

# Clinical practice with anti-dementia drugs: a consensus statement from British Association for Psychopharmacology

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## Abstract

The British Association for Psychopharmacology (BAP) coordinated a meeting of experts to review the evidence on the drug treatment for dementia. The level of evidence (types) was rated using a standard system: Types 1a and 1b (evidence from meta-analysis of randomised controlled trials or at least one controlled trial respectively); types 2a and 2b (one well-designed study or one other type of quasi experimental study respectively); type 3 (non-experimental descriptive studies); and type 4 (expert opinion). There is type 1a evidence for cholinesterase inhibitors (donepezil, rivastigmine and galantamine) for mild to moderate Alzheimer's disease; memantine for moderate to severe Alzheimer's disease; and for the use of bright light therapy and aromatherapy. There is type 1a evidence of no effect of anti-inflammatory drugs or statins. There is conflicting evidence regarding

oestrogens, with type 2a evidence of a protective effect of oestrogens but 1b evidence of a harmful effect. Type 1a evidence for any effect of B12 and folate will be forthcoming when current trials report. There is type 1b evidence for ginkgo biloba in producing a modest benefit of cognitive function; cholinesterase inhibitors for the treatment of people with Lewy body disease (particularly neuropsychiatric symptoms); cholinesterase inhibitors and memantine in treatment cognitive impairment associated with vascular dementia; and the effect of metal collating agents (although these should not be prescribed until more data on safety and efficacy are available). There is type 1b evidence to show that neither cholinesterase inhibitors nor vitamin E reduce the risk of developing Alzheimer's disease in people with mild cognitive impairment; and there is no evidence that there is any intervention that

can prevent the onset of dementia. There is type 1b evidence for the beneficial effects of adding memantine to cholinesterase inhibitors, and type 2b evidence of positive switching outcomes from one cholinesterase inhibitor to another. There is type 2a evidence for a positive effect of reminiscence therapy, and type 2a evidence that cognitive training does not work. There is type 3 evidence to support the use of psychological interventions in dementia. There is type 2 evidence that a clinical diagnosis of dementia can be made accurately and that brain imaging increases that accuracy.

Although the consensus statement dealt largely with medication, the

role of dementia care in secondary services (geriatric medicine and old age psychiatry) and primary care, along with health economics, was discussed. There is ample evidence that there are effective treatments for people with dementia, and Alzheimer's disease in particular. Patients, their carers, and clinicians deserve to be optimistic in a field which often attracts therapeutic nihilism.

## Keywords

Alzheimer's disease, treatment guidelines

## Introduction

The British Association for Psychopharmacology Guidelines outline the scope and targets for treatment of dementia. They are similar to previous guidelines in that they are based explicitly on the available evidence and are presented in terms of the level for that evidence and subsequent recommendations to aid decision making for primary and secondary care clinicians and their associated NHS organizations involved in the recognition, diagnosis and management of people with dementia. They may also serve as a source of information for patients and their carers. A consensus meeting involving experts in the field and consumer representatives independently reviewed a number of key areas and outlined the strength of the evidence and of its clinical implications. The guidelines were drawn up after extensive feedback from participants and underwent independent peer review prior to publication. The guidelines cover the diagnosis of dementia, its treatment with a number of drugs, its management in primary and secondary care and its prevention. The guidelines do not deal directly with drug treatments specifically for behavioural disturbances in dementia (e.g. antidepressants, antipsychotics and sedatives) and concentrate on treatments readily recognized for use in the UK.

The British Association for Psychopharmacology (BAP) is an association of psychiatrists, psychopharmacologists and basic scientists who are interested in the broad field of drugs and the brain. BAP is the largest national organization of its kind worldwide, and runs the *Journal of Psychopharmacology*. The association started publishing consensus statements more than a decade ago, and the first BAP guidelines on depression were considered a landmark publication when published in 1993 (Montgomery *et al.*, 1993). This document, which was updated in 2000 (Anderson *et al.*, 2000), has become the standard of care in many countries since it is considered an accessible consensus to guide practising psychiatrists. The BAP now has a target of publishing one consensus statement per year in the *Journal*. Recent guidelines have covered management of bipolar disorder (Goodwin, 2003) and drug treatments for addiction (Lingford-Hughes *et al.*, 2004), with anxiety (Baldwin *et al.*, 2005). Forthcoming consensus conferences are in planning on child psychopharmacology and schizophrenia, to be held at the Novartis Foundation, London, the venue for all such conferences, which utilize a similar style and process. All guidelines are available via the BAP website (<http://www.bap.org.uk>) and the intention is to update each guideline every 5 years.

Dementia affects about 800 000 people in the UK, of which Alzheimer's disease (AD) is the commonest cause (60%) followed by vascular dementia (VaD, 20%), dementia with Lewy bodies (DLB, 15%) and rarer and reversible causes (5%). These figures include around 20% where there is evidence of mixed pathology. The diagnosis of subtype of dementia is based on clinical history, examination and appropriate investigations. Currently the mainstay of pharmacological treatment for the cognitive deficits of AD are the cholinesterase inhibitors (donepezil, Aricept®; galantamine, Reminyl®; and rivastigmine, Exelon®), which are licensed for the treatment of mild to moderate disease; and memantine, (Ebixa®) licensed for moderate to severe illness. Associated non-cognitive symptoms, often called behavioural and psychological symptoms of dementia (BPSD), are frequently seen in all dementias, cause distress to patients and carers and are a major factor predicting institutional care. Many types of BPSD, including agitation, aggression and psychosis, have traditionally been treated with neuroleptics, especially antipsychotic drugs. However, recent concerns over cerebrovascular adverse events and possible increased mortality has forced consideration of alternative approaches to the treatment of BPSD, including cholinesterase inhibitors, memantine and non-pharmacological therapies such as bright light therapy and aromatherapy. Management of vascular dementia primarily involves the identification and treatment of vascular risk factors, amelioration of BPSD and, where there is coexistent AD, prescription of cholinesterase inhibitors and memantine. DLB is treated symptomatically with cautious use of anti-parkinsonian medication where necessary (L-dopa monotherapy having the least propensity to exacerbate psychosis) and cholinesterase inhibitors. Management of BPSD is essentially similar to that of other dementias with the caveat that antipsychotic drugs should be avoided because of extrapyramidal side effects and the likelihood of prolonged and severe sensitivity reactions.

There are many guidelines available for the diagnosis and treatment of dementia (Burns *et al.*, 2001) but the current initiative was felt to be timely in view of reconsideration by the National Institute for Health and Clinical Excellence in the UK (NICE: [www.nice.org.uk](http://www.nice.org.uk)) of their 2001 guidance on cholinesterase inhibitors and their new assessment of memantine. However, NICE guidance is limited to licensed indications (mild to moderate AD for cholinesterase inhibitors and to severe AD for memantine (subsequently extended to moderate to

severe AD)). At the time of writing (June 2006) NICE have announced that their final appraisal document which says the cholinesterase drugs (donepezil, galantamine and rivastigmine) should only be made available to people with a Mini Mental State Examination score of between ten and 20 i.e. in the moderate to moderately severe stages of the disease. An appeal has been launched against this decision at the time of writing (September 2006, for up-to-date information consult the NICE website). Memantine is not recommended for use on the NHS. It is highly likely that there will be an appeal against this decision (for up-to-date information, consult the NICE website). Other guidelines such as those of the Scottish Intercollegiate Guidelines Network (SIGN) ([www.sign.ac.uk](http://www.sign.ac.uk)), do not provide an adequate focus on psychopharmacology. NICE are currently developing a clinical guideline for dementia which will be available in 2007, covering both medical and social care. The guidelines have been developed for primary and secondary care clinicians and their associated organizations involved in the recognition, diagnosis and management of people with dementia.

## Methodology

A consensus meeting was held in Manchester in October 2005. The authors were selected for their clinical and research experience in the field of dementia care including a carer representative. The group arrived at its decision totally independently and guidelines were prepared following the format of previous BAP consensus meetings on depression, bipolar disorder and substance misuse (Anderson *et al.*, 2000; Lingford-Hughes *et al.*, 2004; Goodwin, 2003). All authors based their evidence summary on their own expert knowledge of the literature combined with a recent literature review in their own specialist area. All relevant papers published up to and including September 2005 were considered.

The objectives of the guideline were to:

- 1 review the evidence for clinical diagnosis of dementia and the place of investigations;
- 2 evaluate clinical trial methodology;
- 3 assess the level of evidence for the efficacy of currently available anti-dementia drugs in all the common types of dementia and, based on that, make recommendations for treatment;
- 4 appraise the evidence for the efficacy of drugs with immediate potential for the treatment of dementia;
- 5 highlight treatment practice in primary and secondary care including prevention.

