# Alzheimer's Society response to assessment report for R111 (August 2010)

## Key points

- As PenTAG acknowledge, although some of the shortcomings of the previous model have been addressed, there are still serious limitations in the current model. We believe addressing these limitations is likely to improve cost effectiveness estimates for all four drug treatments.
- Further work should be done to address these limitations and if it proves impossible to do so, then NICE should accept the academic group's recommendation that it should 'be regarded as an explorative model.'
- Important limitations include:
    - The use of out of date data on service usage and resulting costs of care. Costs of care are fundamental to the outcome of the model and unreliable estimates will seriously bias results.
    - Although it is preferable to use UK data for risk equations and baseline characteristics, we question whether it is possible to generalise the findings of a small Oxfordshire based study to the rest of the UK. We recommend that international data are also used to inform the model, while using UK findings to interpret the international data.
    - The benefits that the drug treatments can bring to carers are not properly incorporated within the model. We maintain using trial data that shows the drug treatments can save carer time is the most appropriate way of addressing this problem.
    - Failure to capture effect on behavioural and psychological symptoms is a very significant limitation of the modelling, given the impact of these symptoms. Further work is required to address this gap.
- The evaluation of memantine is particularly problematic. Not all available trial data has been used, despite it being straightforward to do so. The clinical and cost effectiveness of the behavioural subgroup has not been evaluated. Lack of time is insufficient reason not to do this work.

## Introduction

The Alzheimer's Society welcomes the opportunity to comment on the assessment report. We recognise that the complexities of Alzheimer's disease and the limitations of the research data currently available make this a difficult area in which to undertake health economic analyses.

We welcome the work that PenTAG have done to address some of the criticisms of the previous model, for example the acknowledgement of the heterogeneity of costs and quality of life in the pre-full time care state. Their work represents an important contribution to the debate that NICE's forthcoming appraisal will provoke. However, there are also important aspects that were included in the 2004 model that have been excluded by PenTAG, for example impact on behavioural symptoms. We believe this represents a step-back in terms of the quality of the model. There are also issues from the 2004 model which have not been addressed by the PenTAG model. These include properly incorporating impact on carers and using accurate costs of care.

Indeed, as the PenTAG assessment group themselves note, their model has considerable shortcomings due to a lack of data on important outcomes and cost drivers, as well as the overarching difficulties of producing a model in such a complex disease area. Therefore, we urge the appraisal committee to accept the academic group's recommendation that the model as it stands should 'still be regarded as an explorative model'.

In summary, PenTAG's model indicates:

- "there is clinical benefit from the AChEIs in alleviating symptoms and controlling disease progression in [Alzheimer's disease]" (heading 10);

- "[w]hen considering the AChEIs, there is a 43% probability that best supportive care is *not* the most cost-effective treatment option at a willingness to pay of £30,000 per QALY (and 38% at a willingness to pay of £20,000 per QALY)" (para 7.5). Put another way, there is a real prospect that funding all the AChEIs for all patient groups is a cost effective option, when compared to the hypothetical alternative of best supportive care;

- its implications for service provision are therefore "not clear and will ultimately rest on the interpretation of the new evidence from variety of sources, including this report, in the forthcoming NICE appraisal on this topic." (para 10.2)

Amongst that "new evidence", the PenTAG group noted the existence of "further publications on cost-effectiveness of pharmacological interventions for AD in the general medical literature" which are "generally supportive of the cost-effectiveness of the acetylcholinesterase inhibitors (donepezil in particular) and memantine in the treatment of AD at all stages of disease" along with "some new economic evaluations alongside trials and other studies which appear to offer new evidence[154;159;169.] They support the cost-effectiveness of donepezil and memantine, in contrast to the AD2000 study in the last guidance" (pages 208-209)."

In these circumstances, the appraisal committee will need to focus particularly on the aspects of the PenTAG model where outcomes and benefits were not counted at all, and where the data that was used is an inadequate reflection of the everyday experience of clinicians, carers and patients. Our view is that, in respect of each of these aspects, there are good reasons for believing that the model does not reflect the full extent of the benefits of drug treatment. The appraisal committee is not restricted to using evidence of the kind on which the PenTAG model is based. Indeed it must not, given the reservations candidly expressed by the model's authors.

We have the following specific comments to make:

## 1 Overreliance on the Wolstenholme study to inform the model is inappropriate

Although there are advantages to using UK data on service usage, risk equations and baseline characteristics, we believe it is inappropriate to rely too heavily on the Wolstenholme study for a number of reasons.

