Saturday 6 March 1999

BMJ

Acetylcholinesterase inhibitors for Alzheimer's disease

More benefit may arise from the assessments they necessitate

Papers p 633

The development of effective treatments for Alzheimer's disease has been vigorously pursued over the past few decades. Most recent developments have focused on drugs which inhibit acetylcholinesterase and thus increase the availability of acetylcholine within the brain. In this week's issue a pivotal clinical trial of rivastigmine shows, on average, modest benefits for older people with Alzheimer's disease in cognition, clinical global assessment, and quality of life (as assessed by a carer) (p 633).[1] What does this add to the evidence for these cholinergic treatments?

The evidence to date is that treatments based on the cholinergic hypothesis are essentially symptomatic. No substantial data support the hypothesis that these medications modify the disease—that is, delay its progression. The first drug in this class to show a beneficial effect was tacrine. An early report of dramatic clinical response[2] was not confirmed, and documented hepatotoxicity[3] severely curtailed its use. More recently developed drugs in this class have not, however, been troubled by this side effect.

A systematic review of tacrine did not find convincing evidence for improvement in behavioural disturbance or overall clinical condition,[4] although some improvement was seen in the cognitive decline score on the Alzheimer's disease assessment scale (ADAS-Cog), a common method for assessing cognition in this type of trial. A later systematic review using individual patient data supplied by the original investigators allowed more studies to be included, revealing benefits for both cognition and global clinical impression.[5] This highlights the need to extract good quality data from all relevant studies if meta-analyses are to be meaningful. The size of the effect of differences for the cognitive outcome as measured by the ADAS-Cog was 2.1 points (95% confidence interval 1.4 to 2.8) for tacrine versus placebo over a treatment period of 12 weeks. The odds ratio for any improvement (minimal to marked) on the clinical global impression of change scale for the active group relative to placebo was 1.6 (1.2 to 2.1).

A systematic review of donepezil showed a significant improvement of 2.6 points (1.8 to 3.5) on the ADAS-Cog scale and an odds ratio of 2.4 (1.6 to 3.4) for clinical global impression for the lower dose of 5 mg/day versus placebo, for a treatment duration of 12-24 weeks.[6] There was no evidence of improvement with donepezil on a patient rated quality of life scale, but decreased memory and lack of insight make such ratings problematic in patients with Alzheimer's disease. In this week's study of rivastigmine at the higher dose category the difference in changes on the ADAS-Cog after 26 weeks of treatment was 2.6 points (1.0 to 4.1) for the observed cases analysis but only 1.6 points (0.4 to 2.9) on the more conservative intention to treat analysis.[1] The odds ratio for showing any improvement on clinical global assessment was 2.4 (1.6 to 3.8) on the observed cases analysis. At the higher dose of rivastigmine, however, there were more withdrawals than on placebo and they appeared to be associated with cholinergic side effects including nausea, vomiting, diarrhoea, and abdominal pain.

What is the clinician to make of these modest improvements associated with acetylcholinesterase inhibitors in people with Alzheimer's disease? Firstly the effect is modest but may be more prominent in some patients than others. Secondly, trials to date have focused on patients with mild to moderate disease. There is little evidence that these medications work in patients with either incipient dementia or advanced disease. Thirdly, concerns have been raised about how these modest increases in cognition and global impression translate into clinical effects that can be used in a total care package for people with dementia.[7] In this week's study there is at least some evidence of a modest improvement in carer rated quality of life, but an average change of 2.8 points in a scale with a mean disability score of 54 points does not appear dramatic. Future trials will benefit from the deliberations of the international working group on harmonisation of dementia drug guidelines,[8] but at this stage pharmacoeconomic analysis of dementia drugs is in its infancy. Delays to institutionalisation or extreme dependency, as measured in another study,[9] may be more appropriate end points for this type of analysis.

Clearly, the selection of patients and costs of these treatments raise complex issues. Those clinicians who elect to treat patients with these drugs are likely to pursue cautious therapeutic trials in highly selected patients. Clearly too, these symptomatic treatments for Alzheimer's disease necessitate comprehensive assessment of people with Alzheimer's disease and their carers. These assessment facilities may be as costly as the medications themselves but have the potential to

BMJ 1999;318:615–6

provide better access to services and general support for people with dementia and their carers.

