

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE**Health Technology Appraisal****Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (Review of TA 111)****Final Scope****Appraisal objective**

To review and update as necessary guidance to the NHS in England and Wales¹² on the clinical and cost effectiveness of donepezil, galantamine, rivastigmine and memantine within their licensed indications for the treatment of Alzheimer's disease which was issued in November 2006 (amended September 2007, August 2009).

Background

Dementia is a chronic progressive mental disorder that adversely affects higher cortical functions including memory, thinking and orientation. Alzheimer's disease is the most common form of dementia. It is a degenerative cerebral disease with characteristic neuropathological and neurochemical features. Alzheimer's disease is usually insidious in onset and develops slowly but steadily over a period of several years. It affects predominantly the elderly. Progression is characterised by deterioration in cognition (thinking, conceiving, reasoning) and functional ability (activities of daily living) and a disturbance in behaviour and mood. Changes in one or more of these domains and their effects on the person provide the basis for diagnosis and they are used to assess the severity and progression of the condition.

Population data (2005) for England and Wales show an estimated prevalence of 380,000 people with Alzheimer's disease. The incidence rate for Alzheimer's disease in people over the age of 65 years has been estimated at 4.9 per 1000 person-years in the UK.

¹ NICE Technology Appraisal Guidance No 111 - Donepezil, galantamine, rivastigmine (review) and memantine for the treatment of Alzheimer's disease (amended) (November 2006, amended September 2007, August 2009)

² The Department of Health's remits to the Institute are:

As part of the planned review of guidance on treatment of Alzheimer's disease: to appraise the clinical and cost effectiveness of memantine (Ebixa) for treatment of moderate Alzheimer's disease.

To appraise the clinical and cost effectiveness of medicines which are licensed, at the time NICE prepares its appraisal consultation document, for treatment of severe Alzheimer's disease, including memantine and cholinesterase inhibitors.

The comparison should be in each case between drug therapy (in combination with supportive care) and current treatment alternatives (including best supportive care alone).

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People with Alzheimer's disease lose the ability to carry out routine daily activities like dressing, toileting, travelling and handling money and, as a result, many people require a high level of care. Often, this is provided by a relative, whose own health and quality of life can be affected by the burden of providing care, with some experiencing psychiatric illnesses such as depression and anxiety. Behavioural changes in the person, such as aggression, are particularly disturbing for carers.

Several methods are available to assess the severity of Alzheimer's disease, with different methods used depending on the setting, for example research or clinical practice, and the type of outcome being assessed. Global outcomes measures include the Global deterioration scale (GDS), Clinical Global Impression of Change (CGIC); Clinician's Interview-based Impression of Change (CIBIC) and CIBIC-plus and the Gottfries-Brane-Steen scale. Functional ability and quality of life are assessed using the Progressive Deterioration Scale (PDS), Disability Assessment for Dementia (DAD), the Alzheimer's Disease Cooperative Studies for Daily Living Inventory (ADCS/ADL) and the Instrumental Activities of Daily Living (IADL) scale. Cognitive ability is assessed using the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog – 70 points), the Severe Impairment Battery (SIB) or the MMSE (Mini Mental State Examination – 30 points). MMSE score, for example, denotes the severity of cognitive impairment as follows: mild Alzheimer's disease: MMSE 21–26, moderate Alzheimer's disease: MMSE 10–20, moderately severe Alzheimer's disease: MMSE 10–14, severe Alzheimer's disease: MMSE less than 10. In clinical practice a variety of measures are used to assess disease severity, often in conjunction with clinically-based assessments such as biographical interview.

Management of Alzheimer's disease involves treatment of cognitive, behavioural and psychological symptoms. Non-pharmacological treatment is social support and increasing assistance with day-to-day activities. These include information and education, carer support groups, community dementia teams; home nursing and personal care, community services such as meals-on-wheels, befriending services, day centres, respite care and care homes.