### 1.1 Service usage data within the Wolstenholme study is out of date

It is unfortunate that the PenTAG model contains no up-to-date national estimates of the NHS and PSS costs associated with Alzheimer's disease.

The data on service usage in the Wolstenholme study is out of date, which brings into question the credibility of resulting estimates of cost-effectiveness. We welcome the fact that the costs from the Wolstenholme study are inflated to 2009 prices. However, we firmly believe that data on service usage of less than 100 patients in one locality that dates from 1988 to 1999 will not be representative of national service usage in 2010. This is a limitation of the model acknowledged by PenTAG. As noted by the assessment group, there are fewer people receiving community care services now and those that do have higher needs. Also, people are entering full time care at a later stage of their illness (which means a more intensive and costly service when they do).

Costs of care are fundamental to the outcome of the model. If, in the PenTAG model, pre-institutionalisation costs are overestimated (because people are less likely to receive these services now than they were in 1988-99) and full-time care costs are underestimated (because people in full time care now have higher level needs) the cost-effectiveness of all four drug treatments is likely to be underestimated.

It may well be appropriate to commission a focussed piece of further research on this issue, because an unreliable estimate of costs of care significantly challenges the credibility of results.

Also, in addition to data on service usage being out of date, we are concerned about whether it is possible to generalise the findings of a small Oxfordshire based study involving less than 100 patients to the rest of England and Wales. Oxfordshire is likely to have a lower cost of institutionalised care than urban areas. It is also a relatively prosperous part of the UK so likely to have an inherently healthier population than those living in urban or economically disadvantaged rural areas. A reliable estimate of service usage requires a larger, more representative sample.

### 1.2 There is a range of risk factors for institutionalisation

Reliance on the finding from Wolstenholme that severe dementia is equivalent to institutionalisation is inappropriate, given the findings from a range of other studies that there is a range of factors beyond MMSE score that increase the risk of institutionalisation. These include behavioural symptoms, carer burden and function.[i] [ii] [iii] [iv] We therefore question whether the finding from Wolstenholme that MMSE of 9 is reached at 0.04 years prior to institutionalisation is generalisable beyond that study population.

Failure to recognise the particular importance of behavioural symptoms as a risk factor for institutionalisation has particular significance in the context of this model, because it is excluded as an outcome. Inclusion of behavioural symptoms within the model would give a more realistic understanding of how long drug treatments can delay institutionalisation and would likely increase their cost-effectiveness.

We agree with PenTAG that it is preferable to use UK data to inform risk equations and baseline characteristics. However, given the important additional information that international studies can provide, we believe the most appropriate course of action would be to analyse the findings of both international and UK studies and use UK studies to help interpretation of the results.

## 2 Quality of life of people with dementia

There are limitations to using proxy judgements of quality of life and it is questionable whether carer views on the quality of life of the person with dementia are reliable. The best validated and most widely used quality of life measures in dementia (DemQol and QOL-AD) acknowledge this problem by incorporating information from both carers and people with dementia.

The model's use of carer judgments alone inevitably adds to the need to treat results with caution.

## 3 Carer benefits

We welcome the acknowledgement of the burden this disease places on carers, which is beyond that seen in many other conditions. It follows that treatments that have a clinical benefit to the person with Alzheimer's will also bring important benefits to carers. This is supported by reports from thousands of carers who tell us how much they value these benefits and clinical trials that demonstrate the drug treatments can reduce time spent caring. [v] [vi] A reduction in caring duties is a crucial benefit in the context of this disease and the huge burden it places on carers and the consequences for their own health and general quality of life.

However, impact on carers has not been sufficiently acknowledged within the model.

The Neumann study is still used in the new model as the basis for incorporating a benefit to carer quality of life within the PenTAG model as with that developed by SHTAC. We acknowledge that there are limited data on carer utility, particularly from trials in which a carer was supporting someone taking one of the drug treatments. However, we still believe that in the absence of any good data on carer quality of life, methods should be developed to incorporate the findings from clinical trials that the drug treatments can and generally do reduce the time carers spend caring.

An appropriate financial value should be assigned to this time saved. We believe assigning a value to the time saved is the simplest way of incorporating into this data into the model. It could be considered that there are additional benefits to carers of saved time (spending less time caring is likely to have a positive benefit for carers' own health), but these are difficult to quantify. Furthermore, assigning both a financial value and a health benefit to reduced carer time could be double counting.

What the appraisal committee should not do is assign no, or no significant, value to something which clinicians, carers and patients universally recognise as a very real, widespread benefit of drug intervention. If no means can be found to value carer benefit meaningfully, there can be no sound basis for a cost effectiveness decision.

