Dear Alana,

I will not rehearse the many arguments outlining the numerous objections to the restriction of treatment to moderate AD and the exclusion of memantine in ACD 2, as I was involved in the RCPsych response. This process has been so tortuous and the data has been dealt with in such a piecemeal way that I do not think the committee or anyone else can see the wood for the trees anymore. The resulting ACD2 is seen by many as a face saving compromise, and like most compromises fails to satisfy anyone The unworkability of this as guidance for the NHS is immediately apparent when one has stopped the bargaining and taken a moment to look at the logical consequences of the advice. The original guidance of 2001 was restrictive but provided a workable and cost effective way of rationing these drugs however it offered no treatment option for the more severe patients.

In response to the specific questions you pose.

1. ‘Do you consider that all of the relevant evidence has been taken into account’

I emphatically do not; and whilst I would agree that efficacy and hence registration can only be assessed on well controlled RCT data I realise there is a view that clinical and practice guidance should include other evidence, as indeed your guidance on Social Value Judgements suggests but this review has not even addressed all the RCT data. It has been limited by its narrow interpretation of dementia and has failed to assess the impact of the treatment by equating only the change on a cognitive scale scores to response to treatment. You will now be aware that the metrics of the scales make it statistically inevitable that there will be greater changes in the scale scores in the more severe patients but there is no evidence that there is less benefit in the more mild patients. A MMSE change from 24 -26 brings a patient back into the normal range but a change from 10 -16 whilst correlating to an improvement in the patient does not. It is sadly an unscientific appraisal of the data and fails to take into account the vast amount of data beyond the cognitive scores, and the personal experience from those involved daily with the management of AD - leaving some of the most needy patients in our purview denied the widely recognised standard of care unless they can afford to access it privately.

Trying to make judgements about the management of AD whilst ignoring the data on amnestic minimal cognitive impairment (MCI), seen by many as the very early, or prodromal, stages of AD, is to be doing the job with one hand behind ones back. Two large scale well designed and run studies of donepezil in MCI have shown that there is very little advantage in treating these patients. (Salloway et al Neurology.2004 Peterson et al NEJM 2005)
It is true that this is not the case for clearly diagnosed very mild AD where the drug is effective but this gives a clear guide as to when to start treatment when cost minimisation and rational use of resources is concerned. Clearly patients who have cognitive impairment and no dementia will not benefit and so one should wait to see if dementia develops before starting. If you wish you can advise that in most cases dementia in AD, meaning a cognitive impairment affecting work or social functioning, will not be apparent, in those of average premorbid IQ until MMSE <26 has been reached. MMSE 20 is far too low for the reasons outlined above. But dementia is a clinical diagnosis and is not determined by an MMSE score.

The view that the drugs do not work in severe disease is fallacious as the data has not been considered on the grounds that it is not a licensed indication for the cholinesterases and consequently not included in the HTA. You can give no advice on this other than to leave it to clinical judgement until you review the data. Not to do so is ingenuous and again hampers any kind of rational advice. There are a number of studies one (Feldman et al 2001) showing clearly the effects on all aspects of dementia with donepezil and the pivotal study reported by Reisberg et al (NEJM 2002) with memantine. Presumably the guidelines committee will do so in due course. Consequently the stopping rules are not based on a proper assessment of the data. The tunnel vision shown in this review also fails to consider the effect on the more behaviourally disturbed who score cognitively in the moderate range and for whom these drugs provide enormous relief from hallucinations, delusions and agitation. This is particularly noticeable in the data on the subgroup analyses, requested by the secretariat, on memantine. By definition post hoc subgroup analyses will not be statistically distinct from the whole group as they are not controlled at baseline and that holds for the arbitrary MMSE subgroups the committee has chosen, as well as the behaviourally (BD) group. Yet the BD group, on all parameters cognitive and non cognitive clearly do better on treatment than the whole group not because the drug works better in these patients, it does not, but because without treatment they do so much worse than average. These patients are declining more quickly so the effect of treatment is comparatively greater and arguably of greater cost benefit than those not treated with BD.

2. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate

The clinical effectiveness has not been addressed because of the narrow view of the evidence, as described above, and, as all the data is not considered, including the carer benefits, the cost effectiveness data is very inconsistent. You will know the arguments against the use of qalys in dementia as they were clearly outlined in the NICE 2001 guidance. The fact is that in this condition the greatest quality of life gains will occur by preserving time in the mild stages, even though illness costs are at their least, rather than prolonging time in the moderate and severe stages and this guidance will do just the opposite. The ongoing flaws in the analysis mean that the cost-effectiveness
data is not reliable enough to base the decision to partially remove the only effective drug treatments for this distressing and progressive condition upon. There will be a considerable negative impact on NHS resources of limiting the use of the drugs to the moderate stages of the disease this will be considerably more than the savings on prescriptions - unless forcing patients to taken on private prescriptions which will inevitable keep them above the NHS prescription level for some time is part of some Machiavellian plan. The negative impact of the NICE decisions have already cost us enormous amounts of clinical time in debate, consultation, responding to anxious carers and in writing such reports as these, without considering the costs of the NICE appraisal process and legal advice etc. If the ACD goes unchanged the time that will be spent counseling milder patients and on unnecessary reviews to assess whether they are now severe enough to qualify for treatment will certainly out weigh any savings as well as having a very deleterious effect on the doctor patient relationships.

Frank Dobson when launching NICE in 1999 said:

"Of course guidance from NICE will not remove the need to take account of genuine, good clinical reasons for tailoring the care provided to the needs of individual patients. That will always be something to be decided with the individual patient in the consulting room."

But this is not how NICE guidance is perceived, and the committee knows that, it is seen as determining whether the treatment will be or will not be funded by PCT's who do not have any truck with tailoring care based on the individual patients needs as decided in the consulting room. Thus when you say that there is no justification for treatment below MMSE 10 because you have not looked at the evidence this is seen as evidence of no effect by fundholders. The fact that you have ignored the data on memantine in more severe disease where it has been shown to have has enormous benefits and can be shown to be cost effective even by your own flawed lights is perverse and unethical. One can only assume that this is due to bias against treating this illness. Much is made of the conflict of interest in evidence from pharmaceutical companies but the specialist and voluntary society expert reports are not driven by pharma industry interests but by direct experience in treating, and by the reports of those caring for, patients. The committee would do well to look at itself and question its own bias which is far more malign an influence than any conflict of interest. If doing the right thing is being prevented by fear of losing face, that is evidence of even more profound bias and wholly inappropriate.

3. Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS.

I do not consider them either sound or a rational or workable basis for NHS guidance.

Restricting access to drug treatments to the moderate stages of Alzheimer's disease is contrary to best practice in dementia care. It is contrary to all the basic tenets of medicine; that we should first do no harm and diagnosing
illness and then suggesting we withhold treatment till the condition worsens is an unsustainable position; and that we should encourage early presentation to facilitate diagnosis and early treatment in order to reduce morbidity. It is stabilisation in the early stages of disease that is hugely valued by patients and carers and the first goal of treatment, this is what people with dementia and their carers want not to allow that undermines patient choice which the NHS is so keen to advocate.

Removing memantine the only drug treatment licensed for the moderate to severe stages of Alzheimer’s (a curious decision as this is the group the ACD restricts treatment to) further denies choice for many patients for whom this is the only option. This denies a licensed effective therapy to those who those who score below MMSE 10, and those who score between 10 and 20, but for whom the cholinesterase inhibitors are contraindicated or who cannot tolerate them. This drug has equivalent efficacy to the cholinesterase inhibitors (CHEI’s) for this group of people. The beneficial effects of memantine on behavioural symptoms such as aggression and agitation are particularly important and should be given greater weight in any guidance. These symptoms are particularly distressing for carers and also have a negative impact on the quality of life of people with dementia.

Finally if the recommendation to the NHS not to prescribe memantine is taken in order to prevent co-prescription with CHEI’s, again due to bias about the perceived expense of these drugs, the expert community would be willing to accept there is not enough convincing data to support co-prescription. Evidence of one positive trial in moderate disease and one equivocal study in mild disease is not enough to sustain co-prescription as yet. But denying patients access to memantine a drug from a different class to those approved, which has been shown to be efficacious in the most stringent test ie in patients already on treatment with CHEI’s, is illogical and perverse when approving the use of all three CHEI’s.

To show the difficulty in using the MMSE to grade dementia for those not used to seeing patients with AD or using this scale I attach two sheets from the CAMCOG examinations I undertook on two consecutive new referrals to my memory clinic last June. This requires the patient to copy three drawings generate a clock drawing with the hands set at 10 past 11 and the write a short sentence. As you can easily see one completed the tasks perfectly and one was completely unable to do so and yet they both scored identically on the MMSE score (18/30) which is part of the CAMCOG assessment.
Yours faithfully

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Hon Senior Lecturer in Old Age Psychiatry
Southampton University

NSF Champion for Older People with Mental Illness

Refs


27.6.05

MMSE 18/30

Clock

I am going shopping later
Sentence: *CHOSE = WALL OF HOUSE NOSE*