

Dear Dr Longson,

**Appeal from the Royal College of Psychiatrists  
and the British Geriatrics Society regarding the NICE Final  
Appraisal Document: Donepezil, rivastigmine, galantamine and  
memantine for the treatment of Alzheimer's disease.**

The Royal College of Psychiatrists wishes to strongly object to the FAD and lodge an Appeal against the Guidance. This appeal is jointly with, and fully supported by, the British Geriatrics Society. The appeal is lodged on the following grounds (please note that some points under Ground one also apply under Ground two).

**Ground One**

**The Institute has failed to act fairly and in accordance with the appraisal procedure set out in the Institute's *Guide to the Technology Appraisal Process***

1. The Institute has a duty to consider the wider merits of a technology and not base decisions entirely on QALY estimates, particularly when there are considerable uncertainties regarding the robustness of the health economic data on which they are based. As outlined by Sir Michael Rawlins (BMJ 2004), these include:

- a) **The degree of uncertainty surrounding the estimate involved.** There remain considerable uncertainties regarding the robustness of the health economic data. QALY estimates were considered unreliable by the 2001 Appraisal Committee and given little weight, yet in spite of no new health economic data being made available, much economic modelling has been done by the NICE secretariat during this appraisal. This has resulted in QALY estimates ranging from £5000 to £500,000 per QALY, depending on the assumptions in the model, and resulted in the Appraisal Committee initially rejecting the technology, then subsequently completely reversing that decision based on reanalysis of the same study data. In view of these inconsistencies and hugely variable estimates, there can be little doubt that there is a considerable degree of uncertainty surrounding the QALY estimates.
- b) **The particular features of the condition of the population using the technology.** Again there are especially compelling reasons for approving treatments for Alzheimer's disease, a devastating and terminal illness which causes immense suffering to patients, their carers and a huge cost to society. It should not be forgotten that costs of Alzheimer's disease are in excess of £6 billion per year, while the technologies under consideration currently incur costs of around £50 million per year.
- c) **The innovative nature of the technology.** Cholinesterase inhibitors, and now memantine, are the very first treatments for what was previously an incurable illness. They both have clear

pharmacological and scientific rationale, directly based on what is known about transmitter disturbances in Alzheimer's Disease.

- d) **Where appropriate the wider societal costs and benefits.** Not only are the costs of the untreated illness great, but the benefits of the technology in terms of raising awareness and profile of cognitive impairment in Alzheimer's disease, reducing stigma and improving services has been immense and indeed has previously been recognised as of great importance by the Appraisal Committee. To consider undermining the substantial benefit brought by the new technologies in this regard would have catastrophic consequences for the management of patients within the NHS, especially in regard to encouraging the early recognition and assessment of those with mild to moderate dementia who will be excluded from treatment, with consequent nihilistic attitude developing towards recognition and referral.
- e) **When appropriate, reference to previous appraisals.** Once more, Alzheimer's disease has a compelling case as the current appraisal determination completely reverses that of previous guidance, despite the fact (and we would emphasise this most strongly) there have been neither methodological improvements nor new data since that time which would have allowed a more accurate assessment of cost effectiveness to be performed.

The Appraisal Committee has not given any of these points sufficient consideration. Taken together, they provide a compelling case for why antidementia drugs should be made available for people with Alzheimer's disease within the licensed indication, as they are currently.

2. Under this ground we would also wish to highlight that despite overwhelming comment during the consultation that carer benefits should be included. Instead of using robust data from RCTs on reduction in carer time produced by these drugs (Sano et al, 2003), which could have been costed, the Appraisal Committee chose to apply a (very small) QOL gain to carers – it is not clear from what evidence base this estimate came from, indeed it seems entirely arbitrary. The justification for not using carer time was that it was not appropriate to use a QOL gain as well as a cost, and that cost for informal carers would not normally be included. However, given the particular nature of the condition, and the huge role informal carers play in the care of people with dementia, there should be the inclusion of carer data which is already available from RCTs.

3. We also note that the Appraisal Committee took evidence from patient, carer and professional organisations such as ours. We see no evidence that any significant weight has been given to these groups unanimous view on both the direct benefits of the medications and the broader benefits to dementia care as a whole.