## 4 Responder analysis

We welcome the fact that the PenTAG model acknowledges within the cost assumptions that not everyone will continue on drug treatments. However, we believe a full responder analysis should have been carried out to ensure the assessment reflects clinical practice. Only those who respond should stay on the drug treatment and the mean difference between responders and controls is

likely to be greater than the mean difference between all those in the treatment arm and controls. We believe the mean difference between responders and controls should be used in a sensitivity analysis.

## 5 Clinical effectiveness of memantine

Four memantine trials were excluded from the PenTAG review because they included patients with mild disease and also patients taking an anticholinesterase drugs. However, it would have been straightforward for PenTAG to use individual patient data from these studies to focus on those with moderate to severe disease and also on those who are not taking an anticholinesterase drug. In addition, it is questionable whether it is appropriate to exclude trials in which patients are receiving an anticholinesterase drug. It would be unethical to stop anticholinesterase treatment for the purposes of the trial, because it is now the standard treatment for moderate Alzheimer's. Therefore any future trials would include people who are already receiving anticholinesterase treatment.

Inclusion of all relevant studies is required to provide a robust evaluation of memantine's clinical effectiveness. It is worth noting a conclusion from the most recent Cochrane review of memantine regarding the 2004 NICE review, which also did not use all available evidence, and is likely to apply to the PenTAG review: "the data presented above, which were available to NICE, do not support the committee's conclusion that "the evidence for the clinical effectiveness of memantine was currently insufficient". The weight given in the NICE evaluation to an analysis based on MMSE changes may be inappropriate at lower MMSE levels." (page 14) [vii]

It is wholly unsatisfactory for the minority of trials to be included. Lack of time to analyse the individual patient data is insufficient reason for failing to provide a comprehensive review. We therefore feel this is not a satisfactory evaluation of memantine and further work is required to produce a more robust assessment of memantine.

## 6 Behavioural symptoms

We agree that failure to capture effect on behavioural and psychological symptoms is a very significant limitation of the modelling, given the impact of these symptoms on people with dementia and their carers. This limitation skews the results in respect of AChEI treatment. It also means that one of the greatest clinically observed and most important benefits of memantine treatment is discounted altogether.

We believe their inclusion within the cost effectiveness model would result in improved cost-effectiveness for the four drug treatments, but would be particularly important for memantine.

### 6.1 Behavioural symptoms have significant detrimental impact on people with dementia and their carers and also costs

As outlined in our submission, behavioural symptoms cause significant distress for the person with dementia and family carers, often more so than cognitive problems.[viii] Quality of life for people with dementia is significantly negatively correlated with higher levels of behavioural and psychological disturbance. Behavioural symptoms have been found to account for 52% of variance in quality of life. [ix]

Behavioural and psychological symptoms of dementia (BPSD) are often the symptoms that the carer find most difficult [x] and are a key reason for the person with Alzheimer's going into full time residential care.[i] Carer quality of life is negatively correlated with agitation/aggression as well as total neuropsychiatric inventory (NPI) score.[xi]

Also as stated in our submission, as well as important benefits to quality of life, a reduction in behavioural symptoms could potentially save costs, as studies have found a correlation between NPI and costs.[xii] [xiii]

### 6.2 The four drug treatments have a modest but significant impact on these symptoms

Our submission outlined the evidence that anticholinesterase drug treatments and memantine have a modest but significant beneficial effect on behavioural symptoms.[xiv, xv, vii]

### 6.3 Memantine and behavioural symptoms

It is vital that the economic evaluation of memantine includes impact on behavioural symptoms. The review of clinical effectiveness reported that the two studies considered (Reisberg (2003) and Van Dyck (2007)) found no impact on behavioural symptoms. This contradicts the findings of a recent Cochrane review that found memantine had a significant beneficial effect on behaviour.[vii] As noted with regard to clinical effectiveness of memantine we believe PenTAG should have extracted the relevant data from the four excluded trials.

It is a serious omission to fail to look at the behavioural subgroup (or APS as it is now termed). We described four key reasons why people with Alzheimer's disease with behavioural or psychiatric symptoms represent a meaningful sub-group of patients within our submission. Lack of time is an unacceptable reason for failing to look at this subgroup and we believe it is important that further work is carried out to evaluate the clinical and cost effectiveness of memantine within this subgroup. The value of doing this work is further highlighted by the

urgency, recognised within government policy, of reducing the use of antipsychotic drug treatments, which, although not recommended, are currently used as the first line treatment for behavioural symptoms.