The level of evidence was categorized according to standard criteria with a consequent recommendation for implementation.

### Level of evidence

- 1a evidence obtained from meta-analysis of randomized controlled trials;

- 1b evidence obtained from at least one randomized controlled trial;
- 2a evidence obtained from at least one well-designed controlled study without randomization;
- 2b evidence obtained from at least one other type of well-designed quasi-experimental study;
- 3 evidence obtained from well-designed non-experimental descriptive studies such as comparative studies, correlation studies, case studies;
- 4 evidence obtained from expert committee reports or opinions and of clinical experiences of respected authorities.

### Grade of recommendation

- A required: at least one randomized controlled trial as part of the body of literature of overall quality and consistency addressing specific recommendation (evidence levels 1a and 1b);
- B Availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation (includes evidence levels 2a, 2b and 3);
- C Evidence obtained from expert committee reports and/or clinical experiences of respected authorities (evidence level 4);
- D Indicates absence of directly applicable clinical studies of good quality.

## Evidence-based diagnosis and investigations

Reaching universal agreement on the definition of dementia and the best criteria by which to establish this diagnosis has proved problematic. The criteria of the DSM (version III-R and version IV TR) American Psychiatric Association (APA), 1987; 1994; 2000) have been used the most widely within research settings and have been most clinically applicable. However, their reliance on episodic memory disturbance as a core requirement does not adequately capture the seminal features of non-Alzheimer dementias including frontotemporal dementia (FTD), VaD and DLB. Furthermore, it has been demonstrated that applying other sets of clinical criteria can substantially change the estimates of dementia prevalence (Erkinjuntti *et al.*, 1997).

Currently, dementia is diagnosed into distinct clinical subtypes. The most widely used criteria include: the NINCDS-ADRDA criteria for AD (McKhann *et al.*, 1984), McKhann and Neary criteria for FTD (Neary *et al.*, 1999; McKhann *et al.*, 2001), the NINDS-AIREN criteria for VaD (Roman *et al.*, 1993) and the International Consensus Criteria for DLB (McKeith *et al.*, 1996, 2005). The reported sensitivities and specificities of these criteria vary considerably between studies, without an ideal balance being reached for any of these disorders. Specificity for each of the criteria is generally high (>80%) but sensitivity is often low (20–40% for VaD and DLB criteria in many centres), leading to uncertain classification of dementia subtype in many individual cases clinically. One of the inherent difficulties in the categorical approach to clinical diagnosis is the increasing recognition that the brain is the host of multiple co-morbid pathologies with ageing which impact the

**Table 1** Summary box

Intervention	Level of evidence	Recommendation
<b>Diagnosis and imaging</b>		A
Clinical Assessment	There is <b>type 2</b> evidence that a clinical diagnosis of dementia is accurate and that the use of brain imaging contributes to clinical diagnostic accuracy	
Computed Tomography		
Magnetic resonance imaging		
Positron emission tomography		
Single photon emission tomography		
<b>Treatments</b>		
Non-pharmacological therapies	There is <b>type 3</b> evidence to support the use of psychological interventions in dementia with <b>type 2a</b> evidence that cognitive training does not work and <b>type 2a</b> evidence for reminiscence therapy. Bright light therapy and aromatherapy are supported by <b>type 1a</b> evidence	A
<b>Drug treatments</b>		
Alzheimer's disease	There is <b>type 1a</b> evidence for the efficacy of cholinesterase inhibitors in the treatment for mild to moderate Alzheimer's disease	
Cholinesterase inhibitors		
Donepezil	There is <b>type 2b</b> evidence to support the switching of one cholinesterase to another if the first is not tolerated or is ineffective.	A
Rivastigmine		
Galantamine		
Memantine	There is <b>type 1a</b> evidence of the efficacy of memantine in the treatment of moderate to severe Alzheimer's disease	
	There is <b>type 1b</b> evidence for adding memantine to a cholinesterase inhibitor	
Drugs for dementia with Lewy bodies	There is <b>type 1b</b> evidence to support treatment with cholinesterase inhibitors in Lewy body dementia, both dementia with Lewy bodies and Parkinson's disease dementia, including for neuropsychiatric symptoms	A
Drugs for vascular dementia	There is <b>type 1b</b> evidence to support the use of cholinesterase drugs and memantine in the treatment of cognitive impairment in vascular dementia, though effect sizes are small and may not be clinically significant	A
<i>Ginkgo Biloba</i>	There is <b>type 1b</b> evidence for a modest effect of <i>ginkgo biloba</i> in the treatment of cognitive impairment in dementia though effect sizes are small and may not be clinically significant	A
Vitamin B12/folate	There is currently no evidence to suggest that vitamin B12 and folate are effective in the routine treatment of Alzheimer's disease but trials are ongoing which will provide <b>type 1a</b> evidence	B
Oestrogens	There is conflicting evidence over the use of oestrogens in dementia with <b>type 2a</b> evidence of a protective effect and <b>1b</b> of a harmful effect. Until further evidence is available, oestrogens should not be prescribed for the purpose of preventing or treating dementia	B
Anti-inflammatory drugs	There is <b>type 1a</b> evidence that a variety of anti-inflammatory drugs do not produce benefit in Alzheimer's disease	A
Anti-oxidants	There is <b>type 1b</b> evidence of a delay in the progression of Alzheimer's disease with high dose vitamin E alone, but not when combined with selegiline	B
Metal protein attenuating compounds	There is preliminary <b>1b</b> evidence of their effect in Alzheimer's disease. These agents should not be prescribed until more data on safety and efficacy are available	B
Statins	There is class <b>1a</b> evidence of no effect of statins in the prevention of AD	A
Mild cognitive impairment	There is <b>type 1b</b> evidence that cholinesterase inhibitors and vitamin E are not effective in reducing the risk of developing Alzheimer's disease.	A
Prevention of dementia	There is no evidence to support, at present, any intervention to prevent dementia	B

expression of dementia and which create overlapping and heterogeneous clinical phenotypes. In turn neuropathological diagnoses are increasingly utilizing probabilistic statements (National Institute on Ageing, 1997), an approach taken in the revised DLB criteria (McKeith *et al.*, 2005), while clinical diagnostic criteria for mixed dementia have yet to be formulated.

The current standard diagnostic criteria for diagnosing AD are clinically based, relying largely on history, mental state, cognitive and physical examination and appropriate investigations (largely to exclude another cause for the dementia). The role of neuroimaging and other putative diagnostic markers in blood and CSF remains to be fully determined. Both structural and functional imaging have been extensively investigated for their ability to detect AD and differentiate it from the other dementias. Quantitative MRI differentiates AD from normal ageing (sensitivity/specificity 77–95/40–95%), mild cognitive impairment (MCI) (78–89/71–86%, Jack *et al.*, 1997), FTD (90/93%, Boccardi *et al.*, 2003) but not from VaD or DLB. More clinically applicable visual or linear MRI measures can differentiate AD from normal ageing (75–100/69–96%, Gao *et al.*, 2004) but have achieved mixed results in the differential diagnosis of VaD and DLB (Barber *et al.*, 1999). The demonstration of cortical and/or subcortical vascular changes on structural imaging is an essential component of several sets of diagnostic criteria for VaD. FDG-PET performs comparably to MRI in the differentiation of AD from normal ageing (61–97/70–100%), MCI or other clinic-referred patients (93–94/63–75%, Silverman *et al.*, 2001) and FTD (90–95% accuracy) and some studies suggest utility in differentiating AD from DLB (85–92/80–92%). Its ability to differentiate VaD has not been reliable (75–88/18–90%). However, demonstrating cortical and/or subcortical vascular changes on structural imaging is an essential component of several sets of diagnostic criteria for VaD. Perfusion (blood flow) SPECT has sensitivity of 71% for AD and specificity of 78% for non-AD dementia (Dougall *et al.*, 2004). More specific ligand SPECT may show greater promise, for example dopamine SPECT scanning with fluoropropyl-CIT appears to have particular utility in identifying DLB and PDD from AD (sensitivity/specificity 78–97%/95–94%, Walker *et al.*, 1999; O'Brien *et al.*, 2004) and dopaminergic diagnostic criteria for DLB (McKeith *et al.*, 2005). The incremental value of adding neuroimaging to clinical diagnosis remains to be fully worked out, but may be most helpful in cases that are most clinically uncertain (Jagust *et al.*, 2001), though the current evidence base still does not fully address the key clinical question of the added utility of these diagnostic modalities. Other markers including MR spectroscopy, fMRI, blood and CSF markers still lack the evidence base for their recommendations as standards at the current time, apart from the use of 14–3-3 protein in suspected Creutzfeldt-Jacob disease (CJD). However, promising results for the use of other CSF markers (for tau and amyloid) have been reported by some centres.