4. Over-reliance on the MMSE is both inappropriate and discriminatory. The MMSE is heavily influenced by factors such as age, sex, education, ethnicity and linguistic abilities. The Appraisal Committee acknowledges

these limitations with respect to people with Learning Disabilities and linguistic abilities, but states that these groups will not be disadvantaged by the treatment entry level of MMSE (4.3.13). The committee's opinion that people with learning disabilities should be assessed for treatment according to MMSE criteria lacks credibility. It is the complete opposite to guidance in the draft NICE guideline, 'Dementia: supporting people with dementia and their carers' section 3.6.3 which states, 'The Mini-Mental State Examination is generally unhelpful when used with people with Down's syndrome'. It is unclear whether the subsequent statement in 4.3.13 implies that specialist in learning disability are free to ignore MMSE criteria when initiating treatment. If so, as a matter of equity, all clinicians should be free to exercise their professional judgement as to how reliable an MMSE score is for any individual patient. For example, those with high levels of premorbid ability/education will score above the cutoff suggested (20) for a similar level of dementia severity and so have their treatment unnecessarily delayed. Conversely, those with English as a second language or with low educational attainment will have their treatment stopped prematurely. We have consistently argued previously in our evidence for a more clinically relevant and meaningful assessment of dementia severity, which includes other dimensions apart from cognition, and suggested viable alternatives such as the clinical dementia rating scale.

## **Ground Two**

### **The Institute has prepared guidance which is perverse in the light of the evidence submitted**

1. It is entirely perverse, and totally contrary to the views of the patient, carer and professional groups, that effective therapy should be withheld until the later stages of a neurodegenerative disorder when insight is lost, and functional abilities and independence are already severely compromised. Patients and carers wish to have treatments that maintain them at the highest level of functioning, at a time they have good insight and still the abilities to maintain many of their previous activities and interests. The drugs are still clinically effective at the mild stages. Although there is a suggestion of greater benefit in moderately impaired patients, we urge the greatest of caution when interpreting such results. The MMSE, and the ADAS-cog, are not linear scales with good correlations with disease course. They have clearly been shown to have floor and ceiling effects at late and early stages of the disease respectively, and are only really reliable indicators of disease severity for those in the moderate stages of the illness (e.g. Huppert et al, 2005). The greater degree of cognitive benefit apparently seen in such patients is almost certainly the result of non-linearity of the scale and a ceiling effect. From the data submitted, the global impression of change does not appear to show a similar distinction between mild and moderate/severe groups, thus failing to validate the supposed greater cognitive benefit in more severe patients. Any attempt to deprive more mildly impaired patients of therapy, on the basis of inadequate psychometric properties of assessment instruments, would be entirely wrong. It would also maintain patients for longer in the moderate to severe stages rather than the mild stages of the disease,

which totally defies common sense and logic and is surely not what anyone would want should they develop the illness.

2. The FAD has not properly considered the issue of improving the cost-effectiveness of antedementia drugs by maintaining good responders on treatment. It states that the Committee "was not persuaded" that targeting responders would result in more efficient use of resources, yet this is the way these treatments are currently prescribed. As we have previously argued, it would be quite possible to offer these treatments to those with mild disease, assuming that an appropriate responder definition was applied, yet the Appraisal committee have consistently refused to consider this approach.

3. The importance of early recognition, diagnosis and management of dementia is universally emphasised and advocated by the Department of Health in several key policy documents including PPF and NSF's, both of which prioritise early diagnosis, early intervention and maximising independence for people living in their own homes. The FAD would lead to later referral and later intervention, with the promotion of a nihilistic attitude that dementia would not be worth recognising or referring until subjects had deteriorated until MMSE < 20.

