

Drugs for the treatment of Alzheimer's disease

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Executive summary

1. Introduction

Alzheimer's Society welcomes the review of TA111. It presents an opportunity to develop new methods of appraising the four licensed drug treatments for Alzheimer's disease. The review is taking place in the context of a national policy focus on dementia. This is particularly focused on improving rates of diagnosis and early intervention.

This submission first contains information on Alzheimer's disease and what it is like to live with Alzheimer's disease. It then discusses evidence pertaining to the efficacy of the drug treatments, focussing particularly on consumer evidence. The submission then proceeds to discuss the impact that TA111 has had on the lives of people with dementia and their carers. Finally we make recommendations regarding factors that the current review should consider.

Alzheimer's Society believes drugs for the treatment of dementia should be available on the NHS, following clinical assessments, to all individuals who might benefit. Alzheimer's Society argues that the key to cost-effective, rational treatment is good monitoring.

2. Alzheimer's Society

Alzheimer's Society is the UK's leading care and research charity for people with dementia and those who care for them. It is a membership organisation, which works to improve the quality of life of people affected by dementia in England, Wales and Northern Ireland. Many of our 25,000 members have personal experience of dementia, as carers, health professionals or people with dementia themselves, and their experiences help to inform our work.

The Society provides services through its network of 250 branches, including care services, Alzheimer's Cafes and support groups. It also provides information and advice and campaigns for improved services for people with dementia and funds. In addition, we fund research into dementia through our innovative Quality Research in Dementia (QRD) programme, involving people with dementia and their carers in setting research priorities in the areas of cause, cure and care. We also provide training for health and care professionals and publish a wide range of training materials and books.

3. Background information

3.1 What is Alzheimer's disease?

Alzheimer's disease affects around 416,967 people in England. Alzheimer's is a progressive disease, which means that, over time, carers and people with dementia are coping with a changing pattern of abilities.

In the early stages people can experience memory loss, confusion and mood swings. In the later stages, people will need more support and, eventually, they will need help with all their daily activities. They may fail to recognise even close family members, and may adopt unsettled and unsettling behaviour, such as getting up in the middle of the night or walking away from home and becoming lost.

3.2 What does it feel like to have Alzheimer's disease?

Unless you have Alzheimer's disease, it is impossible to understand the experience fully. It is a frightening disease with symptoms that are progressive and irreversible. The following quote from a person with dementia illustrates the frustration and fear that people face as symptoms of Alzheimer's become apparent:

'I hate myself on a bad day and I hit myself around the head. If I'm on my own it gets worse.'

3.3 Stigma

There is no doubt that considerable fear and stigma still surrounds Alzheimer's disease and dementia. This can prevent people from seeking help from GPs and other professionals. It can stop people from telling friends and family members about their symptoms or diagnosis. The risk is that people become isolated and unsupported.

3.4 The growing recognition that quality of life is possible following a diagnosis of dementia

For many years it was believed that nothing could be done to promote quality of life for people with dementia and there was a sense of hopelessness surrounding the disease. More recently there has been a growing recognition that it is possible to maintain quality of life and that good treatment, care and support can make a real difference to people's lives.

3.5 People with Alzheimer's disease now have a voice

Over recent years many more people with dementia have spoken out about what it is like to live with the illness, as well as what is important to them in terms of the care and support they receive. This should encourage greater public understanding of the illness and enable services to be responsive to the needs of people with dementia.

3.6 Carers of people with dementia

Unpaid carers are a major resource for people with dementia. There are estimated to be 476,000 people in England acting as the primary carers for people with dementia. Two thirds of all people with dementia live in their own homes or the home of their carer. The vast majority of their care is provided by unpaid carers. An important study highlighted that half of all people with dementia in the community received at least 35 hours of informal care per week (Murray et al, quoted in Dementia UK^{vi}).

Many carers report personal satisfaction from their caring role. Significant distress, however, is a reality for many. Depression, emotional and physical exhaustion and general poor health are common, and research shows that carers of people with dementia experience greater strain and distress than carers of other older people.ⁱ Many carers of people with dementia are older people themselves, with physical frailty and health conditions of their own.

4. Are the drug treatments effective?

The most up to date Cochrane reviews conclude that the four licensed drug treatments are clinically effective. This is supported by evidence from people with

dementia and their carers. The drug treatments are not effective for everybody, but for many they bring important benefits and for others they bring a much-valued delay in progression. Benefits reported by focus group participants included reduced confusion and anxiety. Furthermore, increased calmness was valued by both people with Alzheimer's and their carers and brought improvements to quality of life and relationships.

5. Impact of TA111

People with dementia and their carers feel very strongly that those diagnosed with mild Alzheimer's disease since the implementation of TA111 are in a very distressing position. People in the mild stages of the illness are trying to hold on to the life that they have known, while adapting to the onset of Alzheimer's disease. They know they have to wait until symptoms are considerably worse before they can try a drug that could potentially curb progression. But they want the potential delay when symptoms are most mild and quality of life is the best it is likely to be.

Alzheimer's Society is concerned that recommending Ebixa is not prescribed on the NHS removes a useful option for the treatment of people with moderate to severe Alzheimer's disease and behavioural disturbance. The only alternative licensed pharmacological treatment is risperidone and because of the risk of harmful side effects, this should be used only as a last resort in limited circumstances. The recent Department of Health report regarding the use of antipsychotics in people with dementia highlighted the problems, and stipulated a target to reduce antipsychotic prescribing by two thirds in the next three years, emphasizing the need for alternative treatments.ⁱⁱ As discussed in section 6.4.2.5, research suggests Ebixa has a similar effect on behavioural symptoms, yet none of the harmful side effects.

6 Recommendations for the current review of drug treatments for Alzheimer's disease

6.1.1 Quality of life

- We recommend the opportunity is taken to develop a new, more sensitive economic model that captures the contribution of different domains, including cognition, Behavioural and Psychological Symptoms (including behaviour and mood) and function, to cost and health related quality of life.

6.2.1 Benefits to carers

- Effective drug treatments for Alzheimer's disease bring considerable benefits to carers and these benefits should be incorporated into the appraisal in order to generate a robust understanding of whether they are an appropriate use of NHS funds.
- Alzheimer's Society recommends that because of the lack of direct clinical trial evidence relating to carer utility scores, the model should incorporate research evidence that the drug treatments can reduce the amount of time carers spend caring, as this is the only measure of carer benefit directly available from clinical trial data.

6.3.1 Responder analysis

- We recommend that a responder analysis be carried out to provide a cost-effectiveness assessment that reflects reality.

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- The analysis must reflect the fact that for the proportion of people for whom the drugs are ineffective, drug costs will only be incurred during the trial period.

6.4.1 Behavioural and psychological symptoms

- We recommend that the model acknowledges the impact of improved behavioural and psychological symptoms of dementia (BPSD) following effective drug treatment. Key symptoms such as aggression, agitation, psychosis, depression and apathy are linked to quality of life and costs and a model should be developed which captures this.
- Although the response to behavioural and psychological symptoms must be individualised and based on good person centred care the reality is that antipsychotics are widely used as the first-line treatment, and that risperidone is licensed for this purpose. To reflect this, we recommend that the NICE appraisal of memantine uses risperidone as a comparator for the treatment of behavioural symptoms.
- For the assessment of Ebixa we recommend NICE carry out a subgroup analysis of individuals with behavioural symptoms, and a further analysis of individuals experiencing significant behavioural symptoms defined as an NPI score of 4 and above.

6.5.1 Stages of the model

- Alzheimer's Society believes the model developed by NICE should capture the changes to costs and quality of life as Alzheimer's disease progresses

6.6.1 Costs of care

- We recommend the following publications as sources of cost data relating to Alzheimer's disease:
 - Dementia UK provides evidence-based costs for different stages of dementia.^{vi}
 - The annual PPSRU publication Unit Costs of Health and Social Care provides a detailed breakdown of health and social care costs.ⁱⁱⁱ
 - Laing and Buisson Dementia Care Services: UK Market Briefing 2009 that provides details on fee levels for people with dementia in UK care homes.^{iv}
- The model must consider both the wide range of health and social care services utilised by people with dementia and the costs of care for particular groups. For example younger people with dementia and those receiving fully funded NHS care.