In conclusion, the diagnosis of dementia and determination of likely subtypes is currently determined clinically. Neuroimaging (MRI, PET, SPECT) and biomarker studies hold potential to improve diagnostic accuracy, but their incremental value to clinical assessment is not yet fully established. In most clinical set-

tings, routine blood work and selected structural neuroimaging (CT or MRI) are employed, as recommended by many sets of guidelines including those of the UK Royal College of Psychiatrists (RCPSYCH, 2005). More focused imaging, using ligand SPECT, MRI or PET, is reserved for selected cases. Given that, in practice, universal access to structural imaging for all cases of suspected dementia is not yet available in many countries, including the UK, the prioritization of cases with factors associated with a high chance of finding pathology has been proposed.

### *Current recommendations for the use of brain imaging in the diagnosis of dementia*

#### **Computed tomography**

Canadian Consensus Conference on Dementia (Patterson *et al.*, 2001)  
Scan only if:

- Age less than 60
- Rapid unexplained decline in cognition or function (months)
- Short duration (less than 2 years)
- Any new localizing sign (e.g. hemiparesis)
- Recent head trauma
- Unexplained neurological symptoms (eg. headache)
- History of cancer
- Anticoagulants or bleeding disorder
- History of incontinence or gait disorder early
- Unusual or atypical presentation

Royal College of Psychiatrists ('Forgetful but not Forgotten' (CPSYCH 2005)

CT – Age should not be a bar, in an ideal world every patient with suspected dementia should have a CT. Indications include atypical presentation, rapid deterioration, focal signs, recent head injury or incontinence/gait ataxia early in illness. CT less costly and faster than MRI, adequate in most cases.

The value of MRI, SPECT or PET remains to be established but MRI and SPECT can provide valuable additional information.

#### **Magnetic resonance imaging**

- Good utility in separating AD from normal aging/MCI
- Specificity likely too low especially with aging brain;
- Insufficient evidence of utility in differential diagnosis

#### **Positron emission tomography**

- Fair utility in separating AD from normal ageing/MCI and non-AD clinic patients
- Wide specificity range is problematic
- May have utility in differentiating AD from DLB and FTD but not VaD

#### **Single photon emission tomography:**

- Blood flow SPECT has modest utility in separating from normal ageing/MCI/non-AD clinic patients

- May have utility in differentiating FTD from other causes of dementia
- Dopaminergic SPECT may help separate DLB from AD and VaD

## Non-pharmacological therapies

Non-pharmacological treatments for dementia potentially cover a broad expanse of therapies for a variety of indications. A recent Cochrane review (Clare *et al.*, 2006; [www.cochrane.org/reviews](http://www.cochrane.org/reviews)) summarizes the current evidence for cognitive rehabilitation and cognitive training. No studies pertaining to cognitive rehabilitation were identified that met the required quality standards. Six trials were included examining cognitive training, with no evidence of significant improvement.

A further Cochrane review evaluated the potential benefits of reminiscence (Woods *et al.*, 2006). Five studies were included, four of which had extractable data, with a total of 144 participants. Significant improvements were evident in cognition (effect size 0.5,  $p=0.02$ ) and mood. Although this is encouraging, the effect size upon cognition is only about one-fifth of that seen with cholinesterase inhibitors. Whilst reminiscence is not therefore an alternative to pharmacotherapy, further work should examine the potential additive benefits. Although there is limited evidence for unstructured carer support groups, more intensive psychological therapies and specific cognitive behavioural therapy interventions do significantly reduce psychiatric morbidities in care-givers.

An expanding literature does suggest that psychological interventions can improve behavioural symptoms in people with dementia. There are few large randomized controlled trials, but a larger number of cluster trials and case series. Although further information is needed the evidence strongly supports that there is no exacerbation of behavioural symptoms if neuroleptic drugs are

replaced by a psychological therapy. As a first line intervention simple psychological interventions such as structured interaction appear to reduce symptoms of agitation by 25%. Further randomized controlled studies are needed.

Bright light therapy and aromatherapy are effective treatments for behavioural problems and psychiatric symptoms in dementia with evidence of their effect from randomized controlled trials (Burns *et al.*, 2002).

## Clinical trials in dementia

Successful clinical trials in AD in the past decade have led to the regulatory approval of the anti-dementia drugs. With this development there have been new challenges and controversies that have emerged within the design, methods and analysis of clinical trials. (NICE, 2001; Kaduszkiewicz *et al.*, 2005). There are a number of specific controversial issues with clinical trials in AD.

## Duration

With a median survival of roughly 6–8 years from the time of diagnosis there has been concern that trials of  $\leq 6$  months are not clinically meaningful and should be discounted. Though trials with longer-term outcomes would be more informative about the impact of treatments on the whole course of illness, short-term trials of  $\leq 6$  months are sufficient to demonstrate symptomatic cognitive, functional and psychobehavioural benefits. Attrition rates of  $\leq 25\%$  on average. (Rogers *et al.*, 1998; Rosler *et al.*, 1999; Tariot *et al.*, 2000) allow them to be reasonably representative of the enrolled sample. Longer-term trials have the important potential to demonstrate effects on disease milestones, however the high loss to follow-up rates have and will likely continue to undermine

**Table 2** Summary box

Intervention	Level of evidence	Recommendation
Clinical Assessment Computed Tomography Magnetic resonance imaging Positron emission tomography Single photon emission tomography	There is <b>type 2</b> evidence that a clinical diagnosis of dementia is accurate and that the use of brain imaging contributes to clinical diagnostic accuracy	A

**Table 3** Summary box

Intervention	Level of evidence	Recommendation
Non-pharmacological therapies	There is <b>type 3</b> evidence to support the use of psychological interventions in dementia with <b>type 2a</b> evidence that cognitive training does not work and <b>type 2a</b> evidence for reminiscence therapy Bright light therapy and aromatherapy are supported by <b>type 1a</b> evidence	A

their utility (Courtney *et al.*, 2004). Compliance to protocol for subjects in trials who are elderly with care-givers that are stressed is challenging despite best efforts of research centres. The AD 2000 study, the longest placebo-controlled randomized clinical trial conducted to date reported a 66–70% dropout rate at 2 years (Courtney *et al.*, 2004). In trying to keep study samples representative, it is likely that pivotal clinical trials for new AD therapies will continue to be 6–12 months with some effort recommended in the future to extend study duration to 1 year or longer for longer-term disease milestones. Longer-term studies will clearly also be needed to demonstrate effects on disease progression.

### **Clinically meaningful outcome measures in clinical trials**

There are no validated surrogate measures for either AD diagnosis or reliable biomarkers for tracking its longitudinal course. Though neuroimaging and CSF biomarkers have been proposed to track disease course, recent longitudinal MRI and other biomarker data have raised many questions over their interpretation (Fox *et al.*, 2005). Clinical measures have proven to be the most reliable and sensitive at measuring change. Though an objective psychometric outcome measure such as the ADAS-Cog or even the Mini Mental State Examination (MMSE) has no intrinsic clinical meaningfulness, it is clear from natural history and RCT placebo analyses that their change scores are associated with important changes in function, cost and care-giver burden (Feldman *et al.*, 2005). It is likely that clinical measures will continue as the most relevant primary outcomes in demonstrating a treatment effect in AD. It should not be underestimated that small symptomatic benefits also matter a great deal to patients and families facing a long and relentless neurodegenerative disease. For longer-term impact, disease milestones including nursing home placement, are of potential interest; however there is no agreement yet on which milestones are of central importance and free of bias from non-treatment related effects.

### **The use of placebos is still justified**

While there are currently approved therapies for AD that have become a recommended standard of care, their treatment effect size is generally modest and further research directed at improved therapy is needed (Doody *et al.*, 2001). To conduct such research, there are clear needs and advantages of using placebos. However such use of placebos must be carefully considered to allow that research subjects are not exposed to placebo without receiving the usual standard of care. In turn, this will result in add on designs to usual care treatment, or alternatively head to head studies with study designs directed at superiority, equivalence or non-inferiority.