**6.4 Risperidone should be included as a comparator in memantine review**
Risperidone has now has a license for the "short-term treatment (up to six weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others" and should therefore be a comparator within the evaluation of memantine. Data around the level of usage of antipsychotics indicate that they remain the first line treatment of behavioural symptoms, despite guidance strongly advising against this.

As noted in our submission, meta-analyses have found that memantine has a similar effect on behavioural symptoms to neuroleptics, yet none of the harmful side-effects. [vii, xvi] This is in addition to memantine's benefits on other symptoms, including cognition and activities of daily living. Neuroleptic treatments have a detrimental effect on cognition.[xvi] Table 1 presents data regarding the effects of memantine and neuroleptics on NPI and cognition.

Table 1: Effect of memantine and neuroleptic on NPI score and cognition

| **Drug** | **Average change on NPI score** |
|---|---|
| Memantine | -2.76 |
| Neuroleptic | -2.14 |
| | **Average change in cognition** |
| Memantine | 2.97 average improvement (Severe Impairment Battery) |
| Neuroleptic | 0.73 average decline (MMSE) |

Failing to incorporate behavioural symptoms within the model is a significant problem and is a key reason to treat the results with caution. If it is not possible to develop the model so that it addresses this gap other means must be found to count these benefits.

## 7 Mild/moderate subgroup analysis

The PenTAG group does not explain why it was not possible to perform a mild/moderate subgroup analysis within the anticholinesterase review as was done in the previous appraisal. We believe it would have been possible to obtain individual patient data from the pharmaceutical companies and would be interested to hear why this was not pursued. We do not believe a lack of time is sufficient reason.

## 8 Combination therapy

We believe there would be value in further exploring the cost-effectiveness of combination therapy. We note that the study since 2004 found there was no benefit, but that this may have been due to an underlying interaction between galantamine and memantine (AR p.176). Previous trials had indicated that combination therapy was beneficial. We suggest that the original trial be used within a sensitivity analysis.

## 9 Patents coming to an end

We note that the patent for a number of the drug treatments will be coming to an end shortly. We would like to enquire how this will be dealt within the current appraisal of the drug treatments.

## Conclusion

PenTAG have clearly spelt out the limitations of their model and also the important gaps in evidence. Gaps in the evidence regarding impact on quality of life and time to institutionalisation are particularly worrying given they are so important within the economic model. The most significant benefits which the model does not accommodate in any real way are those experienced by carers and in terms of behavioural symptoms.

The evaluation of memantine is particularly problematic, given the failure to include the majority of available trial data and also to incorporate impact on behavioural symptoms. We believe it is imperative that PenTAG do further work to assess the costs and clinical effectiveness of memantine within the behavioural subgroup. Lack of time is not a sufficient reason to fail to do this.

No sound decision can be made on cost effectiveness without grappling with and addressing these shortcomings. The PenTAG group itself implicitly acknowledges as much.

We welcome the improvements that have been made to the model since 2004 and would recommend consideration be given to the further improvements we have outlined above. We also recommend that consideration be given to the alternative models put forward by the manufacturers, as they may provide further guidance to the committee. However, given the acknowledged problems in developing a robust model in this complex disease area we recommend that the results of all three models be used as a starting point by the appraisal committee. We believe it is likely that when the increased costs of institutional care and additional known benefits are factored in along with the PenTAG

model outputs, the case for making drug treatment widely available, subject to proper clinical controls, will become compelling.

**Editorial comments:**

- Page 47 – this states that there are 520k people with Alzheimer's disease in England and Wales. However, on page 42 it states that there are 520k in UK with Alzheimer's and of these 449k live in England and Wales
- P47 - It states that finally financial costs fall mostly on social services as patients move to institutional care. This should also acknowledge the group of people who will be receiving NHS continuing care (NHS CC) because their needs are judged to be primarily health needs. Although there are no data on how many people with dementia are receiving NHS CC, at the end of March 2009 there were 46,599 in England in total receiving NHS CC, of which a significant proportion will be people with dementia.
- Page 49 – This page outlines the National Dementia Strategy for England. It should make clear that this Strategy applies to England and a separate Dementia Action Plan has been developed for Wales.
- Page 234 – Dementia UK was a report commissioned by the Alzheimer's Society, not the Alzheimer's Trust as stated.
- Appendix 17 (row 16) - We would like clarification on the statement 'Baseline characteristics for the prediction of institutionalisation from the UK data do not include variables for psychiatric symptoms, therefore no treatment effects on psychiatric symptoms are assumed. However, the PenTAG model does incorporate a treatment on psychiatric of behavioural symptoms in addition to cognitive symptoms.'

## References


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