1. Introduction

Alzheimer's Society strongly welcomes the review of TA111. It presents an opportunity to develop new methods of appraising the four licensed drug treatments for Alzheimer's disease. We believe drugs for the treatment of dementia should be available on the NHS, following clinical assessments, to all individuals who might benefit. Alzheimer's Society argues that the key to cost-effective, rational treatment is good monitoring.

This review is taking place in the context of important developments in dementia policy in recent years. This is in part a response to the recognition of the growing numbers of people with dementia in the UK. The Dementia UK report found:

- There are 560,000 people in England have dementia (just over half with Alzheimer's disease)
- There are 476,000 unpaid carers of people with dementia in England.
- Numbers of people with dementia are projected to increase by nearly 40 per cent in the next 15 years.
- The annual economic burden of late-onset dementia in England is £14.3 billion, or £25,391 per head.

In addition, reports such as the National Audit Office (2007) 'Improving services and support for people with dementia'^v have highlighted the ongoing problems in dementia care. These include low rates of diagnosis and early intervention - only a third to a half of people ever receive a diagnosis. Also the quality of many services is unacceptably low and staff lack training in dementia care. These problems lead to inefficient use of resources.

There has been a national push to improve the support and services available to people with dementia. The Department of Health stated that dementia was a national priority in 2007. In particular the first National Dementia Strategy for England was published. This emphasised the need to focus on early intervention. Alzheimer's Society welcomed and was closely involved in the development of the Strategy.

Gathering evidence from Alzheimer's Society membership

During the course of the previous appraisals of these drug treatments, Alzheimer's Society gathered a considerable amount of knowledge regarding its' memberships views of the drug treatments. To inform its submission it carried out a questionnaire in 2004 of over 4,000 people to gather their experiences of the four drug treatments.

This evidence remains relevant and therefore it has not been necessary to repeat such a large-scale evidence collection. We did carry out a series of four focus groups of people with Alzheimer's disease and their carers to gather an up to date understanding of people's experience of the drug treatments and the impact of TA111.

We spoke to 30 people. These people were contacted through our branches in Aylesbury, Fenland and Brighton and also through the Alzheimer's Society Living with Dementia network. This is a network of people with a dementia diagnosis who input into the Society's work in a variety of ways.

This submission first contains information on Alzheimer's disease and what it is like to live with Alzheimer's disease. It then discusses evidence pertaining to the efficacy of the drug treatments, focussing particularly on consumer evidence. The submission then proceeds to discuss the impact that TA111 has had on the lives of people with dementia and their carers. Finally we make recommendations regarding factors that the current review should consider.

2. Alzheimer's Society

Alzheimer's Society is the UK's leading care and research charity for people with dementia and those who care for them.

Alzheimer's Society is a membership organisation, which works to improve the quality of life of people affected by dementia in England, Wales and Northern Ireland. Many of our 25,000 members have personal experience of dementia, as carers, health professionals or people with dementia themselves, and their experiences help to inform our work.

Through our 250 branches, we provide services and support for people with dementia and their carers. Our branch services include day care and home care for people with dementia, Alzheimer's Café's and innovative 'singing for the brain' sessions, as well as memory-book projects and group outings.

The Society provides reliable and up to date information via factsheets, newsletters and other publications as well as the Society's dementia helpline.

We campaign for the needs and interests of people with dementia and their carers to be recognised in improved health and social care and for greater public awareness of dementia.

We fund research into dementia through our innovative Quality Research in Dementia (QRD) programme, involving people with dementia and their carers in setting research priorities in the areas of cause, cure and care.

We provide training for health and care professionals and publish a wide range of training materials and books.

3. Background information on living with Alzheimer's disease

3.1 What is Alzheimer's disease?

Alzheimer's disease is the most common cause of dementia, affecting around 416,967 people in the UK.^{vi}

Alzheimer's disease is a physical disease affecting the brain. During the course of the disease, 'plaques' and 'tangles' develop in the structure of the brain, leading to the death of brain cells. People with Alzheimer's also have a shortage of important chemicals in their brains. These chemicals are involved with the transmission of messages within the brain.

Alzheimer's is a progressive disease, which means that, over time, more parts of the brain are damaged. As this happens, the symptoms become more severe, meaning that carers and people with dementia are coping with a changing pattern of abilities over time.

3.1.1 Early stages of Alzheimer's disease

People in the early stages of the disease may experience lapses of memory and have problems finding the right words. They may:

- become confused, and frequently forget the names of people, places, appointments and events:

'I used to have a very good memory and suddenly I found that words that I knew the meaning of I was not able to give their meaning... that told me something was wrong.'

Person with dementia

- experience mood swings. They may feel sad or angry. They may feel scared and frustrated by their increasing memory loss:

'He would get angry at things, it was terrible going out in the car... he would lose his temper. It was so unlike him, his personality changed in my eyes.'

Carer

- become more withdrawn, due either to a loss of confidence or to communication problems:

'If we're in company John just withdraws – unless we're with friends who he's particularly relaxed with. I don't really know why, but he used to say to me, 'You think I'm stupid', which of course I didn't – but that was a big reaction. So I wonder if he withdraws because he's worried about saying something silly.'

Carer

3.1.2 Later stages of Alzheimer's disease

As the disease progresses, people with Alzheimer's will need more support from those who care for them. Eventually, they will need help with all their daily activities. People may:

- Fail to recognise even close family members, or be unable to find their way around their own home.
- Gradually lose their ability to wash, dress and feed themselves
- Become immobile, making use of a hoist necessary for safe transfer.
- Find it difficult to eat and, later, to swallow.
- Lose control of their bladder; some people may also lose control of their bowels.
- Experience hallucinations and delusions.
- Adopt unsettled and unsettling behaviour, such as getting up in the middle of the night or walking away from home and becoming lost.
- Experience problems communicating. Many people with dementia communicate through behaviour that may be seen as challenging, for example hitting out. This can and often does lead to overuse of sedatives.
- Frequently experience marked apathy

While these are some common symptoms of Alzheimer's disease, it is important to remember no two people are likely to experience Alzheimer's disease in the same way.

3.2 What does it feel like to have Alzheimer's disease?

Unless you have Alzheimer's disease, it is impossible to understand the experience fully. It is a frightening disease with symptoms that are progressive and irreversible. The following quotes from individuals with dementia and carers illustrate the frustration and fear that people face as symptoms of Alzheimer's become apparent:

'I hate myself on a bad day and I hit myself around the head. If I'm on my own it gets worse.'

'From a very free spirited person to all of a sudden not being able to make a decision and it was very, very frustrating and all this aggression came out. It was like walking on eggshells for me.'

'He used to be an engineer and he was very precise in everything he did and now when he gets problems doing things he gets very frustrated. Very frustrated. He gets angry and he'll shout at me, "I never used to be like this".'

3.3 Stigma

There is no doubt that considerable fear and stigma still surrounds Alzheimer's disease and dementia. This can prevent people from seeking help from GPs and other professionals. It can stop people from telling friends and family members about their symptoms or diagnosis. The risk is that people become isolated and unsupported.

'My mother was not ignorant of dementia - her mother and aunt had both developed it in their late sixties. She covered up her failings herself, and described her lack of comprehension as due to "deafness". She dreaded what might be coming, and thought a diagnosis would precipitate loss of her house and her independence at the very least.'

Many people still believe it is an inevitable part of growing older. Also, the perception remains that people with Alzheimer's will have no quality of life and can no longer participate in family or wider society.

'Everybody I have met has been absolutely amazed that a) I can still talk and still think, and b) that I have a diagnosis of dementia. They do not understand it. I think that is indicative of what the public is like.'

'It's as though that's it, you are dribbling and nodding, and that's Alzheimer's. That's the picture of Alzheimer's. But we are still all here talking perfectly normally. We have got Alzheimer's of some form, we are not nodding and dribbling.'

Unfortunately, low levels of understanding about dementia extend to some health professionals. Repeated studies by the National Audit Office have found GPs' knowledge of dementia is insufficient. There has been no improvement in GP knowledge and awareness of dementia over five years. Furthermore, only 77% of GPs feel early diagnosis of dementia is important.^{vii}

'The GP said, 'Oh well, we all get old sometimes.'