### **Disease modifying effect**

The demonstration of disease modifying effects of emerging AD therapies is presently elusive as there are no surrogate measures

and as there is uncertainty surrounding the interpretation of biomarker results. For an AD therapy to be able to make a claim of a disease modifying effect it will likely be necessary to have both a sustained long-term symptomatic effect as well as an effect on the underlying disease biology. Though some designs have been proposed including a delayed start and early withdrawal problems have been identified with each to a point that a statistically significant effect during a withdrawal period or in a delayed start would not constitute sufficient evidence for a disease modifying effect. At the biological level, the absence of a surrogate marker and the uncertainty of interpretation of effects on CSF biomarkers challenge our ability to detect a biological effect on the disease pathogenesis. Future biomarker research could however change this perspective and offer a clear pathway to studies on disease modification. At the present time it can be anticipated that studies undertaken to demonstrate a disease modifying effect will generate significant controversy over the interpretation of their outcomes.

### **Randomized controlled trials may be biased in favour of drug effects**

Within AD clinical trials the application of the analytic technique of intention to treat – last observation carried forward which has been a regulatory standard – has come under significant criticism. Whereas it was assumed to be a conservative imputation technique as withdrawing subjects were deprived of potential treatment benefit, it has also been appreciated that it may bias results in favour of treatment in several ways. Early dropouts related to drug intolerance would result in a carrying forward of the results of a significant percentage of trial participants in the treatment group before they had declined, particularly if the drug therapy had a high rate of early dropout during the titration phase. Though one view would be that this is biased against the drug an alternative view would be that within a neurodegenerative disease with an expected progressive rate of decline a carry forward of last value prior to dropout would benefit the treatment arm significantly. The longer the trial the stronger this effect might have. In turn alternative imputation schemes are receiving renewed attention including mixed effects models, regression techniques or assigning an average or worst case outcome scenario to dropouts. There will need to be some insistence that peer reviewed journals address these methodological points in publication to have the necessary influence on the regulatory agencies to influence a change in policy to ITT LOCF. The use of multiple comparisons and the correction of the level of significance is also emerging as a contentious issue and will need resolution. Whereas the case can effectively be made for a resetting of significance levels on secondary outcome measures, the primary outcomes for which a power analysis and sample size has been determined a priori should be able to survive without correction for multiple comparisons.

Other issues that have received attention include the highly selected nature of the samples within AD clinical trials and the difficulties with generalizability of study results. The current generation of RCTs has focused in pivotal studies on individuals without significant co-morbid medical illnesses, generally without active neuropsychiatric symptoms and with stable or highly

restricted use of concomitant medications. This had led to expressed concern around the lack of attention to safety and efficacy data within the real populations that medications will be used by. Effectiveness studies to supplement efficacy studies within drug development would likely fill this need but represent a significant shift in attention by pharmaceutical manufacturers to gather effectiveness data within the process for approval of new medications. Finally the need for economic studies that support new medications is becoming an issue of increasing importance as the approval of unreimbursed medications will lead to significant restriction in treatment availability. Both modelling and real patient pharmacoeconomic studies are needed with expert input into the designation of quality adjusted life years (QALYs).

### Drug treatments for Alzheimer's disease

There are currently two classes of drugs approved for the treatment of AD the cholinesterase inhibitors, tacrine, donepezil, rivastigmine and galantamine and the NMDA receptor antagonist memantine.

#### Cholinesterase inhibitors

There are now at least 30 randomized controlled trials demonstrating efficacy of the cholinesterase inhibitors in various stages of the disease with a variety of different outcome measures (Rogers *et al.*, 1998; Burns *et al.*, 1999; Rosler *et al.*, 1999; Farlow *et al.*, 2000; Raskind *et al.*, 2000; Tariot *et al.*, 2000; Reisberg *et al.*, 2003; Bullock *et al.*, 2005). However, there is ongoing debate as to the clinical relevance of the reported outcomes in relation to the cost of the drugs and the prevalence of the disease. The debate is fuelled by the fact that outcomes for registration of the drugs were based on tests of cognition and global assessments that do little to capture changes in behaviour which are key symptoms of the

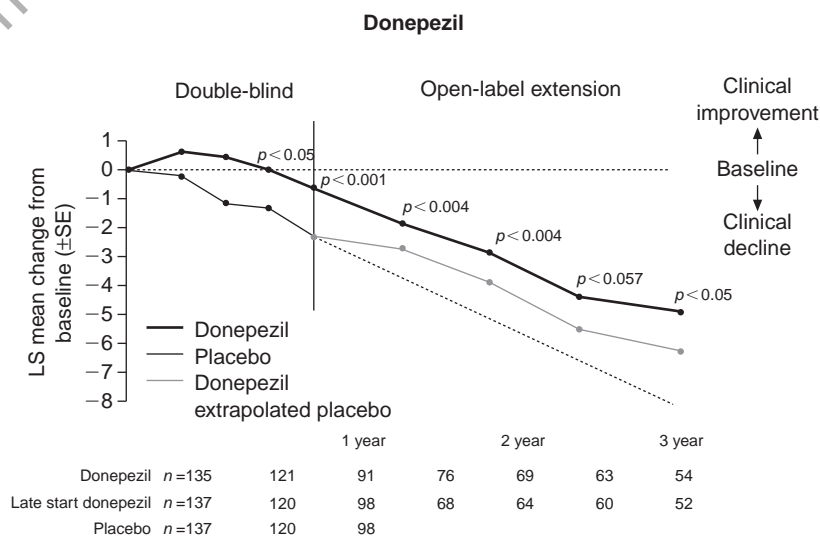
disease and the enhanced quality of life for the patients and intimate carers that have been reported. These drugs are symptomatic treatments and AD is a chronic neurodegenerative disease with progressive deterioration. Evaluation of any symptomatic benefit therefore needs a comparison with the position of an untreated patient, not with that of the patient's own baseline. The expense of these drugs has led many funding agencies to approve their use contingent on a monitoring process unprecedented in other common diseases and based on improvements against baseline. There is no evidence to suggest that a drug which has an effect in AD will not have an effect at all stages of the disease. What is clear is that when the effects are small they will be more apparent in trials when the crude tests we use are most sensitive, when floor and ceiling effects are less and this is in the moderate stages of the illness (Feldman *et al.* 2001). The effects of the treatments do persist for some years in open label naturalistic studies and have been demonstrated for 1 year in placebo-controlled trials (Winblad *et al.*, 2001; Doraiswamy *et al.*, 2002; Geldmacher, 2003). Longer placebo-controlled trials will not have been undertaken for ethical reasons. It is likely that the current drugs will continue to have a place in AD treatment but will be part of a therapy which will include drugs affecting the underlying disease processes and other symptomatic treatments.

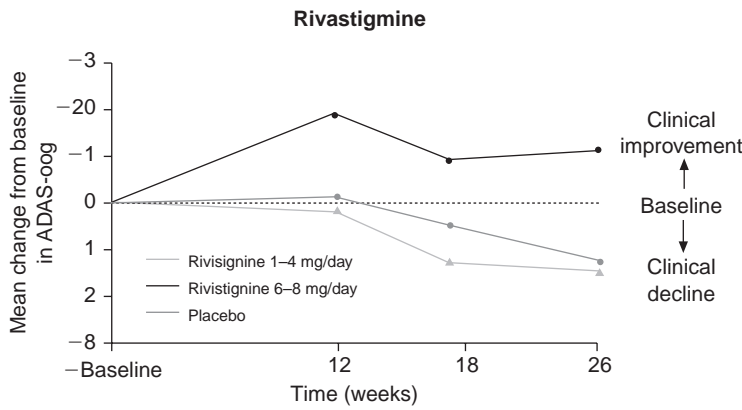
#### Memantine

Memantine, an NMDA receptor antagonist has been licensed for the treatment of severe dementia (and more recently this has been extended to include moderate dementia). Key studies (Winblad and Porfius, 1999; Reisberg *et al.*, 2003, Tariot *et al.*, 2004) have confirmed effectiveness over a range of outcome measures.