Leon Flicker *Professor of geriatric medicine*

University Department of Medicine, Royal Perth Hospital, GPO Box X2213, Perth, WA 6847, Australia (leon.flicker@rph.health.wa.gov.au)

1 Rösler M, Anand R, Cicin-Sain A, Gauthier S, Agid Y, Dal-Bianco P, et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international, randomised controlled trial. *BMJ* 1999;318:633-40.
2 Summers WK, Majovski LV, Marsh GM, Tachiki K, Kling A. Oral tetrahydroaminoacridine in long-term treatment of senile dementia, Alzheimer type. *N Engl J Med* 1986;315:1241-5.
3 Ames DJ, Bhathal PS, Davies BM, Fraser JR, Gibson PR, Roberts S. Heterogeneity of adverse hepatic reactions to tetrahydroaminoacridine. *Aust NZ J Med* 1990;20:193-5.
4 Qizilbash N, Birks J, Lopez Arrieta J, Lewington S, Szeto S. The efficacy of tacrine in Alzheimer's disease. In: Cochrane Collaboration. *Cochrane Library*. Issue 4. Oxford: Update Software, 1998.
5 Qizilbash N, Whitehead A, Higgins J, Wilcock G, Schneider L, Farlow M for the Dementia Trialists' Collaboration. Cholinesterase inhibition for Alzheimer's disease: a meta-analysis of the tacrine trials. *JAMA* 1998; 280:1777-82.
6 Birks J S, Melzer D. The efficacy of donepezil for mild and moderate Alzheimer's disease. In: Cochrane Collaboration. *Cochrane Library*. Issue 4. Oxford: Update Software, 1998.
7 Melzer D. New drug treatment for Alzheimer's disease: Lessons for healthcare policy. *BMJ* 1998;316:762-4.
8 Whitehouse PJ. The International Working Group on Harmonization of Dementia Drug Guidelines: past, present, and future. *Alzheimer Dis Assoc Disord* 1997;11(suppl 3):2-5.
9 Sano M, Ernesto C, Thomas RG, Klauber MR, Schafer K, Grundman M, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. *N Engl J Med* 1997;336:1216-2.

Something borrowed from the blues?

We can use Lawrence inquiry findings to help eradicate racial discrimination in the NHS

News p 625
Personal view p 679
Reviews p 678

The Lawrence inquiry into racism in the police, published last week in Britain, is notable for its robust definition of institutional—rather than individual—racism.[1] The report follows an inquiry into the racist murder of a black teenager, Stephen Lawrence, and details the failure of London's Metropolitan Police to investigate the murder properly. It found no policies that deliberately discriminated but that when policies were enacted they produced differential treatment for white and black people. In examining the organisational failings surrounding the murder investigation the inquiry team, chaired by William Macpherson, has offered a way of looking at and tackling racism at organisational level that has implications far beyond the police force. As the report concludes, "It is incumbent upon every institution to examine their policies and the outcomes of their policies and practices to guard against disadvantaging any section of our communities."[1]

Allegations of racial discrimination are not new in the NHS. There is evidence of poorer access to and use of services by minority ethnic patients[2,3]; of differences in the treatment of minority and majority ethnic groups[4]; of differences in infant mortality, perinatal mortality, and morbidity and mortality from several adult diseases[2,3]; and of discrimination in recruitment to medical school, examinations while at medical school, shortlisting for jobs once qualified, and the possession of merit awards.[5,6] These have been detailed for nearly 20 years, but the 358 mentions of "racism" or "racial discrimination" in the *BMJ* since January 1996 (full text search on www.bmj.com) show that the debate is still current.

As with the police, doctors have taken offence at the perceived slur of racism in their ranks.[7] As with the police, the discussion has centred on whether there is intent to discriminate rather than what can be done about disparities.[7] How can there be racism if there are no racists or racist policies? Understanding the concept of institutional racism[8] is the key to understanding why the Lawrence inquiry team has used it to plot a way forward for the police and why it may be the key to the development of a truly equitable NHS.[8]

The concept of institutional racism allows us to:

(1) Focus on the actions of institutions rather than individuals. People may act in good faith and not harbour racist attitudes but perpetuate discriminatory practices because of systems set up by the institution.

(2) Target the results of practice rather than the intent. Proved disparities in health, the reasons for them, and the ways that services can change to reduce disparities between groups should be the focus for action rather than proving intent or racist ideology.

(3) Acknowledge that the connection and interaction between medicine and a discriminatory social world may be important in producing the disparities. Poor educational provision for some minority groups limits the proportion available for entry to medical school because of the rigid academic criteria for entry.

(4) Take into account how the history of the NHS affects patients' perceptions. For example, knowledge of high rates of more coercive treatment of African-Caribbeans by psychiatrists may lead to a delay in presentation with mental illness.

(5) Acknowledge other forms of social stratification and their effects. For instance, gender, social class, or sexual orientation may interact with racial group to increase disparities.

(6) Acknowledge the fact that racism changes with time and with the type of institution. Overt racism may be replaced by more subtle racism, but the disparities between ethnic groups may remain the same.

(7) Identify the problem as ideological. Health disparities are brought about and perpetuated not only by culture, class, and sociopolitical forces external to medicine but also by the ideology of the medical profession. This ideology leads to ineffective or no action in the face of disparities and to a lack of concerted effort to teach or discuss racism in medicine in undergraduate and postgraduate curriculums. Moreover, the emphasis on the biomedical model undermines the anthropological research which is

BMJ 1999;318:616–7