'Our experience (and that of the majority of people we know with a diagnosis) is that it is a battle of wills to get taken seriously when the condition is mild, to get out of the "you're depressed" rut and actually get to see the appropriate specialist in the first place.'

3.4 The growing recognition that quality of life is possible following a diagnosis of dementia

For many years it was believed that nothing could be done to promote quality of life for people with dementia and there was a sense of hopelessness surrounding the disease. More recently there has been a growing recognition that it is possible to maintain quality of life and that good care and support can make a real difference to people's lives.

Memory assessment services have developed across the UK and can provide access to diagnostic procedures, as well as a range of health and social care services. An evaluation of the Croydon Memory Service model found those referred to the service had improved quality of life compared with baseline.^{viii}

Evidence is also developing for the potential for interventions such as cognitive stimulation therapy to improve quality of life as well as cognition.^{ix}

In addition to specific interventions, it is now clear that the skill of dementia care staff in providing good person centred care makes a significant difference to quality of life. Furthermore, the communication skills and approaches of staff are also important to people's quality of life. CSCI reported that even a 'neutral' style of communication can lead to people becoming distressed or withdrawn. Friendly and warm communication helped people to feel happy and relaxed.^x

This evidence refutes assumptions that attempts to improve the wellbeing of people with Alzheimer's are futile. It is also an incentive to develop dementia services so that they are able to deliver these potential benefits.

Alzheimer's Society believes that drug treatments should never be a replacement for good quality services. The drugs should be viewed as a potential enhancement to a good quality care package. They may improve people's ability to communicate with care staff and increase motivation to become engaged in occupation or activities, and can help people better achieve their goals. The temporary slowing of symptoms in the earlier stages of Alzheimer's disease enables people to contribute to the planning of their future care and to ensure that the care package meets their needs. In the later stages, Ebixa may improve communication and interaction with carers and care staff.

3.5 People with Alzheimer's disease now have a voice

Over recent years many more people with dementia have spoken out about what it is like to live with the illness, as well as what is important to them in terms of the care and support they receive. This should encourage greater public understanding of the illness and enable services to be responsive to the needs of people with dementia.

The delay in deterioration experienced by those who respond well to drug treatment will help support people to continue speaking out about their wishes and preferences.

'I wouldn't be here saying this if it wasn't for the drug treatments.'
Focus group participant who has Alzheimer's disease

3.6 Carers of people with dementia

There are approximately 476,000 people in England acting as the primary carers for people with dementia. Two thirds of all people with dementia live in their own homes or the home of their carer. The vast majority of their care is provided by unpaid carers. An important study found that half of all people with dementia in the community received at least 35 hours of informal care per week (Murray et al, quoted in Dementia UK^{vi}).

Carers are needed to provide emotional support, reassurance and help with a range of tasks, such as bathing and dressing. Sleep disturbances are common in dementia and mean that caring is a 24 hour job for many carers. Because dementia is a progressive condition, carers will find they are required to provide increasingly intensive support.

Many carers report personal satisfaction from their caring role. Significant distress, however, is a reality for many. Depression, emotional and physical exhaustion and general poor health are common, and research shows that carers of people with dementia experience greater strain and distress than carers of other older people.^{xi} Many carers of people with dementia are older people themselves, with physical frailty and health conditions of their own.

Caring can be an emotionally draining experience. Carers are forced to come to terms with irreversible and upsetting changes in their relationships. Many carers report being cut off from their former social circles which brings feelings of isolation and depression. The following quotes express the range of pressures that carers of people with dementia face:

'Just the memory of Alan getting up every half hour gives me the wobbles ... It was that aspect of caring that wore me out completely.'

'The hardest thing to bear is the total responsibility – about trivial things! It's the kind of responsibility that you take for granted when it's for babies or children – they eat what you offer them. But knowing that my father is increasingly dependent on me for what he eats, what he wears, when he washes, whether or not he goes out... that's harder.'

'The biggest problem was that to stop her wandering away I had to lock the door. She resented that very much – the fact that I'd locked her in – and resorted to blows in the end. The emotional impact of someone who is genuinely frustrated in their wish – trying to reconcile that with the fact that you know you can't let her out because of the danger – trying to reconcile those two things was very, very difficult.'

'I don't know what he wants, and for him to try and tell me what he wants sometimes is impossible, which is very sad because I am so tired that I lose my temper, which everyone keeps telling me is only natural but you feel awful after you've done it because you think he can't understand me so why am I doing it.'

Financial hardship is a stark reality for many carers of people with dementia. Despite carers of people with dementia saving the country £6 billion a year, many carers have to use their private savings and assets to meet the cost of caring for a relative. Research by Carers UK found that 72% of carers were worse off financially as a result of becoming carers (Carers UK, 2007). The reasons cited for this include the additional costs of disability, giving up work to care, the inadequacy of disability benefits and the charges for services.

Because much of the care for people with dementia is classed as 'social care' services are means tested. People with dementia can live for many years with the condition and therefore can be liable for thousands of pounds of care charges. Families are often left with very limited resources to look after themselves in later life.

Carers also face reduced opportunities to work and earn an income. Many carers are forced to give up work altogether, and with this they lose not just income, but skills, pension benefits and opportunities for re-employment. This can be particularly

difficult for younger people with dementia and their carers who are more likely to have financial commitments such as dependent children and mortgage repayments.

4. Are the drug treatments effective?

4.1 Cochrane reviews

- The most recently published Cochrane review of the clinical effectiveness of the anticholinesterase drug treatments concluded that they are efficacious for mild to moderate Alzheimer's disease.^{xii} It found that:

'The results of 10 randomized, double blind, placebo controlled trials demonstrate that treatment for 6 months, with donepezil, galantamine or rivastigmine at the recommended dose for people with mild, moderate or severe dementia due to Alzheimer's disease produced improvements in cognitive function, on average –2.7 points (95%CI –3.0 to –2.3, $p < 0.00001$), in the midrange of the 70 point ADAS-Cog Scale. Study clinicians rated global clinical state more positively in treated patients. Benefits of treatment were also seen on measures of activities of daily living and behaviour. None of these treatment effects are large. The effects are similar for patients with severe dementia, although there is only very little evidence, from only two trials.'

- The most recent Cochrane review of Ebixa also concluded that it was clinically effective.^{xiii}

'Memantine has a small beneficial, clinically detectable effect on cognitive function and functional decline measured at 6 months in patients with moderate to severe Alzheimer's Disease (AD).'

4.2 Consumer evidence

Alzheimer's Society carried out a large survey ending in 2004 to inform our submission to the previous appraisal of these drug treatments and the results remain relevant to the current review.^{xiv, xv} The results are presented in appendix one, in summary:

Over 4,000 questionnaires were returned. Of these, 2,672 (66 per cent of total respondents) had experience of Aricept, Exelon, Reminyl or Ebixa. This is a significant body of consumer expertise.

While not in the form of a controlled trial, patient/carer accounts are a fundamental part of the evidence base. While the data from randomised, placebo-controlled clinical trials provide objective evidence of the effectiveness of drugs on psychometric scales, results from these studies give little insight into what these drug treatments mean for 'real' people.

Furthermore, randomised clinical trials have assessed only a limited number of outcomes, which may not be the most important parameters for people with Alzheimer's disease, and which may therefore lead to an underestimate of the true effect size of therapy. The experience of people with Alzheimer's disease and their carers is critical to understanding the spectrum and size of potential benefits.

4.2.1 Questionnaire results

When asked, 'Taking everything into consideration, do you feel that the drug treatment you have received worked?', 73 per cent of respondents with a diagnosis of Alzheimer's disease and experience of the anti-dementia drugs, said 'yes'.