The Cochrane Collaboration ([www.cochrane.org/reviews](http://www.cochrane.org/reviews)) contains information on a number of interventions for dementia. For example, its latest release confirms evidence for the efficacy for the cholinesterase inhibitors and memantine, notes some evidence

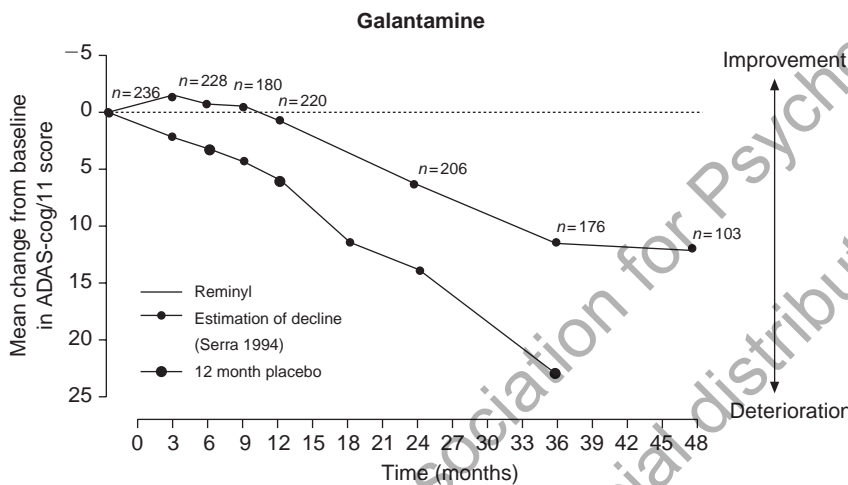
**Figure 1** Effect of Donepezil for Alzheimer's disease. Source: Winblad *et al.* 16th Congress, 20-24 September, 2003, Prague, Czech Republic.





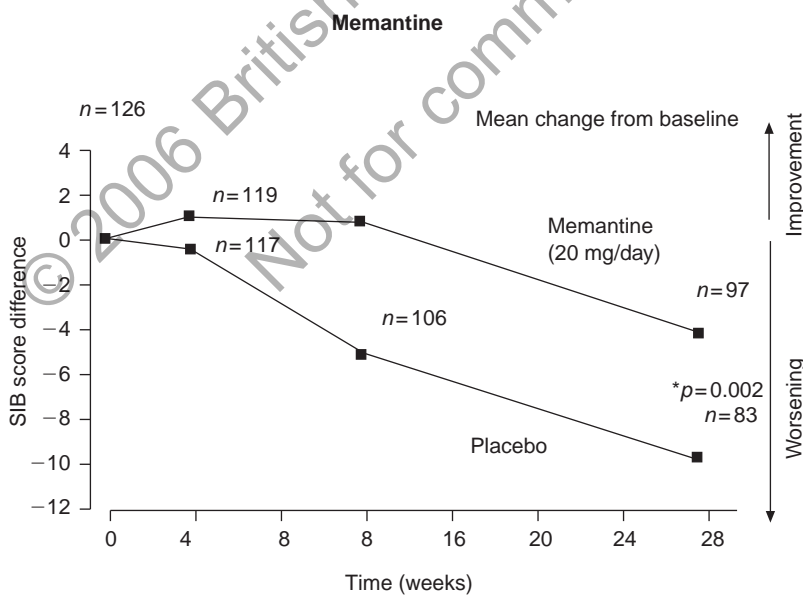
**Figure 2** Effect of Rivastigmine for Alzheimer's disease. Adapted from Rösler et al., 1999.

\* $p < 0.05$  versus placebo



**Figure 3** Effect of Galantamine for Alzheimer's disease

Open-label 12 month extension of two double-blind studies with open-label extension in patients with medium-to-moderate AD



**Figure 4** Effect of Memantine for Alzheimer's disease. Source: Reisberg et al., 2003.

for the efficacy of *gingko biloba*, notes the conflicting evidence for the benefit of vitamin E and shows no evidence for the efficacy of folic acid (with or without vitamin B<sub>12</sub>): no evidence for ibuprofen or cloquinol for the treatment of dementia or for the role of statins in the prevention of dementia.

The UK National Institute for Clinical Excellence (NICE) issued draft guidance in 2005 expressing the view that anti-dementia drugs should not be reimbursed on the National Health Service. As a result of a furore from patient groups, industry and professionals, NICE reconsidered this decision and in January 2006 the revision suggested that the cholinesterase inhibitors should be available on the NHS (but only for the treatment of people with moderate AD defined as a MMSE score of between ten and 20) and that memantine should not be reimbursed. If accepted, this further consultation draft guidance puts to great disadvantage people with mild stages of illness and does not take into account the variability in scores which can be obtained on the MMSE as well as those situations where the score may not be reliable (e.g. in the presence of sensory impairments, medical comorbidities and cultural factors). It also leaves one group of patients (those with severe dementia) without a treatment option.

## Comparative trials

A number of comparator trials have been undertaken mostly of short duration and open-label nature and have failed consistently to demonstrate any significant differences in efficacy between the drugs (Wilcock *et al.*, 2003; Wilkinson *et al.*, 2003; Jones *et al.*, 2003). The major differences that are found are in the frequency and type of adverse events.

### Cholinesterase inhibitors – comparative Studies

- Donepezil vs rivastigmine – Wilkinson *et al.*, 2002
  - No difference in efficacy marked difference in tolerability and ease of use in favour of donepezil
  - Criticised short duration (12 weeks) and using SPC titration
- Donepezil vs galantamine – Jones *et al.*, 2004
  - Advantage for donepezil on cognition and ADL
  - Criticized for short duration (12 weeks) and influence of titration
- Galantamine vs donepezil – Wilcock *et al.*, 2003
  - moderate AD MMSE 9–18 ‘blinded rater’ 52 week study
  - no difference on primary or secondary outcomes
- Rivastigmine vs donepezil – Bullock *et al.*, 2005
  - 2 yr RCT, *n* = 998, MMSE 10–20, very slow titration
  - No difference on primary outcome – SIB
  - twice dropouts on Riv in titration phase 48% vs 37% overall

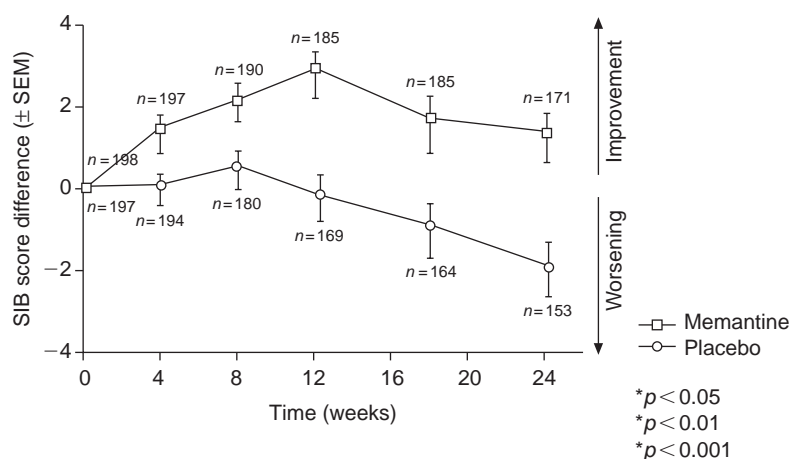
## Switching and combination therapy

The rationale for switching cholinesterase inhibitors among the three available drugs rests on their different chemical classes and pharmacological properties. The reasons for switching are twofold: poor tolerability and/or lack of perceived efficacy. There are few studies, and none of switching to donepezil. In case of poor tolerability of donepezil, rivastigmine may be tolerated (Bullock and Connolly, 2002; Auriacombe *et al.*, 2002). A switch without washout of the previous drug is recommended mainly on theoretical grounds for galantamine (Maelicke, 2001; Wilkinson and Howe, 2005) and absence of side effects in two retrospective studies of switching from donepezil or rivastigmine to galantamine (Edwards *et al.*, 2004a) and donepezil to rivastigmine (Sadowsky *et al.*, 2005). There is one case report of a fatal adverse event during transition from donepezil to rivastigmine (Taylor *et al.*, 2002).

Efficacy of the switch has been evaluated in two published open-label studies: a retrospective study of 40 patients showing that half of those switching due to lack of efficacy benefited from the switch, although this benefit was not clearly defined (Bullock and Connolly, 2002). In another study, out of 304 patients experiencing lack of efficacy with donepezil, 167 (55%) were improved or stabilized after 6 months rivastigmine on a global measure and MMSE (Auriacombe *et al.*, 2002). A prospective study of 202 AD patients has evaluated the switch from donepezil or galantamine to rivastigmine over a 16 week period, with 93 patients being stabilized (17.9%) or improved (28.4%) on MMSE scores.