NICE guidance (Technology Appraisal 111 [see appendix] and Clinical Guideline 42) recommends the three acetylcholinesterase (AChE) inhibitors donepezil, galantamine and rivastigmine as options in the management of patients with Alzheimer's disease of moderate severity only (for people with a MMSE score of between 10 and 20 points). Treatment with AChE inhibitors is initiated by specialists in the care of patients with dementia (that is, psychiatrists including those specialising in learning disability, neurologists, and physicians specialising in the care of the elderly), who seek carers' views on the patient's condition at baseline. Patients maintained on treatment with AChE inhibitors are reviewed every 6 months by MMSE score and global, functional and behavioural assessment. Treatment is discontinued when patient's MMSE score falls below 10 points. Memantine is not recommended as a treatment option for people with moderately severe to severe Alzheimer's disease except as part of well designed clinical studies.

The technologies

Donepezil (Aricept, Eisai), rivastigmine (Exelon, Novartis), and galantamine (Reminyl, Shire) are AChE inhibitors, which work by increasing the concentration of acetylcholine at sites of neurotransmission. Galantamine also acts by modulating activity at nicotinic receptors. Donepezil, rivastigmine and galantamine have marketing authorizations in the UK for the treatment of adults with mild to moderately severe Alzheimer's dementia.

Memantine (Ebixa, Lundbeck) is a voltage-dependent, moderate-affinity, uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist that blocks the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction. It has a UK marketing authorisation for the treatment of people with moderate to severe Alzheimer's disease. In 2005 there was an extension of the approved indication for memantine to include the treatment of moderate to moderately severe Alzheimer's disease. Originally, memantine was approved in Europe for the treatment of moderately severe to severe Alzheimer's disease.

Intervention(s)	<p>The following interventions will be appraised in accordance with their marketing authorisations as follows:</p> <p>For the treatment of mild to moderately severe Alzheimer's disease:</p> <ul style="list-style-type: none">• Donepezil• Galantamine• Rivastigmine <p>For the treatment of moderate to severe Alzheimer's disease:</p> <ul style="list-style-type: none">• Memantine
Population(s)	Adults with Alzheimer's disease

Comparators	<p>For people with mild disease:</p> <ul style="list-style-type: none"> • Treatment without AChE inhibitors <p>For people with moderate disease:</p> <ul style="list-style-type: none"> • Donepezil • Galantamine • Rivastigmine • Memantine • Treatment without AChE inhibitors or memantine <p>For people with severe disease:</p> <ul style="list-style-type: none"> • Treatment without memantine
Outcomes	<p>The outcome measures which may include:</p> <ul style="list-style-type: none"> • measures of severity and response to treatment • behavioural symptoms (e.g. neuropsychiatric inventory, NPI) • mortality • ability to remain independent • admission to full-time care • health-related quality of life of patients and carers (analyses should be carried out separately for patients alone, and for patients and carers combined) • adverse effects of treatment
Economic analysis	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p>

Other considerations	<p>Guidance will only be issued in accordance with the marketing authorisation.</p> <p>If evidence allows, interventions will be compared with each other, in sequential use, or as combination therapy, within their licensed indications.</p> <p>Treatment without AChE inhibitors or memantine is considered to be social support and assistance with day-to-day activities. These may include: information and education, carer support groups, community dementia teams, home nursing and personal care, community services such as meals-on-wheels, befriending services, day centres, respite care and care homes.</p> <p>If evidence allows, the following subgroups will be considered: subgroups based on disease severity, previous response to treatment, presence of behavioural disturbance or presence of comorbidities such as cerebrovascular disease).</p>
Related NICE recommendations	<p>Related Technology Appraisals:</p> <p>NICE Technology Appraisal Guidance No 111 - Donepezil, galantamine, rivastigmine (review) and memantine for the treatment of Alzheimer's disease (amended) (November 2006, amended September 2007, August 2009)</p> <p>Related Guidelines:</p> <p>Clinical Guideline No 42, November 2006, 'Dementia: supporting people with dementia and their carers in health and social care'.</p>

Appendix: Current NICE Guidance (TA 111)**1 Guidance**

This guidance applies to donepezil, galantamine, rivastigmine and memantine within the marketing authorisations held for each drug at the time of this appraisal; that is:

- donepezil, galantamine, rivastigmine for mild to moderately severe Alzheimer's disease
- memantine for moderately severe to severe Alzheimer's disease.