This result was the same as that of the questionnaire carried out by the Alzheimer's Society in 2000. It is also similar to an Australian consumer survey, which found 70% of those who had experience of drug treatments for dementia felt they were effective.^{xvi}

The survey asked people to list up to five ways in which the treatment was helpful. The following table summarises the top ten responses that we received:

Table 1: Reported benefits of the four licensed drug treatments

Benefit	No of responses	Percentage of all responses	Percentage of people reporting
Slowed/stabilised illness	1045	25%	39%
Happier/brighter/more aware/more active	550	13%	21%
Improved/helped memory loss	491	12%	18%
Calmer/less aggressive	324	8%	12%
More independent/taking care of personal needs	238	6%	9%
Showed an interest in things	219	5%	8%
Improved conversation/speech	187	4%	7%
Less confused/better understanding	183	4%	7%
Better quality of life	137	3%	5%
Restored/more confident	105	2%	4%

Each respondent could give up to five responses. The results are therefore shown as the proportion of all responses and the proportion of people responding.

Importantly the benefits experienced extended well beyond stabilization of illness and improvements in function and cognition. This illustrates that the narrow focus of measures incorporated in clinical trials does not reflect the full spectrum of benefit that is important to people with AD, and will therefore underestimate the effect size of treatment. We completed a further factor analysis which highlighted function, behaviour and mood as the most frequently highlighted benefits.

4.2.2 Focus group discussions

Of the 30 people participating in the focus groups held to gather up to date experiences of drug treatment, 21 people had experience of one of the four drugs either as a person with Alzheimer's disease or a carer. One person had experience of treatment with Ebixa in addition to an anticholinesterase drug. The groups reported a range of experiences.

Eight people reported improvements following initiation of drug treatment. Increased calmness and a reduction in outbursts of temper were particularly common. People explained the benefits this brought to the quality of life of the person with Alzheimer's disease and their carer. In particular, a reduction in aggression and agitation brings obvious benefits to relationships:

'I call Aricept my wonder drug. What sort of improvements? Temper, I never used to have a temper, but then I could have killed him. I tried to smother him one night with a pillow. That's all stopped.'

'She was calmer and she responded better to things you want her to do. If I was helping her then she would respond.'

In addition, people reported being less confused. This enabled them to be more independent, cope with day-to-day life and keep themselves occupied. It also eased the burden for the person caring for them.

'Because for a while I stopped taking it. I got worse. I forgot things. In fact I got much worse. I did stupid things at home. When you're living by yourself, having to run the house, you soon begin to learn that you really aren't functioning as you should and you go and hammer the doctor to give you the drugs again. I found it difficult to remember anything and I also got things mixed up.'

*'She has meals on wheels coming in every day and they deliver between 12 and 2. Before she went on the drugs, all three of them and in between times, she'd be phoning me up getting all stressed saying 'they've not turned up yet, you'll have to get on to them.' And I'd say, 'well, they've got till 2pm.' Now she is on the new drug she's calmed down and quite accepting that they might not get there till half one.'*¹

Four people reported that the drug did not lead to improvements in a person's condition but appeared to slow progression. They felt that this is an important benefit. Although individuals were clear that eventually the disease would take its toll and people would become increasingly disabled, they very much valued treatment which extended the period of time during which symptoms are more mild than they would otherwise be. One carer who reported that progression had slowed in comparison to before treatment had the beneficial effect of the drug confirmed once his wife entered a clinical trial investigating the efficacy of combined Aricept and Ebixa. It transpired that she was put in the double placebo arm:

'For four weeks we didn't notice a change and then suddenly the symptoms went off the scale. She wouldn't get up, wouldn't eat, wouldn't drink, didn't know who I was. Wouldn't, wouldn't, wouldn't. So I cried for help. My consultant contacted the researchers and it transpired she was on a double placebo. So she was put straight back on Aricept. It's shown me the benefit the drug is still giving her. Above all it was her personality. During that short space of time there was no spark of the person that I'd known for a long time. Even now, although her abilities have declined, she is still

¹ This person's mother had done well on the low dose of Aricept, but experienced side effects once on the higher dose. She has since tried Exelon and again experienced side effects on the higher dosage. She has recently started Reminyl, with no problems so far and benefits as described above.

sparky and happy and cheerful and laughs and jigs about the house to Abba and we can still have a pleasant life together, which clearly if she wasn't on the medication wouldn't happen.'

Four people explained that they did not know whether the drug treatment had any effect because they did not know what would have happened without it. However, they were keen for drug treatment to continue while the clinician thought it appropriate.

One person reported that the person they cared for had tried an anticholinesterase drug treatment, but they had asked for it to stop because of side effects.

Two people reported that the drug treatments were not effective and so prescription was stopped. Two people (a person with Alzheimer's disease and the person caring for them) reported that it was too soon to tell whether treatment was effective.

It is impossible to predict in advance who will derive benefit from drug treatment. Alzheimer's Society believes the key to cost-effective prescribing is careful monitoring and ensuring only those who benefit from treatment continue to take the drugs after an initial trial period. While many people with dementia and their carers are disappointed that the drugs do not bring benefit, they are grateful for being given the opportunity to try treatment.

5. Impact of TA111

'We've got the sword of Damocles hanging over our heads, with Alzheimer's disease. Aricept makes the cord a bit stronger.'

'When you look at this gentleman here, who, on the face of it, looks young and healthy and you think they might be able to prolong that... to keep him like that. Why wait until he goes downhill ... until he gets worse. Give him a chance to try it.'

'In our remaining years, we want the best we can get. So if we can get quality of life, in the early stages, we'll take the drug, we want to delay it.'

All members of the focus groups were clear that the drug treatments are not a cure. They also understood that they do not work for everybody and there may be side effects. If the drug treatments are effective people knew that improvements might be seen or the effect may be a slowing of progression.

However, in the context of a debilitating and progressive disease where a person gradually becomes completely dependent, a slowing of progression or maintenance of specific abilities in the early stages is considered extremely important. So while people accept that the drug treatments may not work, they feel a trial of treatment at the earliest opportunity is vital.

Anticholinesterase drugs

People with dementia and their carers feel very strongly that those diagnosed with mild Alzheimer's disease since the implementation of TA111 are in a very distressing position. People in the mild stages of the illness are trying to hold on to the life that they have known, while adapting to the onset of Alzheimer's disease. They know they have to wait until symptoms are considerably worse before they can try a drug that could potentially curb progression. But they want the potential delay when symptoms are most mild and quality of life is the best it is likely to be.

And whilst the onset of dementia can be a frightening time, focus group members explained that it was possible to adapt to the mild symptoms. People with Alzheimer's explained that they knew they made mistakes, got confused and forgot things. But while the symptoms were mild they could cope. Carers also explained that it was possible to carry on enjoying life together and they could cope with the strain. So if this period could be prolonged it should be.

'I make mistakes. I put the teabags in the freezer. But I laugh about it, it happens. It's not going to kill me. You adapt.'

'But my life has changed. I do different things now. I'm a different person. I've had to change everything. But it's not bad now.'

A key reason that people would value a potential delay in progression in the mild stages is the maintenance of individuality. While symptoms are mild people can carry on with many day-to-day activities and are not completely reliant on the person or services caring for them. Members of the focus groups explained how important this

was to them. As symptoms progress, dependence increases and relationships change irrevocably.

'I think anything that can improve quality of life and delay onset of even the small things. It's the simple things. Like being able to do the things that you've always been able to do as an individual. Not having to have someone do things for you. Being able to do the washing up and drying up. People lose their individuality, their identity and their self-esteem and they become frustrated.'

'She's now experiencing toilet problems, because the toilet has fallen off her radar. So I have to take her. It's managing that side of life. That's only a relatively recent development. It's one of the next stages. I expected it to come. The medicine she's on has clearly delayed it. It's meant that we've had a longer better life and that's what your after.'

The previous NICE evaluation found that while the drug treatments were clinically effective in this stage, they were not cost effective. We believe a more sensitive model may produce a different result. It is also vital that NICE give considerable weight throughout the appraisal to the view held extremely strongly by people with Alzheimer's disease that the goal of anticholinesterase treatment should be the extension of the period during which symptoms are most mild.

Ebixa

The recommendation that Ebixa should not be available except for as part of a clinical trial has meant there is no licensed drug treatment for the severe stage of Alzheimer's disease recommended for use on the NHS. Only one member of the focus group had experience of Ebixa. He found that it helped to delay progression of symptoms.