Trials using combination therapy with cholinesterase inhibitors are rare. A retrospective chart review yielding 56 subjects out of 130 screened studied vitamin E in combination with donepezil, as compared to an historical control group of untreated patients from the CERAD database, and showed that patients treated with combination therapy declined over 1 year at a significantly lower rate (no control group with either donepezil or vitamin E alone) (Klatte *et al.*, 2003). One randomized controlled study (Tariot *et al.*, 2004) explored the addition of memantine or placebo to patients stable on donepezil in severe AD. This study showed a better outcome in the memantine group than in the placebo group after 24 weeks for measures of cognition (Severe Impairment Battery), function (ADCS-ADL), neuropsychiatric symptoms (NPI) and global measure of change (CIBIC-Plus), with good tolerability. This study did not include arms with memantine alone or an increased dose of donepezil and so it is uncertain whether the advantage was additive or synergistic. Finally, those patients who were switched from donepezil or galantamine to rivastigmine and did not respond were added memantine (open-label): out of 86 patients receiving additional memantine for 12 weeks, 67 (77.9%) had a stable or better MMSE score.

The cost of the two classes of currently licensed treatments has prevented the widespread use of them in combination or exploration of doses higher than are currently approved.



**Figure 5** Addition of memantine to donepezil. Source: Tariot *et al.*, 2004.

**Table 4** Summary box

Intervention	Level of evidence	Recommendations
Cholinesterase inhibitors and memantine	There is <b>type 1a</b> evidence for the efficacy of cholinesterase inhibitors in the treatment for mild to moderate AD and <b>type 1a</b> for memantine in more severe illness	A
Switching between cholinesterase inhibitors or adding memantine	There is <b>type 2b</b> evidence to support the switching of one cholinesterase to another if the first is not tolerated or ineffective. There is <b>type 1b</b> evidence for adding memantine to a cholinesterase inhibitor	A

## Drugs for Dementia with Lewy Bodies (DLB)

The pharmacological management of DLB can be one of the most challenging issues facing neurologists, psychiatrists, geriatricians, primary care physicians or others caring for older people. Prescribing considerations for patients with Parkinson's disease and dementia (PDD) are broadly similar. Polypharmacy is the norm with multiple pharmacological treatment targets including motor parkinsonism, cognitive failure, psychiatric symptoms and autonomic dysfunction. The positive effects of cholinesterase inhibitors seen in many DLB patients contrast with the severe, sometimes fatal, neuroleptic sensitivity reactions that are seen in up to 50% of patients exposed to such agents, including the atypical antipsychotics (McKeith *et al.*, 1992; Aarsland *et al.*, 2005). There is an intermediate responsiveness to anti-parkinsonian agents. (Bonelli *et al.*, 2004; Molloy *et al.*, 2005) Since there are no treatments currently licensed for DLB, all prescribing to this group of patients is essentially 'off-licence'. In addition to the medico-legal and liability issues that this can pose for prescribers, health-care providers may be reluctant to reimburse drug costs for DLB patients.

Levodopa monotherapy is the preferred option in DLB with response rates of around 50% (Bonelli *et al.*, 2004, Molloy *et al.*, 2005). Medication should generally be introduced at low doses and increased slowly to the least dose required to minimize dis-

ability. Patients and carers will usually indicate when they feel that the lower acceptable limit of anti-parkinsonian treatment has been reached. Other anti-parkinsonian medications including selegiline, amantadine, COMT inhibitors anticholinergics and dopamine agonists are contraindicated in view of concerns about inducing confusion and psychosis.

Placebo controlled RCTs of rivastigmine have shown benefits in DLB (McKeith *et al.*, 2000) and PDD in addition to which there is some short-term (Reading *et al.*, 2001, Maclean LE, 2001) and long-term open-label data (Grace *et al.*, 2001). With donepezil there is a double-blind cross-over study in PDD (Aarsland *et al.*, 2002) and a series of open label studies in DLB (Shea *et al.*, 1998, Kaufer *et al.*, 1998), including one reporting a rebound worsening of neuro-psychiatric symptoms, when treatment was stopped abruptly (Minett *et al.*, 2003). Although reinstatement of treatment may reverse such deterioration, it is recommended that DLB patients who are assessed as responding to anticholinesterase inhibitors are maintained on treatment long term. Attempts at switching from one anticholinesterase inhibitors to another were similarly associated with clinically significant withdrawal effects and the authors did not recommend this treatment strategy (Bhanji and Gauthier, 2003). With galantamine there is as yet only preliminary open-label data (Aarsland *et al.*, 2003; Edwards *et al.*, 2004b). Apathy, anxiety, impaired attention, hallucinations, delusions, sleep disturbance, and cognitive changes are the most fre-

quently cited treatment-responsive symptoms. Improvements are generally reported as greater than those achieved in AD. (Samuel *et al.*, 2000).

Taken overall, the effects of the three available anti-cholinesterase inhibitors appear similar, with doses in the same range as used in AD. Parkinsonian signs do not generally worsen on treatment. Predominant adverse effects are cholinergic in nature (nausea, vomiting, anorexia and somnolence) and are generally rated as mild or moderate. Hypersalivation, rhinorrhoea and lacrimation were recorded in approximately 15% of DLB and PDD patients treated with donepezil (Thomas *et al.*, 2005) and postural hypotension, falls and syncope are possibly also increased. This is consistent with the pre-existing autonomic dysfunction in DLB and such symptoms are likely to occur with all pro-cholinergic agents.

Rivastigmine and donepezil have also been used in dementia associated with Parkinson's disease (Emre *et al.*, 2004, Thomas *et al.*, 2005) and have showed positive effects on cognition and global functioning of a similar magnitude to Alzheimer's disease. Case reports of the use of memantine in DLB are still very limited and some but not all suggest that its symptomatic effects may be variable with potential to worsen delusions and hallucinations (e.g. Sabbagh *et al.*, 2005, Ridha *et al.*, 2005). At the present time SSRI and SNRIs are probably the preferred pharmacological treatments for depression. Tricyclic antidepressants and those with anticholinergic properties should be avoided. REM sleep behaviour disorder can be treated with clonazepam 0.25 mg at bedtime, titrated slowly monitoring for both efficacy and side effects (McKeith *et al.*, 2005). Anticholinesterase inhibitors may also be helpful for disturbed sleep.

## Drugs for vascular dementia

Treatment of VaD has encompassed many different pharmacological strategies over the years, mostly with disappointing results. The advent of cholinesterase inhibitors for probable AD and

reports in some studies of cholinergic deficits in the brain in some people with vascular dementia, has stimulated trials to evaluate cholinesterase inhibitors and memantine in vascular dementia.

There have been two well-conducted 6 month randomized controlled trials of donepezil in mild to moderate VaD (Black *et al.*, 2003; Wilkinson *et al.*, 2003), using outcome measures borrowed from the AD trials. In general, the outcome of these relatively short-term trials suggested that donepezil was of some benefit in terms of cognitive improvement, but effects on global outcome and ADL were mixed, with no clear dose response evident (Malouf and Birks, 2005). There has been one published RCT of galantamine in VaD, though results are difficult to interpret as the study involved not just patients with VaD, but also mixed dementia, i.e. a combination of both vascular and Alzheimer's dementias. Overall, galantamine was of benefit, but it was difficult to interpret largely non-significant findings in the 'pure' vascular dementia subgroup because outcome measure were the study was not powered at this level (Erkinjuntti *et al.*, 2002; Erkinjuntti *et al.*, 2004).

Rivastigmine has been the subject of small-scale and open-label studies, e.g. in sub-cortical vascular dementia (Moretti *et al.*, 2001), but as yet there is no conclusive data from adequately conducted randomized controlled trials (Craig and Birks, 2005), though such trials (VANTAGE) are ongoing.

Memantine is an NMDA receptor antagonist which has also been evaluated in vascular dementia in two randomized controlled trials of 6 months' duration (Orgogozo *et al.*, 2002; Wilcock *et al.*, 2002). Clinical evaluation of cognition showed some benefits, but this was difficult to discern at a general clinical level at 6 months (Sastre *et al.*, 2005). However, *post hoc* analysis suggested that there is a possibility that memantine may be more effective in people with small vessel disease (Wilcock *et al.*, 2000a).

In summary, there is evidence suggesting that at least one cholinesterase inhibitor may have significant cognitive benefit to patients with mild to moderate vascular dementia, albeit so far only with evidence accumulated over 6 months. Memantine may also be helpful in the context of improving cognition. However,

**Table 5** Summary box

Intervention	Level of evidence	Recommendations
Treatment with cholinesterase inhibitor	There is <b>type 1b</b> evidence to support treatment with cholinesterase inhibitors in Lewy body dementia, both dementia with Lewy bodies and Parkinson's disease dementia (including for neuropsychiatric symptoms)	A

**Table 6** Summary box

Intervention	Level of evidence	Recommendations
Treatment with cholinesterase drugs and memantine	There is <b>type 1b</b> evidence to support the use of cholinesterase drugs and memantine in the treatment of cognitive impairment in vascular dementia, though effect sizes are small and may not be clinically significant	A

effects appear less consistent in studies to date than for AD and it is unclear whether the clinical effect size is sufficient to justify routine use of these treatments in vascular dementia.

