. Subsequent studies have shown numerous other neurotransmitter and neuropeptide abnormalities and the underlying theoretical framework of the cholinergic hypothesis has been undermined. Nevertheless, the changes in choline

acetyltransferase activity remain the most consistent ones described and are the only ones to have been shown to correlate significantly with the severity of the condition.^{7,8}

The therapeutic strategies that have been developed on the basis of this finding and are aimed at increasing concentrations of acetylcholine in the brain are (a) the use of phosphatidyl choline (lecithin), the dietary source of choline, as a substrate loader; (b) cholinergic agonists such as arecoline and bethanecol chloride; (c) cholinesterase inhibitors such as physostigmine; and (d) combinations of the above. Lecithin was rapidly

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abandoned because of results based on hasty and poorly conducted trials. Although one study did show modest effects in a subgroup of patients,⁹ the substance is difficult to use in its pure state and the benefits are probably more interesting theoretically than practically. Cholinergic agonists, infused by intraventricular pumps, are associated with significant surgical risks and have not been shown to produce improvement commensurate with the risk.¹⁰ Physostigmine by injection does undoubtedly improve memory¹¹ but given orally is too brief and irregular¹² in its effects. Trials are now being conducted on a slow release preparation.¹²

Current interest is focused on tacrine (tetrahydroaminoacridine, THA) used either alone or in combination with lecithin. A much criticised clinical trial of this powerful cholinesterase inhibitor was published in 1986.¹³ It was heralded by an editorial in the *New England Journal of Medicine* as a "triumph for the scientific method"¹⁴ and received somewhat uncritical praise in an editorial in the *Lancet*.¹⁵ Despite numerous reservations about this trial many clinicians have thought it worth while to attempt to investigate tacrine more rigorously. Pilot studies have produced encouraging results,¹⁶ although some patients have had to be withdrawn because of apparently reversible changes

EDITORIAL COMMENT

Alzheimer's disease is a socially crippling and scientifically challenging disease. The clear message from these two thoughtful articles is that despite an enormous investment in research there has been no clear breakthrough in the treatment. It will be of great interest to see whether the preliminary suggestion of benefit in association with tacrine

is confirmed by subsequent analysis. In the meantime the approach to individual patients with Alzheimer's disease has to be based on a pragmatic strategy for the alleviation of symptoms, although even here there is a surprising lack of information on the established place of neuroleptics in management. Alzheimer's disease remains one of the great challenges of neuropharmacology.—PETER C RUBIN, *professor of therapeutics, University of Nottingham*

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in liver enzyme activities. Large double blind clinical trials are currently under way in Canada, the United States, France, Sweden, and Britain. My research group is currently conducting a large double blind crossover study, and a preliminary analysis by the person holding the code suggests that there is clear evidence of significant therapeutic benefit for tacrine treatment over placebo.

If the drug does indeed work it might have nothing to do with its action as a cholinesterase inhibitor as it has numerous other actions, including blockade of potassium channels¹⁷ and inhibition of monoamine oxidase.¹⁸ These and other mechanisms are receiving separate experimental attention. Thus the search for its mechanism of action may lead to the development of more effective and possibly safer drugs.

Advance in knowledge and method

The search for an effective drug to treat Alzheimer's disease has already led to a great improvement in the method for evaluating substances that may alter cognitive function and has generated a good deal of information about the neurochemistry of the condition which may prove valuable in the long run. This is probably the most powerful argument for using drugs aimed specifically at Alzheimer's disease.

Hope

Finally, the process of investigating these drugs, provided that they are not oversold with unjust claims to effectiveness, produces a more hopeful atmosphere for those who have the misfortune to bear the considerable burden of caring for affected relatives. In the words of one such carer, "I was told my husband would become a cabbage. The fact that something is being attempted does make things easier even if it only turns out to help others in the future."

Thus, although there is as yet no clear evidence that drugs targeted at Alzheimer's disease are currently useful in individual patients, there are some hopeful

indicators. Also, more general and indirect benefit is already accruing in terms of knowledge about the condition, ways of testing drugs which might help, and improvement of the social and intellectual climate surrounding it.

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2 Insufficient evidence of worthwhile benefit

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What after all is Alzheimer disease? Is it a disease, or as I believe, a group of diseases . . . ? It is a disease we cannot actually diagnose and cannot cure. We know very little about it, although we now talk a great deal about it. We can only study it with great difficulty. We cannot precisely identify it or measure its severity, and we have no available animal models.

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Doctors who look after elderly people are constantly confronted by the misery caused by Alzheimer's disease. Uncomfortable or risky side effects might be acceptable if a drug were of real use, yet we as psychiatrists do not prescribe any of the drugs which are said to influence the underlying pathophysiology of the disease (box). We believe that none of them has yet been shown to give benefit of practical or sustained value.^{2,6}

These heterogeneous drugs include some with a rational basis for their use (such as those influencing neurotransmitter systems) and some for which there is little rationale (such as opiate antagonists). Many of the trials have been inadequate; some of their deficiencies are described by Butler.¹ If Alzheimer's disease is heterogeneous⁶ and the age of onset or the subtypes are

not identified in drug trials then both false positive and false negative results will be more common. If the diagnosis of the disease is inaccurate or insensitive patients with mild disease (or those with the early stages of the disease) who might be expected to benefit most from treatment may not be identified. If outcome measures are too crude they may not detect subtle but important improvement.

The correction of neurotransmitter deficits that have been unequivocally shown in Alzheimer's disease and which theoretically might be expected to produce most benefit has been extensively attempted and includes some trials that meet rigorous standards. One such trial, that of Little *et al*,⁷ found that the modest improvement produced by lecithin (a cholinergic precursor) was in the most aged subjects who did not comply well with the dosage regimen. Thus the postulation of a "window" effect (as well as an age effect) was thought to be necessary to substantiate these claims of therapeutic efficacy—but no other similar findings are available. Cholinomimetic agents have short half lives, and many—for example, tacrine (tetrahydroaminoacridine, THA) and arecoline—have serious adverse side effects. To overcome these

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