The evidence from our questionnaire completed in 2004 found that of the 377 people who had tried Ebixa, 75 per cent thought they had benefited, 15 per cent thought they did not experience benefit and 10 per cent had no opinion. Scientific evidence also supports the conclusion that Ebixa is clinically effective,^{xiii} particularly for reducing agitation (see section 6.4.2.5).

Alzheimer's Society is concerned that recommending Ebixa is not prescribed on the NHS removes a useful option for the treatment of people with moderate to severe Alzheimer's disease and behavioural disturbance. The only alternative licensed pharmacological treatment is risperidone and because of the risk of harmful side effects, this should be used only as a last resort in limited circumstances. The recent Department of Health report regarding the use of antipsychotics in people with dementia highlighted the problems, and stipulated a target to reduce antipsychotic prescribing by two thirds in the next three years, emphasizing the need for alternative treatments.^{xvii} As discussed in section 6.4.2.5, research suggests Ebixa has a similar effect on behavioural symptoms, yet none of the harmful side effects.

Alzheimer's Society recommends that Ebixa be available across the whole of the UK on the basis of assessed clinical need.

6. Recommendations for the current review of drug treatments

6.1 Quality of life

6.1.1 Recommendation

- **We recommend the opportunity is taken to develop a new, more sensitive economic model that captures the contribution of different domains, including cognition, behavioural and psychological symptoms (including behaviour and mood) and function, to cost and health related quality of life.**

6.1.2 Background

Measuring quality of life has been an ongoing problem since NICE first reviewed the drug treatments for Alzheimer's disease. In 2000 the assessment group concluded that there was inadequate research to develop a robust estimate of health related quality of life (HRQL). In 2004 the assessment group used research by Neumann. There was a discussion of the limitations of this paper, for example it was based on proxy views, it was a US sample and it was a cross sectional one off study. It therefore did not meet the criteria of the NICE reference case. We recommend that Neumann is not used in the current review because of its limitations.

The current review is an opportunity to develop new methods of capturing quality of life within the model. Research into quality of life in dementia has progressed with the development of the DEMQOL work and also goal attainment scaling.^{xviii} This work enables a focus on the domains that impact most on health related quality of life in people with dementia. In particular, work on DEMQOL found that behavioural and psychological symptoms of dementia (BPSD) and age correlated with quality of life. Cognition did not correlate with quality of life.^{xix}

In the absence of direct measurement of quality of life in clinical trials, there may be value in investigating the use of proxy measurements, for example clinical global impressions (CGI) or Neuropsychiatric Inventory (NPI). However, Banerjee notes that because of the complexity of quality of life in dementia, simple proxy substitutions are likely to miss important factors, so the results would have to be treated with caution.^{xix}

We suggest work to develop a model that uses available data to capture the contribution of MMSE score, NPI score (including key symptoms such as agitation/aggression, psychosis, depression and apathy) and functional ability to quality of life and costs. However, it is important to note that these factors are not completely independent and this would have to be accounted for within the model. **Existing UK datasets are currently available which could enable this work to be undertaken expeditiously.**

Alzheimer's Society believes that if no satisfactorily robust method of capturing quality of life can be developed, then the results of economic modelling will have to be treated with considerable caution.

6.2 Inclusion of carer benefits

6.2.1 Recommendation

- **Effective drug treatments for Alzheimer’s disease bring considerable benefits to carers and these benefits should be incorporated into the appraisal in order to generate a robust understanding of whether they are an appropriate use of NHS funds.**
- **Alzheimer’s Society recommends that because of the lack of direct clinical trial evidence relating to carer utility scores, the model should incorporate research evidence that the drug treatments can reduce the amount of time carers spend caring, as this is the only measure of carer benefit directly available from clinical trial data.**

6.2.2 Background

As explained in section 1.6 family carers are the mainstay of support for people with Alzheimer’s disease, and it is the support from carers that is pivotal in enabling people with dementia to live in their own homes for as long as possible. Although providing this support is something that many carers gladly do, it is extremely stressful, and takes a large toll on people’s physical and mental health.

The benefits of effective drug treatment are felt keenly by the carer, as well as the person with Alzheimer’s. Reports from our membership explain very clearly how carers benefit from improvements such as improved memory and ability to carry out activities of daily living, reduced apathy and aggression, and increased independence.

‘Life was easier when he wasn’t constantly flying into tempers. Definitely that was the case when he started the low dose of Aricept. Before, it would be every day he’d shout at me... “I’m going, you said this, you said that”...And it stopped a lot of that.’

‘Well, she was put on the low dose of Aricept and it really seemed to make a lot of difference to begin with. She was less muddled. I used to get telephone calls saying ‘the TV doesn’t work, you’ll have to buy me a new one.’ I’d drive all the way over and switch it on. When she started on the Aricept she started being able to manage the television very, very well. I guess I was always on edge. I couldn’t bare the thought of her being in her flat without her television or anything.’

The reduction in behavioural symptoms, particularly agitation, which Ebixa can bring, will have important benefits to carers. These are the symptoms that carers find most stressful^{xx} and carer quality of life is negatively correlated with agitation/aggression as well as total neuropsychiatric inventory score (NPI).^{xxi}

There is also research evidence that the drug treatments can reduce the time spent caring.

- Memantine can reduce time spent caring by 51.5 hours per month.^{xxii}
- Anticholinesterase drug treatments can reduce time spent caring by 1.1 hour per week.^{xxiii}

Books such as “The 36 hour day”, which describes the caring experience, emphasise the enormous value of this saved time.^{xxiv} In addition, there is research evidence

linking the amount of time spent caring and key quality of life indicators such as depression.

We firmly believe that an appraisal of Alzheimer's drugs must incorporate benefits to carers if it is to properly assess the value of the treatments. During the previous appraisal of anticholinesterase drugs NICE incorporated benefits to carers, in the form of a 0.01 utility gain. However, it is acknowledged that the evidence base to support particular utility scores is lacking. No studies have been carried out in the UK investigating the quality of life of carers of people who are taking the drug treatments.

In light of this, Alzheimer's Society maintains the most appropriate solution is to use research evidence that the drug treatments can reduce the time spent caring. This is the only measure of carer benefit directly available from clinical trial data. 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, but these are difficult to quantify and describe. Furthermore, assigning a cost and a benefit to reduced carer time could be double counting.

SCIE's discussion paper 'SCIE's work on economics and the importance of informal care'^{xxv} takes forward the debate around incorporating carer benefit in economic evaluations. It proposes that economic evaluations within social care adopt a broad societal perspective because of the range of stakeholders involved in social care provision and the complexity of funding arrangements. SCIE believes the value of informal care should be recognised, given its importance in sustaining the social care system.

SCIE argues that due to these complexities of the social care system, the way in which economic evaluation is applied in the health sector cannot simply be transferred for use in social care. However, we believe arguments put forward around capturing the broad benefits of an intervention and valuing informal carers can be applied in evaluations of health interventions in conditions such as Alzheimer's, where a broad range of agencies are involved in providing support and such a large proportion of care is provided by informal carers.

We support Professor Peter Smith's comments at the Health Select Committee inquiry into NICE that it would be appropriate for NICE to develop its methods to incorporate wider benefits.

"[NICE] has been wise to keep the definition quite narrow and constrained so that everyone knows what it is trying to achieve with its figures, but I would hope that as we gain experience its methodology could begin to embrace broader benefits, and broader costs, associated with treatments."

6.3 A responder analysis should be carried out

6.3.1 Recommendation

- **We recommend that a responder analysis be carried out to provide a cost-effectiveness assessment that reflects reality.**
- **The analysis must reflect the fact that for the proportion of people for whom the drugs are ineffective, drug costs will only be incurred during the trial period.**

6.3.2 Background

As explained in section 2 not everyone with Alzheimer's disease benefits from the drug treatments. It is not currently possible to determine in advance who will benefit. However, a system of careful monitoring enables the drug treatment to be stopped in people who are not benefiting. Alzheimer's Society believes this is the key to cost-effective treatment. Individuals do not want to take ineffectual and unnecessary drug treatments.

In line with a wide range of consultees who participated in the previous appraisal, Alzheimer's Society firmly believes that a responder analysis that replicates real life prescribing practice would provide the most useful assessment of the effectiveness of these drug treatments.

