4 Niemeyer L, Jacobs K, Reynolds-Lynch K, Bettencourt C, Lang S. Work hardening: past, present and future—the Work Programs Special Interest Section National Work Hardening Outcome Study. *Am J Occupational Ther* 1994;48:327-39.
5 van Tulder M, Ostelo R, Vlaeyen J, Linton S, Morley S, Assendelft W. Behavioural treatment for chronic low back pain (review). *Cochrane Database Syst Rev* 2000;2:CD002014.
6 Crowther R, Marshall M, Bond G, Huxley P. Vocational rehabilitation for people with severe mental disorders (review). *Cochrane Database Syst Rev* 2001;2:CD003080.
7 *Comparison of workers compensation arrangements in australian jurisdictions*. Melbourne: Heads of Workers Compensation Authorities, 2000.
8 Campbell Research and Consulting. *National return-to-work monitor 1999/2000*. Melbourne: Campbell, 2000.
9 Wallace N, Hall M, Kotzman D, Poon S. *Deterring reconsiderations: An analysis of disputed claims in COMCARE*. Melbourne: Transformation Management Services, 1996.

Drugs for Alzheimer's disease

Cholinesterase inhibitors have passed NICE's hurdle

Alzheimer's disease, the commonest cause of dementia in older people, affects 4% of the over 65s and 20% of the over 80s,[1 2] with around 400 000 sufferers in the United Kingdom.[2] The prevalence of the condition will double over the next 50 years. As well as causing immense distress to patients, their carers, and families, dementia is estimated by the Audit Commission to cost the United Kingdom £6.1bn a year (at 1998-9 prices), with £3.3bn of this direct spending by health and social services.[3] The National Institute for Clinical Excellence (NICE) has reviewed the available drugs for Alzheimer's disease and declared them clinically effective in reducing the burden of disease in some patients.

The aetiology of Alzheimer's disease remains unknown, and no treatments reverse or stabilise the disease. Current management focuses on establishing an accurate clinical diagnosis, ensuring appropriate services are provided, supporting carers, and treating associated non-cognitive problems. Within the past three years three cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) have been licensed in the United Kingdom for use in mild to moderate Alzheimer's disease. These drugs are a rational therapy based on the core deficit in the disorder, that of cholinergic deficit.[4] These compounds represent symptomatic treatments and have been shown in several large, multicentre, randomised, double blind, placebo controlled trials to improve cognitive function, global outcome, and activities of daily living.[5–9] There is also accumulating evidence that they may improve non-cognitive symptoms such as psychosis and apathy.[9] The mean effect of drug over placebo represents an improvement in cognition roughly equivalent to stemming 6-12 months of natural decline in untreated patients. When the drug is withdrawn the clinical gain is reversed, and there are no convincing clinical data that these drugs modify the disease.

Group means hide a marked heterogeneity of response as 40-50% of patients show a definite clinical improvement (≥4 points on the Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog)), while 20% show a strong response (≥7 points on the ADAS-cog, equivalent to stemming a year or more of natural cognitive decline). Responders are maintained above baseline for 12-18 months on both cognitive and non-cognitive measures.[10] Numbers needed to treat for significant clinical improvement are 3-7.[11] No reliable predictors of response have emerged, and in each patient careful assessment of benefit needs to be undertaken after two to four months of treatment. Both efficacy and side effects (mainly gastrointestinal problems) are similar between compounds.

Since the licensing of the first drug (donepezil) in the United Kingdom in 1997 inconsistent availability within clinical practice has resulted in geographical inequities in availability. Initial scepticism over these compounds was fuelled by the late publication of key trial data, initial lack of clear effects on activities of daily living scores, and difficulties in determining cost effectiveness. The latter remains a problem as economic analyses have been forced to use short term trial data to predict long term outcome (for example, delay in admission to institutional care). However, most economic analyses clearly show either cost neutrality or cost effectiveness in favour of these agents.[12] Though more data are needed, the evidence to date suggests that the modest cost of these agents (£800-£1200 a year) would be more than offset by savings elsewhere, though not necessarily within the healthcare system.

Summary of NICE guidance on antidementia drug use

- All three drugs (donepezil, rivastigmine, and galantamine) should be available in the NHS for those with mild and moderate Alzheimer's disease
- The diagnosis must be made by a specialist according to standard diagnostic criteria
- Cognition, global and behavioural functioning, and activities of daily living must be assessed before prescription, which is limited to secondary care. Cognitive function (mini-mental state examination (MMSE)) score must be >12
- Compliance must be assured
- Drug should be continued only after assessment at 2-4 months showing: improvement or no deterioration in MMSE score; evidence of global improvement on behavioural or functional assessment
- Patients to be reviewed every 6 months and treatment continued only while MMSE score remains >12
- Drug costs may be about £42m/year, which may be offset by delay into residential care
- Specialised secondary care services need expanding, particularly memory clinics

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The National Institute for Clinical Excellence's recent guidance recommends when and how cholinesterase inhibitors can be prescribed (see box). These guidelines are sensible and will facilitate equitable availability for patients with mild to moderate Alzheimer's disease across the United Kingdom while providing structure for clinical practice which requires standardised monitoring of progress and discontinuation of treatment in the absence of benefit. Nevertheless, it may be hard to observe the guidance's recommendation not to prescribe these agents to patients when their mini-mental state examination score falls below 12—that is, when they enter a more severe stage of illness.