*Ginkgo biloba* extract is derived from the dried leaves of the ginkgo tree (*Ginkgo biloba* L.; more commonly known as the 'maidenhair' tree), the last remaining member of the ginkgoaceae family. This tree has survived unchanged in China for more than 200 million years and there is a history of its medicinal use for millennia (Foster and Tyler, 1999). It is currently a popular drug in Europe for circulatory conditions (Schilcher, 1988) and the evidence is now growing for its use in the symptomatic treatment of dementia (Ernst and Pittler, 1999; Birks and Grimley Evans, 2005). There is considerable heterogeneity between the *Ginkgo* studies and methodological problems abound. Many are very short (12 weeks or less), have small numbers, poor internal validity (no imputation, unclear concealment), and use idiosyncratic outcome measures.

The most recent Cochrane Review (Birks and Grimley Evans, 2005), which was last updated in August 2004, identified 33 randomized placebo-controlled trials. However, all of these studies had weaknesses and most were of very poor quality. Diagnosis is often unclear (many reports are from before more standardized diagnoses) both in terms of criteria and means of assessment and it is doubtful if most of the studies included only dementia subjects at all. Adequacy of randomization and blinding is also doubtful and a large number of early studies (from Germany mainly) produced strikingly positive findings and none were negative (making publication bias in such small trials highly likely). Dosage of *Ginkgo* varied, other medication was often not taken into account and duration of treatment was usually short for dementia studies (that is, less than 6 months). Birks and Grimley Evans were not able to undertake an ITT analysis and report on a completers analysis a range of favourable cognitive and non-cognitive outcomes for *Ginkgo*. However in one study (Le Bars *et al.*, 1997), subjects were removed or allowed to withdraw for unclear reasons; and on contacting the lead author Birks and Grimley

Evans were told they were removed for compassionate reasons to be given *Ginkgo*. The Cochrane conclusion was that a large well-designed study using ITT analysis is needed.

## Vitamin B<sub>12</sub>/folate

An association exists between cognitive impairment and deficiency of vitamin B<sub>12</sub> and/or folate. Sensitive diagnostic tests, including assays of the related metabolites methylmalonic acid and homocysteine, allow detection of early, subtle deficiency. Homocysteine has attracted particular interest. It is an intermediary amino acid in methionine metabolism and its elimination is B<sub>12</sub>, folate and B<sub>6</sub> dependent, hence its blood levels increase with deficiency of these vitamins.

Elevated plasma homocysteine is associated with an increased risk of vascular disease and vascular dementia (Homocysteine Studies Collaboration, 2002). There are also widely confirmed reports of elevated blood levels in patients with AD and MCI (McCaddon *et al.*, 1998; Clarke *et al.*, 1998; Lehmann *et al.*, 1999). Homocysteine levels predict cognitive decline in healthy elderly (McCaddon *et al.* 2001), and hyperhomocysteinaemia is an independent risk factor for the development of dementia, including AD.

Two systematic reviews identified four intervention trials of vitamin B<sub>12</sub> with folate, and two trials of B<sub>12</sub> alone (Malouf *et al.*, 2003). The reviewers concluded there was no benefit from either intervention compared with placebo on any measures of cognition for healthy or cognitively impaired or demented people. However, these trials were all underpowered 'pilot' studies ( $n=11-139$ ) of short duration (1 to 5 months). Four larger studies are now underway to assess the effects of vitamins in slowing progression in Alzheimer's disease, stroke prevention and two studies in MCI. One study from the Netherlands is assessing the effects of folic acid or placebo in people with hyperhomocysteinaemia and the results on cognitive function are very encouraging.

**Table 7** Summary box

Intervention	Level of evidence	Recommendations
<i>Ginkgo biloba</i>	There is <b>type 1b</b> for a modest effect of <i>Ginkgo</i> in the treatment of cognitive impairment and dementia, though effect sizes are small and may not be clinically significant	B

**Table 8** Summary box

Intervention	Level of evidence	Recommendations
B <sub>12</sub> and folate in AD	There is currently no evidence to suggest that vitamin B12 and folate are effective in the routine treatment of Alzheimer's disease but trials are ongoing which will provide <b>1a</b> evidence	D

## Oestrogens

Systematic reviews and meta-analyses of cohort and case-control studies have reported oestrogen use to be associated with a reduction in the risk of developing AD of 29% to 34%, (LeBlanc *et al.*, 2001; Nelson *et al.*, 2002). However, randomized trials have failed to find any clinically meaningful evidence of benefit in treating patients with pre-existing mild-moderate AD with oestrogen (Henderson *et al.*, 2000; Mulnard *et al.*, 2000; Wang *et al.*, 2000). At some time points on some tests significant differences were identified, although these were on occasion in favour of placebo. Consequently the Cochrane Review (of five trials including 210 women with AD) concluded that hormone replacement therapy and oestrogen replacement therapy (HRT/ERT) is not indicated in AD and only a transient benefit of oestrogen on memory may occur with oestrogen treatment (Hogervorst *et al.*, 2005).

A primary prevention trial, the Women's Health Initiative Memory Study, a placebo-controlled, double-blind, randomized intervention study, examined the possible benefit of HRT/ERT in reducing the frequency of or time of onset of dementia in postmenopausal women (participants were 65–79 at entry). Adverse outcomes led to both arms being terminated early (treatment was linked to increased stroke, coronary heart disease, venous thromboembolism and breast carcinoma). The use of unopposed oestrogen ( $n=1464$  vs  $n=1483$  on placebo) for about 7 years was associated with a non-significant increased risk of dementia, hazard ratio 1.49 (95%CI 0.83–2.66) (Shumaker *et al.*, 2004), and treatment with combined oestrogen and progestin for about 4 years ( $n=2229$  vs 2303 on placebo) led to a doubling of dementia risk, hazard ratio 2.05 (95%CI 1.21–3.48). Combining these two

groups, there was a significant increase in dementia in women taking HRT, hazard ratio 1.76 (95%CI 1.19–2.60) (Shumaker *et al.*, 2004).

## Anti-inflammatory drugs

The finding of inflammatory changes at autopsy and on brain imaging, with the knowledge that inflammation can cause and exacerbate neuronal loss, had led the inflammatory hypothesis of Alzheimer's disease. Several, though not all, case control studies suggested that use of anti-inflammatory drugs was associated with decreased risk of dementia and AD. Prospective studies have generally supported this view (Szekely *et al.*, 2004). However, several randomized controlled trials of a variety of anti-inflammatory drugs including chloroquine, prednisolone, ibuprofen, naproxen and COX inhibitors (Aisen *et al.*, 2003; Reines *et al.*, 2004) in established AD have been negative (Imbimbo 2004). All anti-inflammatory drugs can have significant and potentially dangerous side effects. They have not, to date, been shown to be effective in AD and their role in prevention remains to be established.

## Antioxidants

Oxidative stress may be important in the development of dementia and occurs when the cellular production of reactive oxygen species overwhelms the natural defence of antioxidants leading to cell death through apoptosis and necrosis. Randomized inter-

**Table 9** Summary box

Intervention	Level of evidence	Recommendations
Oestrogens	There is conflicting evidence over the use of oestrogens in dementia with <b>type 2a</b> evidence of a protective effect and <b>type 1b</b> of a harmful effect. Until further evidence is available, HRT should not be prescribed for the purpose of preventing or treating dementia.	B

**Table 10** Summary box

Intervention	Level of evidence	Recommendations
Anti-inflammatory drugs in AD	There is <b>type 1a</b> evidence that a variety of anti-inflammatory drugs do not produce benefit in Alzheimer's disease	A

**Table 11** Summary box

Intervention	Level of evidence	Recommendations
Antioxidants	There is <b>type 1b</b> evidence of a delay in the progression of Alzheimer's disease with high dose vitamin E alone, but not when combined with selegiline	B

vention studies have examined only vitamin E and *Gingko biloba*. The only randomized trial of vitamin E supplementation in AD examined survival to predetermined end points (death, institutionalization, severe dementia or loss of two or three basic activities of daily living) over 2 years (84 on placebo, 85 on vitamin E) (Sano *et al.*, 1997). After adjustment for baseline MMSE (but not before) vitamin E delayed time to end point by 230 days (risk ratio 0.47,  $p=0.001$ ); mean MMSE scores were 11.3 in the vitamin E group and 13.3 in the placebo group. However, there were no differences in a range of secondary outcome measures including ADAS-Cog and MMSE, while a combined vitamin E/selegiline group failed to show any benefit.