During the previous appraisal a survey of memory clinics was carried out to assess the proportion of people continuing on the drug treatment after an initial trial. We recommend that a similar exercise be carried out to provide current data on drug usage. This data should be used to inform the responder analysis and in particular the duration of drug prescription in non-responders, a key part of the cost model for responder analysis.

It is vital that the analysis accurately reflects the cost of drugs, specifically that only a proportion of people will be prescribed the drugs for the duration of the model. The model must reflect that, for a proportion of people, drug costs will only be incurred for an initial trial period.

6.4 Incorporating impact on behavioural symptoms

6.4.1 Recommendation

- **We recommend that the model acknowledges the impact of improved behavioural and psychological symptoms of dementia (BPSD) following effective drug treatment. Key symptoms such as aggression, agitation, psychosis, depression and apathy are linked to quality of life and costs and a model should be developed which captures this.**
- **Although the response to behavioural symptoms must be individualised and based on good person centred care the reality is that antipsychotics are widely used as the first-line treatment and risperidone is licensed for this purpose. To reflect this, we recommend that the NICE appraisal of memantine use risperidone as a comparator for the treatment of behavioural symptoms.**
- **For the assessment of Ebixa we recommend NICE carry out a subgroup analysis of individuals with behavioural symptoms, and a further analysis of individuals experiencing significant behavioural symptoms defined as an NPI score of 4 and above.**

6.4.2 Background

Behavioural symptoms are an important aspect of Alzheimer's disease, with implications for quality of life and costs. These symptoms include agitation, aggression, apathy, wandering, shouting, repeated questioning, sleep disturbance, depression and psychosis. The current response to these symptoms from health and social care services is acknowledged to be inadequate. The four licensed drug treatments can offer a positive alternative and therefore it is important to consider behavioural symptoms and their treatment within the context of this appraisal.

6.4.2.1 Impact of behavioural symptoms

Behavioural symptoms cause significant distress for the person with dementia and family carers, often more so than cognitive problems.^{xxvi} 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.^{xix}

BPSD are often the symptoms that the carer find most difficult^{xxvii} and are frequently cited as a reason for the person with Alzheimer's going into full time residential care. Carer quality of life is negatively correlated with agitation/aggression as well as total neuropsychiatric inventory (NPI) score.^{xxviii} Staff can also find the symptoms very difficult to respond to appropriately. Although they are often perceived to be solely a symptom of dementia, these behaviours can also be an expression of the unmet needs of an individual, for example boredom or frustration.

6.4.2.2 Prevalence of behavioural symptoms

Research evidence shows that between 53% and 98% of all people with dementia experience behavioural and psychological disturbances, depending on the specific assessment tools and populations studied.^{xxix} The following prevalence rates have been reported for the different symptoms: apathy/indifference (67%), aberrant motor behaviour (53%), depression/dysphoria (52%), anxiety (49%), and agitation/aggression (45%).^{xxx}

These symptoms can occur at any stage of the illness, but the frequency and severity of symptoms increase as the illness progresses.^{xxix} The type of symptoms experienced also changes and people are more likely to experience multiple symptoms as the illness progresses. Teng and Cummings (2007) report the following overall prevalence rates of behavioural symptoms as well as the prevalence of individual symptoms at different stages of Alzheimer's disease As noted the severity and number of symptoms experienced by individuals increases with severity of Alzheimer's:^{xxix}

Table 2: The prevalence of behavioural symptoms at different stages of Alzheimer's^{xxix}

Stage of Alzheimer's disease	Percentage of people experiencing behavioural symptoms	Prevalence of individual symptoms most common at that stage
Mild (MMSE 21 – 30)	80-90%	Dysphoria, 50%, Apathy 51%, irritability 38%
Moderate (MMSE 11 – 20)	95%	Apathy 80%, anxiety 65%, agitation 55%
Severe (MMSE less than 11)	Virtually all	Apathy 80%, anxiety 65%, agitation 55%

There is not a linear increase in behavioural symptoms as cognition worsens. Longitudinal studies have demonstrated a poor correlation between worsening cognitive and behavioural symptoms. Teng and Cummings (2007) report that it is likely that behavioural symptoms and cognitive symptoms are independent and represent a separate manifestation of the underlying neuropathological processes of the disease.

6.4.2.3 Behavioural symptoms increase the costs of dementia

As well as the significant detriment to quality of life, the presence of behavioural symptoms also increases costs. Beeri (2002) found 28% of costs of care were due to care directly associated with behavioural and psychological symptoms.^{xxxii} Herrmann (2006) found the incremental cost of a one-point increase in NPI score was US\$30 a month. A regression analysis of individual symptoms found apathy and hallucinations contributed significantly to increased costs.^{xxxii} A 2002 study by Murman found similar results, with the incremental cost of a one-point increase in NPI score representing US\$247 – 409 per year.^{xxxiii}

6.4.2.4 Antipsychotics are frequently used as the first-line treatment, despite serious side effects

As explained by the NICE/SCIE dementia clinical guideline the response to these symptoms must be individualised and tailored 'given the range of challenging behaviour and the many factors associated with it.' The guideline outlines the thorough assessment that should take place at the earliest opportunity to establish what factors may be causing the behaviour and the requirement to develop an individually tailored care plan to address the behaviour.

However, in contravention of the NICE/SCIE dementia guideline, the evidence is clear that prescription of antipsychotic drug treatments is frequently the first-line treatment.^{xvii} They are, in effect, the standard treatment for the management of concomitant behavioural symptoms in people with Alzheimer's disease. In the UK the only drug with a relevant licence is risperidone, which is indicated 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". We recommend that the NICE appraisal of memantine use risperidone as a comparator for the treatment of behavioural symptoms.

There is evidence that risperidone and aripiprazole are useful in reducing aggression and risperidone reduces psychosis, but due to the serious side effects associated with antipsychotic drugs they are not considered to be appropriate except for in very limited circumstances. The serious detrimental effects associated with antipsychotic drugs include increased mortality, strokes and fractures; many of which have considerable cost implications.

A recent report carried out for the Department of Health by Professor Sube Banerjee found that around 180,000 people with dementia are treated with antipsychotic medication across the country per year.^{xvii} The government accepted Professor Banerjee's recommendation that the number of prescriptions should be reduced by a third over two years. The first stage in achieving this is a national audit to be carried out in 2010. Therefore, it is likely to be some considerable time before a significant reduction in antipsychotic prescribing is achieved.

6.4.2.5 Ebixa is effective at reducing neuropsychiatric symptoms

There is evidence that Ebixa has benefits in terms of reduced neuropsychiatric symptoms, particularly agitation.

Research found memantine treatment produced statistically significant benefits over placebo in NPI total score and in NPI single items.^{xxxiv, xxxv} Memantine is particularly effective for the treatment of the specific behavioural syndrome agitation, rather than for psychosis or other behavioural symptoms. Importantly, agitation/aggression is the NPI variable most closely linked to carer quality of life.

Meta-analyses have found that memantine has a similar effect on behavioural symptoms to neuroleptics, yet none of the harmful side-effects.^{xiii, xxxvi} This is in addition to memantine's benefits on other symptoms, including cognition and activities of daily living.^{xiii} Neuroleptic treatments have a detrimental effect on cognition.^{xxxvi} Table 3 presents data regarding the effects of memantine and neuroleptics on NPI and cognition.

Table 3: 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)

Alzheimer’s Society believes that the impact of behavioural symptoms must be given considerable weight in the analysis of Ebixa. A reduction in these symptoms following prescription of Ebixa would have benefits to quality of life of the person with dementia as well as their carer. Decreasing NPI scores would also lead to a reduction in costs. A reduction in the use of antipsychotics would reduce the risk of the harmful side effects of these drugs as well as reduce the costs of prescribing antipsychotic drugs. Risperidone should be used as a comparator in this analysis.

6.4.2.6 The assessment of Ebixa should include a subgroup analysis of individuals with behavioural symptoms

We believe that, as well as incorporating reduction in behavioural symptoms with the main analysis of Ebixa, it would be appropriate to carry out a subgroup analysis of individuals with behavioural symptoms, and a further analysis of individuals experiencing significant behavioural symptoms defined as an NPI score of 4 and above.