4. The reliance placed on QALYs as the sole basis for assessing cost-effectiveness in Alzheimer's disease is severely flawed. This point was made by the College and several other groups at the original (2001) appraisal, when it was accepted. When the trials were conducted there were no robust validated measures for assessing quality of life in Alzheimer's disease. The current cost utility analysis relies totally on data from a single unreplicated US study that relied on carer proxies responding on behalf of patients using the Health Utilities Index 2 (HUI2) (Neumann et al 1999; Neumann et al 2000). These need to be treated with extreme care. In a further study when the HUI2 and the HUI3 were compared, marked differences were seen (Neumann et al 2000). This strongly suggests there will be considerable instability in utility estimates derived from such scales, which is highly likely given that neither scale has been psychometrically evaluated in dementia, and certainly not for proxy use, so reliability and validity are unknown. Neumann et al (1999) themselves acknowledge the need for caution and for further research into the use of proxy respondents. The use of proxy measures that have not been specifically developed for and tested in dementia has now clearly been shown to be invalid, with several recent studies demonstrating major inconsistencies and disagreements with very poor correlations between different proxies (Boyer et al 2004; Coucill et al 2001). Alternative methods of assessing quality of life in dementia are being developed and validated, for example the concepts of personhood and the methodology of dementia care-mapping (Fossey et al 2002; Williams and Rees 1997) and a recently completed Health Technology Assessment-funded programme to generate a disease-specific measure of health-related quality of life in dementia (Smith et al 2005). As well as HTA, both the Department of Health and the Medical Research Council have also recognised this inadequacy, for example the MRC Health Services Collaborate has just been awarded over £8 million (2004-2009), with one

of the major projects being to develop and validate such measures in older people (<http://www.hsrc.ac.uk/www.mrc.ac.uk>). The current Technology Appraisal states that *"A scarcity of data was identified to inform on this (sic QoL) issue, which is of great importance in cost-effectiveness analysis when decision makers are seeking summary cost-effectiveness estimates presented as cost per QALY"*. NICE has a duty to be evidence based, but when that evidence clearly points to, not only an inadequate evidence base but an unreplicated and non-validated one, then using QALYs derived from such data cannot be defended, especially as the sole basis for decision making when the drugs have (as acknowledged by NICE) proven efficacy.

5. The approach taken is inconsistent and contradictory when compared with the previous 2001 appraisal, when problems with use of QALY's in AD were acknowledged.

In the 2001 assessment, under which the drugs were approved under certain restrictions, the Technology Appraisal did not include a formal health economic analysis using QALY's because of recognised methodological weaknesses. The report stated *"at present there is simply inadequate research available to understand the QoL impact and thus economic modelling ...ought to be regarded cautiously"*. The Appraisal advocated *"primary research specifically on whether or how QALYs can be calculated in people with cognitive impairment since this is a contentious issue compounded by the fact that carers may be poor proxies"*.

6. Most significantly, no important new research in this area has become available that could either better inform the current appraisal or justify a change in that position. Indeed, as cited above, that which has been published casts even more doubt on the use of proxies and the QALY approach in dementia. It is, therefore, all the more remarkable and unacceptable that the SHTAC Assessment Group have attempted to calculate QALYs based on proxy utility scores, not from any new data, but from a single (old) study which was accessible to but ignored by the previous HTA. Thus the very same evidence base has been treated totally differently by the two different Appraisal Committees. NICE has a responsibility to ensure some consistency across time, and in the absence of any new data to change the 2001 position it is unclear how use of the QALY in dementia by the SHTAC Assessment Group could possibly be justified now as the key decision making tool when it was not in 2001.

7. Non-availability of antidementia drugs, which have significant effects on behaviour and psychosis, will result in increased prescription of typical and atypical antipsychotics drugs, which can have severe side effects and are now known to be associated with increased morbidity (stroke risk) and mortality.

8. The FAD requires the withdrawal of medication when people decline to a MMSE score of 10. In recommending this, the Appraisal Committee has clearly acted outside its remit. It did not look at any evidence for cost effectiveness below MMSE of 10, since it is outwith the licensed indication, and so there are no grounds for suggesting discontinuation when people reach a score of below 10. The Appraisal Committee can only make

guidance on the areas covered by the evidence examined. They should simply say that medications should be made available for people with a MMSE score as low as 10 but they are unable to comment on scores below this and should not advocate withdrawal.

9. There will continue to be very strong demand for treatments from the majority of patients with mild dementia, because of their proven efficacy. All those with AD who can possibly afford to seek drugs privately will do so. As a result, a patient group who are among the least well off and most vulnerable in society, will be forced to pay £1000 per year for treatments freely available to some UK patients now and in most other countries. The NICE decision would, therefore, de facto lead to severe inequities and unduly penalise a particularly vulnerable group in society. Ironically, such patients will then qualify for NHS prescription when their dementia severity increases to MMSE of 20.

## References

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