Preliminary evidence indicates that these agents may have value in other dementias, such as dementia with Lewy bodies, and for people with severe dementia and psychiatric and behavioural problems, though the evidence is as yet inadequate for a clear treatment recommendation. We support the institute's view that these are priority areas for further research, as are rigorous studies to determine whether cholinesterase inhibitors can modify the course of disease. However, the wider availability of these drugs will make research into the latter difficult if not impossible.

The wider availability of these treatments will probably have other benefits. Early referral of patients will no longer be seen as pointless, and this may lead to a paradigm shift from care towards treatment. The guidance recognises this by emphasising that secondary care services, particularly memory clinics, need to be developed, though expansion of services needs to be in line with evidence of effectiveness. Although only the first step in the development of treatment for dementia, these drugs have led to a new mood of optimism about the management and future prospects for this devastating illness.

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JOB and CB were external experts to the NICE appraisal determination and both have accepted hospitality and honoraria for lectures from Novartis, Pfizer, Shire, and Janssen. JOB is on advisory boards for Janssen and Pfizer, CB for Novartis and Shire.

1 Hofman A, Rocca WA, Brayne C, Breteler MM, Clarke M, Cooper B, et al. The prevalence of dementia in Europe: a collaborative study of 1980-1990 findings. Eurodem Prevalence Research Group. *Int J Epidemiol* 1991;20:736-48.
2 Cognitive function and dementia in six areas of England and Wales: the distribution of MMSE and prevalence of GMS organicity level in the MRC CFA Study. The Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). *Psychol Med* 1998;28:319-35.
3 Audit Commission. *Forget me not.* Portsmouth: Holbrooks, 2000.
4 Perry EK, Tomlinson BE, Blessed G, Bergmann K, Gibson PH, Perry RH. Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia. *BMJ* 1978;ii:1457-9.
5 Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group *Neurology* 1998;50:136-45.
6 Corey-Bloom J, Anand R, Veach J. A randomised trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. *Int J Geriatric Psychopharmacol* 1998;1:55-65.
7 Rosler 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;318:633-8.
8 Raskind MA, Peskind ER, Wessel T, Yuan W. Galantamine in AD: A 6-month randomized, placebo-controlled trial with a 6-month extension. The Galantamine USA-1 Study Group. *Neurology* 2000;54:2261-8.
9 Tariot PN, Solomon PR, Morris JC, Kershaw P, Lilienfeld S, Ding C. A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. *Neurology* 2000;54:2269-76.
10 Matthews H, Korbey J, Wilkinson D, Rowden J. Donepezil in Alzheimer's disease—eighteen months results from Southampton Memory Clinic. *Int J Geriatric Psychiatry* (in press).
11 Allen H. Anti-dementia drugs [editorial]. *Int J Geriatric Psychiatry* 1999;14:239-43.
12 Whitehouse PJ, Winblad B, Shostak D, Bhattacharjya A, Brod M, Brodaty H, et al. First International Pharmacoeconomic Conference on Alzheimer's Disease: report and summary. *Alzheimer Disease and Associated Disorders* 1998;12:266-80.

BMJ Christmas revue

Send us your sketches, songs, ravings, and suggestions on saving the NHS

Last year we held the first ever *BMJ* Christmas revue, and it was a huge success. Phil Hammond, the compere, was on devastating form, teasing mercilessly a cabinet minister who was brave enough to turn up. Many of the sketches were both witty and acutely observed: the word revalidation will forever make me think of a faltering pianist being hit with a frying pan. The singing was brilliant, the dancing irrepressible, and the band funky. The pace hardly faltered, and we all had a great time. So we've decided to do it again. This year's revue will be on Wednesday 28 November at the Conway Hall, Red Lion Square, London WC1.

We've also decided—at Phil's suggestion—to experiment with a theme. Copied from Labour's ludicrous slogan from the last but one election it's "48 minutes to save the NHS." But songs and stomps are still fine: indeed, they may be the best way to save the NHS. We would like you to send us your contributions, which should not be longer than five minutes, by the end of September.* You might send us words on paper, audiotapes, or videotapes. You can even send us single sentences on ideas to save the NHS: Phil will then weave them into his badinage. Last year we offered everybody who submitted something a five minute slot, and most accepted. This year we may well have to be more selective. We'll supply Phil, a highly adaptable band, lights, sound systems, a stage manager, and the day to rehearse. You supply the talent. And Phil is pitching the idea on "48 minutes to save the NHS" to Radio 4. So this could be your big break.

Richard Smith *editor, BMJ*

*Please send contributions to: Mrs Gaby Shockley, BMJ, BMA House, Tavistock Square, London WC1H 9JR.

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