As we explained during the course of the previous appraisal, there are four key reasons why people with Alzheimer’s disease with behavioural or psychiatric symptoms represent a meaningful sub-group of patients.

1. A number of studies using cluster analysis or principle component analysis techniques have shown distinct groups of individuals with behavioural/psychiatric symptoms emerging as independent clusters.^{xxxvii}
2. The course of Alzheimer’s disease is different for individuals with behavioural or psychiatric symptoms, with more rapid decline evident in individuals experiencing these symptoms; and demonstrating that this sub-group of people has a different prognosis.^{xxxviii}
3. Genetic studies have linked identified polymorphisms to key behavioural and psychiatric symptoms and post-mortem studies have demonstrated different profiles of neurochemical changes in these individuals. This clearly indicates important biological associations which strongly support the validity of people with behavioural or psychiatric symptoms as a distinct sub-group.^{xxxix}
4. Behavioural and psychiatric symptoms form a distinct and important clinical treatment indication in people with Alzheimer’s disease, for which pharmacological treatments are frequently prescribed.

Anticholinesterase and BPSD

NICE/SCIE guideline concluded there was evidence that donepezil can produce benefits in terms of reduced neuropsychiatric symptoms and agitation/aggression that outweigh the risk of adverse events. The Cochrane reviews of the different cholinesterase inhibitors indicate a benefit of >2 points on the total NPI, but the

CALM-AD trial found that these drugs were no better than placebo in the short term treatment of agitation over 12 weeks.^{xi} Further clarification is provided by the work of Feldman and colleagues who profiled the pattern of improvement, demonstrating that the maximal benefits were seen in mood symptoms such as depression, anxiety and apathy. These were also highlighted as key symptoms responding to cholinesterase inhibitor therapy in our 2004 patient survey. This is important as these are all symptoms which lead to added disability and impairment and deteriorate quality of life as well as increasing costs.

A meta-analysis of US and European data from clinical trials found a reduction in neuroleptic use from 25 per cent to 9 per cent following anticholinesterase treatment.^{xii}

6.5 Stages of the model

6.5.1 Recommendation

- **Alzheimer's Society believes the model developed by NICE should capture the changes to costs and quality of life as Alzheimer's disease progresses**

6.5.2 Background

Alzheimer's Society believes the two-stage model used to inform TA111 was too limited. Using entry into full time care as the only cost driver is too simplistic and does not capture the important transitions that will occur as Alzheimer's disease progresses.

We believe using entry into full time care as the primary endpoint when assessing the mild and moderate subgroups separately was particularly inappropriate. Firstly, the length of time between mild Alzheimer's and the need for full time care requires considerable extrapolation to calculate the likely impact on cost. Secondly, it does not capture important differences in the cost of care and quality of life between mild and moderate disease.

Although the trajectory of the disease varies between individuals in terms of symptoms experienced and rate of progression, in general in the mild stages people will be autonomous, will contribute to the family, function independently without substantial need for practical supervision or hands on assistance and a number of individuals may even be able to continue working. As the disease progresses, people begin to require more practical assistance and become less independent. As described in sections 2 and 3, these changes will impact on health related quality of life for both the individual with Alzheimer's disease and their carer. These changes in the level of support required are also reflected in the infrastructure of care payments and care services that are needed to support people, all of which have considerable cost implications.

We recommend that NICE develop a model that is better able to capture changes in costs of care and quality of life that occur as Alzheimer's disease progresses:

6.5.2.1 Costs of the Alzheimer's disease at different stages

Dementia UK provides data on annual cost per person with dementia at different stages of the illness and in different settings.^{vi} This is presented in table 4.

Table 4: Costs per person with dementia

	NHS	SSD	Informal care	Accommodation	Total
People in the community with mild dementia	£2,508	£4,935	£9,246	0	£16,689
People in the community with moderate dementia	£2,430	£6,224	£17,223	0	£25,877
People in the community with severe dementia	£2,639	£7,738	£27,096	0	£37,473
People in supported accommodation	£1,334	£378	£938	£28,646	£31,296

6.5.2.2 Utility scores should be adjusted according to the stages of Alzheimer’s disease.

The NICE Decision Support Unit acknowledged in their response to comments on the executable model that utility scores should be adjusted according to stage of Alzheimer’s. They stated that the utility values corresponding to the ADAS-cog scores of 21, 12.5 and 4 determined by the two equations used are 0.72, 0.83 and 0.94 respectively.

The DSU were concerned that the scores generated may be considered ‘inappropriately high’. They state “for patients with a mean age of 75 yrs the generated value is in excess of that for the otherwise healthy population (75yrs and over =0.73 according to the MVH study reported in Kind et al 1998). Indeed, the mean at age 45-54 is only 0.85.” However, we are not aware that NICE alter utility scores according to age, independently of health condition.

6.6 Costs of health and social care services

6.6.1 Recommendation

- **We recommend the following publications as sources of cost data relating to Alzheimer's disease:**
 - **Dementia UK provides evidence-based costs for different stages of dementia.**^{vi}
 - **The annual PPSRU publication Unit Costs of Health and Social Care provides a detailed breakdown of health and social care costs.**^{xiii}
 - **Laing and Buisson Dementia Care Services: UK Market Briefing 2009 which provides details on fee levels for people with dementia in UK care homes.**^{xliii}
- **The model must consider both the wide range of health and social care services utilised by people with dementia and the costs of care for particular groups. For example younger people with dementia and those receiving fully funded NHS care.**

6.6.2 Background

People with Alzheimer's disease will use a wide range of health and social care services. The evidence on costs of care for people with dementia that will be required to inform the model will depend on the structure of the model. However, we suggest NICE uses the sources listed above in addition to other available up to date, UK based data on costs of care.

In addition, it is important to consider particular groups of people with Alzheimer's disease in order to get an accurate understanding of the costs of the disease:

- People with dementia whose needs have been identified as primarily health needs and who have their care funded by the NHS. NHS continuing care packages can cost well over £1,000 per week.
- The costs of care for younger people with dementia and specialist residential or nursing home care (often costing more than £1,500 per week).
- Research tells us that over a five-year period the majority of people would be expected to move to a more specialised level of care (figures from Ballard *et al*, 2002).^{xliiv} In addition, 10 per cent of the people moving care facilities require a period of time in psychiatric in-patient facilities (a standard admission would be four to eight weeks) to stabilise the situation before the transfer to a new care facility can be achieved.

In relation to the costs of care, it is worth considering that the quality and level of services provided to people with dementia and their carers vary considerably around the country. Laing and Buisson (2009) address this issue in relation to care homes.^{xliiii} They found the average weekly fee charged for people with dementia (across private and voluntary nursing and residential homes) was £573 (£469 - £673). However, they calculated that a fair price for a home meeting all National Minimum Standards (NMS) for Care Homes for Older People was £615 (private nursing or residential care for people with dementia in the provinces – costs are higher in London). Although NMS are now replaced by Health and Social Care Act 2008 (Registration Requirements) Regulations 2009, we know that most homes did not meet even the minimum standards required of them. The average percentage of standards met by

care homes for older people was 82%.^{xiv} We believe there is a strong argument to use cost of care that meets at least the basic statutory requirements.

NICE will also be aware that the range and type of services that people receive may change over the next few years as the National Dementia Strategy for England is implemented. For example, people may be able to take advantage of new services such as dementia advisors and peer support networks.

In addition, the proposed changes to the social care system will also impact on the costs of supporting people with Alzheimer's disease. For example, some people living at home may have their personal care funded rather than the current system of means-testing for personal care. In addition, there may be radical changes in the funding of residential long-term care.

NICE will have to come to a decision about how to address these expected changes and we would be happy to offer our advice and support in the decision making process.

