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WHEN THE DRUGS DON'T WORK

'I repeated the MMSE and Mr P scored 20/30, six points less than December 2004. He continues on rivastigmine 3 mg bd. He will be reviewed in 6 months' time.'

Cognitive enhancers have been licensed for the treatment of dementia in the UK since 1997. They increase brain levels of acetylcholine, known to be depleted in Alzheimer's disease (AD). They presented a first glimmer of hope for treatment of dementia — one of the most distressing conditions we encounter in general practice. In the UK alone 700 000 people are affected, and annual costs of dementia care in the UK are in excess of £6 billion. In 2001 the National Institute for Clinical Excellence, responding to the *National Service Framework for Older People*, recommended that cognitive enhancers be used throughout the UK for the treatment of mild to moderate dementia. By 2004 British GPs were prescribing £38 million's worth of donepezil, galantamine and rivastigmine. £38 million, it is worth pointing out, buys rather a lot of day care.

Then came AD2000.¹ AD2000 was the first large randomised controlled trial, publicly and not pharma funded, to assess AD drugs. There was a problem. Donepezil didn't work very well. Yes, small improvements in tests of cognitive and functional ability, an average gain in the donepezil over placebo group in MMSE of 0.8 (in a 30 point scale). Not statistically significant. Primary endpoints (time to institutional care, progress of disability) — no difference between donepezil and placebo. NICE announced a review of cognitive enhancers. Should they be prescribed more narrowly? If at all?

At which point cue howls of protest. First, and predictably, manufacturers are unamused. *'Eisai and Pfizer have great concerns about the design and conclusions of the AD2000 trial ...'; 'We feel that the findings of this trial ... should be considered alongside the wealth of evidence-based data and clinical experience of approved drugs, involving thousands of patients ...'; '(AD2000) makes bold claims against the use of donepezil ... but inappropriately extrapolates them to other drugs with cholinergic effects ...'*² Psychiatrists are similarly unamused. One can see why. Young psychiatrists, thrilled by advances in 21st century neurosciences, find rejection of such key and innovative new drugs hard to bear. However, psychiatrists also wrestle with conflicts of interests. Like cardiologists they seem incapable of supplying editorial for major journals without pharma caveats. This is

not good for their image — in my local trust (where sales of AD drugs are more than 50% greater than the national average), according to a psychiatric colleague, the only place where you won't find pharma reps is on the ward round, 'and that's only a matter of time'.

Meanwhile, politicians had general elections to win — in March 2005 John Reid, then Secretary of State for Health, was typically forthright. The provisional NICE revision of cognitive enhancers did not adequately assess quality of life issues, nor societal cost-effectiveness. Odd, that, as AD2000 specifically addressed both issues.

Understandably, patient groups were appalled that cognitive enhancers were suddenly fallible. After all organisations like the Alzheimer's Society and Alzheimers Scotland had been desperate for years to see some form of effective treatment develop. They had campaigned honourably against 'postcode prescribing' of cognitive enhancers, demanding quite correctly that if there was firm evidence of benefit then all patients should have access to treatment. But similarly, if, with time, that evidence base begins to weaken, then surely there must be pause for reflection. They must also guard against reliance upon charitable donations from pharmaceutical companies, whose motives may not always be purely philanthropic.

In June 2005 another large RCT on cognitive enhancers or vitamin E versus placebo appeared, in the *New England Journal of Medicine*,³ this time looking at the role of both agents in delaying progression of mild memory impairment to dementia. Vitamin E did not work at all, and cognitive enhancers only weakly.

Where then does this leave us as GPs? In the case of Mr P, when his drugs aren't working, we should gently try to stop them. We should not collude.

And when we get a letter like this next one, we should be angry: *'Mrs T's daughter also feels that day care would be helpful too but they are aware of the waiting list which is currently 18 months.'* What's the use of cognitive enhancers when there is no access to care that indubitably does work?

Alec Logan

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