The benefits of these drugs for patients with other forms of dementia (for example, vascular dementia or dementia with Lewy bodies) have not been assessed in this guidance.

- 1.1 The three acetylcholinesterase inhibitors donepezil, galantamine and rivastigmine are recommended as options in the management of patients with Alzheimer's disease of moderate severity only (that is, subject to section 1.2 below, those with a Mini Mental State Examination [MMSE] score of between 10 and 20 points), and under the following conditions:
- Only specialists in the care of patients with dementia (that is, psychiatrists including those specialising in learning disability, neurologists, and physicians specialising in the care of the elderly) should initiate treatment. Carers' views on the patient's condition at baseline should be sought.
 - Patients who continue on the drug should be reviewed every 6 months by MMSE score and global, functional and behavioural assessment. Carers' views on the patient's condition at follow-up should be sought. The drug should only be continued while the patient's MMSE score remains at or above 10 points (subject to

section 1.2 below) and their global, functional and behavioural condition remains at a level where the drug is considered to be having a worthwhile effect. Any review involving MMSE assessment should be undertaken by an appropriate specialist team, unless there are locally agreed protocols for shared care.

When using the MMSE to diagnose moderate Alzheimer's disease, clinicians should be mindful of the need to secure equality of access to treatment for patients from different ethnic groups (in particular those from different cultural backgrounds) and patients with disabilities.

- 1.2 In determining whether a patient has Alzheimer's disease of moderate severity for the purposes of section 1.1 above, healthcare professionals should not rely, or rely solely, upon the patient's MMSE score in circumstances where it would be inappropriate to do so. These are:
- where the MMSE is not, or is not by itself, a clinically appropriate tool for assessing the severity of that patient's dementia because of the patient's learning or other disabilities (for example, sensory impairments) or linguistic or other communication difficulties **or**
 - where it is not possible to apply the MMSE in a language in which the patient is sufficiently fluent for it to be an appropriate tool for assessing the severity of dementia, or there are similarly exceptional reasons why use of the MMSE, or use of the MMSE by itself, would be an inappropriate tool for assessing the severity of dementia in that individual patient's case.

In such cases healthcare professionals should determine whether the patient has Alzheimer's disease of moderate severity by making use of another appropriate method of assessment. For the avoidance of any doubt, the acetylcholinesterase inhibitors are

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recommended as options in the management of people assessed on this basis as having Alzheimer's disease of moderate severity.

The same approach should apply in determining for the purposes of section 1.1 above, and in the context of a decision whether to continue the use of the drug, whether the severity of the patient's dementia has increased to a level which in the general population of Alzheimer's disease patients would be marked by an MMSE score below 10 points.

- 1.3 When the decision has been made to prescribe an acetylcholinesterase inhibitor, it is recommended that therapy should be initiated with a drug with the lowest acquisition cost (taking into account required daily dose and the price per dose once shared care has started). However, an alternative acetylcholinesterase inhibitor could be prescribed where it is considered appropriate having regard to adverse event profile, expectations around concordance, medical comorbidity, possibility of drug interactions and dosing profiles.
- 1.4 Memantine is not recommended as a treatment option for patients with moderately severe to severe Alzheimer's disease except as part of well-designed clinical studies.
- 1.5 Patients with mild Alzheimer's disease who are currently receiving donepezil, galantamine or rivastigmine, and patients with moderately severe to severe Alzheimer's disease currently receiving memantine, whether as routine therapy or as part of a clinical trial, may be continued on therapy (including after the conclusion of a clinical trial) until they, their carers and/or specialist consider it appropriate to stop.