References

- ⁱ Moise P, Schwarzing M, Um M-Y (2004) *Dementia Care in 9 OECD Countries: A Comparative Analysis*. Paris: DELSA/ELSA/WD/HEA.
- ⁱⁱ Banerjee S (2009) *The use of antipsychotic medication for people with dementia: Time for action*. A report for the Minister of State for Care Services by Professor Sube Banerjee. Department of Health
- ⁱⁱⁱ PSSRU (2009) *Unit Costs of Health and Social Care*. PSSRU.
- ^{iv} Laing and Buisson (2009) *Dementia Care Services: UK market briefing 2009*. Laing and Buisson.
- ^v National Audit Office (2007) *Improving services and support for people with dementia*. NAO
- ^{vi} Knapp M, Prince M, Albanese E, et al (2007). *Dementia UK: The full report*. London: Alzheimer's Society.
- ^{vii} National Audit Office (2010) *Improving dementia services in England – an interim report*. London.
- ^{viii} Banerjee S, Willis R, Matthews D, et al (2007). Improving the quality of dementia care – an evaluation of the Croydon Memory Service Model. *International Journal of Geriatric Psychiatry* 22(8):782-8.
- ^{ix} NICE/SCIE (2007) *Dementia: the NICE/SCIE guideline on supporting people with dementia and their carers in health and social care*. London.
- ^x Commission for Social Care Inspection (2008) *See me not just the dementia*. London.
- ^{xi} Moise P, Schwarzing M, Um M-Y (2004) *Dementia Care in 9 OECD Countries: A Comparative Analysis*. Paris: DELSA/ELSA/WD/HEA.
- ^{xii} Birks J (2006) Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database of Systematic Reviews*. Issue 1.
- ^{xiii} McShane R, Areosa Sastre A, Minakaran N (2006) Memantine for dementia. *Cochrane Database of Systematic Reviews*. Issue 1.
- ^{xiv} Alzheimer's Society (2004) Submission to the NICE appraisal of drug treatments for Alzheimer's disease. London.
- ^{xv} Ballard C, Sorensen S, Sharp S (2007) Pharmacological therapy for people with Alzheimer's disease: the balance of clinical effectiveness, ethical issues and social and healthcare costs. *Journal of Alzheimer's Disease*. 12(1):53-9.
- ^{xvi} Alzheimer's Australia (2005) *Consumer medication survey*. Alzheimer's Australia.
- ^{xvii} Banerjee S (2009) *The use of antipsychotic medication for people with dementia: Time for action*. A report for the Minister of State for Care Services by Professor Sube Banerjee. Department of Health
- ^{xviii} Rockwood K, Fay S, Song X, et al (2006) Attainment of treatment goals by people with Alzheimer's disease receiving galantamine: a randomized controlled trial.. Video-Imaging Synthesis of Treating Alzheimer's Disease (VISTA) Investigators. *Canadian Medical Association Journal*. 174(8):1099-105.
- ^{xix} Bannerjee S, Smith S, Lamping D (2006) Quality of life in dementia - more than cognition. An analysis of associations with quality of life in dementia. *Journal of neurology, neurosurgery and psychiatry*. 77(2):146-148.
- ^{xx} Hart DJ, Craig D, Compton SA et al (2003) A retrospective study of the behavioural and psychological symptoms of mid and late phase Alzheimer's disease. *International Journal of Geriatric Psychiatry*. 18(11):1037-42.
- ^{xxi} Shin IS, Carter M, Masterman D et al (2005) Neuropsychiatric symptoms and quality of life in Alzheimer's disease. *American Journal of Geriatric Psychiatry*. 13(6):469-74.
- ^{xxii} Wimo et al (2003) Resource utilisation and cost analysis of memantine in people with moderate to severe Alzheimer's disease. *Pharmacoeconomics*. 21(5):327-40.
- ^{xxiii} Wimo A et al (2004) Impact of donepezil treatment for Alzheimer's disease on caregiver time. *Current Medical Research and Opinion*. 20(8):1221-5.
- ^{xxiv} Mace N and Rabins P (1999) *The 36-hour day*. John Hopkins University Press: Baltimore.
- ^{xxv} Francis J and McDaid D (2009) SCIE's work on economics and the importance of informal care. In PSSRU (2009) *PSSRU Unit costs of health and social care 2009*. PSSRU.
- ^{xxvi} Deimling GT and Bass DM (1986) Symptoms of mental impairment among elderly adults and their effects on family caregivers. *Journal of Gerontology*. 41:778-84.
- ^{xxvii} Hart DJ, Craig D, Compton SA et al (2003) A retrospective study of the behavioural and psychological symptoms of mid and late phase Alzheimer's disease. *International Journal of Geriatric Psychiatry*. 18(11): 1037-42.
- ^{xxviii} Shin IS, Carter M, Masterman D et al, Neuropsychiatric symptoms and quality of life in Alzheimer's disease (2005) *American Journal of Geriatric Psychiatry*. 13 (6): 469-74.
- ^{xxix} Teng E and Cummings J (2007) Behaviour. In Gauthier S (ed) *Clinical diagnosis and management of Alzheimer's disease*. Informa Healthcare.

-
- ^{xxx} Gauthier S (2002) Efficacy of Donepezil on Behavioral Symptoms in Patients With Moderate to Severe Alzheimer's Disease. *International Psychogeriatrics*. 14(4): 389-404.
- ^{xxxix} Beerli MS, Werner P, Davidson M *et al* (2002) The cost of behavioral and psychological symptoms of dementia (BPSD) in community dwelling Alzheimer's disease patients. *International Journal of Geriatric Psychiatry*. 17(5): 403-8.
- ^{xxxix} Herrmann N, Lanctot KL, Sambrook R *et al* (2006) The contribution of neuropsychiatric symptoms to the cost of dementia care. *International Journal of Geriatric Psychiatry*. 21(10):972-6.
- ^{xxxix} Murman DL, Chen Q, Powell MC, *et al* (2002) The incremental direct costs associated with behavioural symptoms in Alzheimer's disease. *Neurology*. 59: 1721-9.
- ^{xxxix} Gauthier S, Wirth Y, Mobius H (2005) Effects of memantine on behavioural symptoms in Alzheimer's disease patients: an analysis of the Neuropsychiatric Inventory (NPI) data of two randomised, controlled studies. *International Journal of Geriatric Psychiatry*. 20(5):459-64.
- ^{xxxix} Gauthier S, Loft H, Cummings J (2008) Improvement in behavioural symptoms in patients with moderate to severe Alzheimer's disease by memantine: a pooled data analysis. *International Journal of Geriatric Psychiatry*. 23: 537–545.
- ^{xxxix} Schneider L S, Dagerman K, Insel P S (2006a) 'Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials'. *American Journal of Geriatric Psychiatry* 14: 191-210.
- ^{xxxix} Lyketsos CG, Sheppard JM, Steinberg M *et al* (2001) Neuropsychiatric disturbance in Alzheimer's disease clusters into three groups: the Cache County study. *International Journal of Geriatric Psychiatry*. 16(11):1043-53.
- ^{xxxix} Rosen J and Zubenko GS (1991) Emergence of psychosis and depression in the longitudinal evaluation of Alzheimer's disease, *Biological Psychiatry*. 29(3): 224-32.
- ^{xxxix} Holmes C, Smith H, Ganderton R *et al* (2001) Psychosis and aggression in Alzheimer's disease: the effect of dopamine receptor gene variation. *Journal of Neurology, Neurosurgery and Psychiatry*. 71(6): 777-9.
- ^{xli} Howard R, Juszczak E, Ballard C, *et al* (2007) Donepezil for agitation in Alzheimer's disease: a randomized placebo-controlled trial (The CALM-AD Trial). *New England Journal of Medicine*. 357 1382-1392.
- ^{xli} Passmore P (2005) Pharmacological Treatment of Alzheimer's Disease, at *Managing Dementia*, Glasgow (presented meta analysis of Bullock 2001 and Cummings 2004).
- ^{xlii} PSSRU (2009) *Unit Costs of Health and Social Care*. PSSRU.
- ^{xliii} Laing and Buisson (2009) *Dementia Care Services: UK market briefing 2009*. Laing and Buisson.
- ^{xliiv} Ballard C *et al* (2002) Can psychiatric liaison reduce neuroleptic use and reduce health service utilisation for dementia patients residing in care facilities? *International Journal of Geriatric Psychiatry*. 17:140-5.
- ^{xliiv} CSCI (2009) *The state of social care 2008*. London.