A recent randomized trial compared progression to possible or probable AD in subjects with amnesic mild cognitive impairment (Petersen *et al.*, 2005). Subjects received vitamin E (2000 IU), donepezil (10 mg) or placebo for 3 years. All additionally received multivitamins, containing 15 IU of vitamin E. There was no difference between vitamin E ( $n=257$ ) and placebo ( $n=259$ ) groups in progression (hazard ratio 1.02 (95%CI 0.74–1.41) or in any of a large number of secondary measures, including ADAS-Cog and MMSE.

## Metal protein attenuating compounds

Clioquinol is the first in a class of drugs called metal protein attenuating compounds (MPACs). These low molecular weight, bio-available drugs are known to affect copper and zinc levels through buffering i.e. reducing levels where concentrations are high (e.g. neuronal synapses) and increasing levels where levels are unusually low. The most compelling evidence for efficacy comes from an Australian 36 week double-blind RCT, where, in a *post hoc* analysis, patients with more severe disease showed significantly less cognitive decline than controls. It was also demonstrated that in milder patients, clioquinol treatment stopped the elevation of plasma amyloid normally observed with worsening disease in the early stages (Ritchie, 2001). This class of drugs affects metal–protein interactions at levels that do not cause systemic effects through metal ion depletion, though in previous studies of clioquinol worrying optic side effects have been found. Further studies of newer agents, free of such potential side effects, are required.

## Statins and dementia

The 3-hydroxy-3-methyl-glutaryl-enzyme A reductase inhibitors (statins) effectively reduce serum cholesterol concentrations.

Large clinical trials demonstrate statins have a key role in the prevention of vascular events as secondary prevention following myocardial infarction and ischaemic stroke (Collins *et al.*, 2002) and in primary prevention of MI and stroke in high-risk patients with elevated blood pressure (Sever *et al.*, 2003). Several mechanisms have been suggested through which cholesterol lowering might modulate AD including inhibition of amyloid production or by increasing amyloid precursor protein trafficking through non-amyloidogenic pathways. Other non-cholesterol lowering mechanisms of statins have been suggested including neuroprotective, antioxidative properties and inhibition of butyryl cholinesterase (Darvesh *et al.*, 2004).

Statins differ in their lipophilicity with lipophilic statins (simvastatin) crossing the blood–brain barrier more effectively than hydrophilic statins (pravastatin, atorvastatin). Cholesterol enriched diet feeding of New Zealand White rabbit increases brain  $\beta$  amyloid levels with significant reductions after removing cholesterol from the diet (Sparks *et al.*, 1994). However the role of cholesterol in AD pathogenesis is likely to be complex. Increased cellular cholesterol concentrations may increase  $\beta$ -amyloid production but oligomeric  $\beta$ -amyloid may decrease cellular cholesterol and low brain cholesterol concentrations may promote neurodegeneration. The extent to which lowering peripheral serum cholesterol affects brain cholesterol concentrations is unclear (Kivipelto *et al.*, 2005).

A number of cohort studies have suggested elevated cholesterol is associated with an increased risk of developing dementia. Elevated cholesterol levels in midlife increase later risk of AD (Kivipelto *et al.*, 2001). In a retrospective cohort study smoking, hypertension, high cholesterol and diabetes at midlife were each associated with a 20–40% increase in risk of developing dementia (Whitmer *et al.*, 2005). In a cross-sectional analysis of three hospital databases to explore the relation between statin therapy and AD, statin use was associated with a lower prevalence of AD (Wolozin *et al.*, 2000). In a nested case-control study using the General Practice Research Database the adjusted relative risk of dementia among patients receiving statin therapy was 0.29 (Jick *et al.*, 2000). The considerable reduction in risk associated with statins observed in such studies could be caused by individuals receiving statins having other characteristics associated with a lower risk of dementia i.e. bias by indication. This bias seems more likely in dementia studies as other evidence suggests that more affluent individuals with higher educational achievement are more likely to request and receive statin therapy. In support of this a community cohort study found that every use of statins was not associated with the risk of dementia but current use of statins was associated with a reduced hazard ratio of 0.69 (Rea *et al.*, 2005). A

**Table 12** Summary box

Intervention	Level of evidence	Recommendations
Metal protein attenuating compounds	There is preliminary <b>type 1b</b> evidence of the effect in Alzheimer's disease. These agents should not be prescribed until more data on safety and efficacy are available	B

recent prospective cohort study examined the prevalence and incidence of dementia over 5 years in 5029 older subjects found statin use was inversely associated with dementia (OR 0.44) but that statin use in patients without dementia was not associated with a subsequent reduced incidence of dementia (Zandi *et al.*, 2005).

Two large randomized placebo-controlled trials (Heart Protection Study and PROSPER) have examined the effects of statins on cognitive decline and dementia as secondary study end points (Shepherd *et al.*, 2002). HPS enrolled 20 536 subjects aged 40–80 years with high risk of coronary heart disease, treated hypertension, diabetes mellitus, or occlusive non-coronary artery disease to simvastatin 40 mg/day or placebo for 5 years and reported a 24% relative risk reduction in cardiovascular events. Using an end of study telephone administered assessment of cognitive function no difference in proportions of participants with cognitive impairment was found with similar numbers reported to have developed dementia in each group (0.3%). PROSPER studied the effects of 40 mg/day pravastatin for 3 years in 5804 subjects aged 70–84 years with a history of, or risk factors for, vascular disease and reported no significant effect on cognitive function. Whilst these studies indicate that the benefits of statins in preventing dementia remain unproven, a substantial proportion of UK clinicians favour the use of statins in primary and secondary prevention of vascular cognitive impairment (Suribhatla *et al.*, 2005).

Preliminary results from a pilot proof of concept 1 year randomized placebo-controlled trial of atorvastatin 80 mg daily in 67 patients with mild to moderate AD (MMSE 12–28) were recently published (Sparks *et al.*, 2005). ADAS-Cog scores in the atorvastatin population were 3.5 points superior to the placebo group at 6 months ( $p < 0.003$ ) with borderline significance at 12 months ( $p = 0.55$ ). An earlier 26-week randomized placebo-controlled study in 44 patients with AD found a small reduction in MMSE score in patients given simvastatin (80 mg/day) (Simons *et al.*, 2002). These results are promising but larger longer duration clinical trials are needed to establish whether statin therapy is of benefit in the treatment of AD. Two randomized placebo-controlled studies of 18 months duration are examining the effects of statins on cognitive function in AD patients: CLASP examining simvastatin in 400 patients and LEAD examining atorvastatin in 600 patients.

## Mild cognitive impairment

Mild cognitive impairment (MCI) appears to be a stage where people have the early neuropathology of a dementia, particularly AD, but have not yet reached the clinical criteria. Transition to dementia is frequent, 10–15% per year (Grundman *et al.*, 2002). There remains controversy over whether MCI represents a separate diagnostic entity, a stage of very early dementia or a part of normal ageing. Goals of MCI treatment would be symptomatic improvement but, more particularly, delay or prevention of subsequent cognitive decline and dementia. Vitamin E and cholinesterase inhibitors have been investigated in well-conducted RCTs in MCI, though to date all proved negative, as defined by their primary outcomes. A significantly increased mortality in two unpublished studies of galantamine in those given active medication remains to be explained.

## Clinical practice with anti-dementia drugs – a physician's perspective

Diagnosing and managing dementia is a complex task that needs a systematic approach. The key element of geriatric medicine is the assessment of older people who usually have multiple problems. The four giants of geriatrics – immobility, instability, incontinence

Sponsor	Agent	Duration	No.	End point
ADCS	Don/VitE*	3 yrs	769	AD
Cortex	Ampakine	4 weeks	160	Symptoms
Merck	Rofecoxib	2–3 yrs	1200	AD
Novartis	Rivastigmine	3–4 yrs	1018	AD
Janssen	Galantamine	2 yrs	780	Symptoms
Pfizer	Donepezil	24 weeks	269	Symptoms
UCB	Piracetam	52 weeks	200	Symptoms

**Figure 6** Clinical trials in Mild Cognitive Impairment. Source: Petersen *et al.*, 2005.

**Table 13** Summary box

Intervention	Level of evidence	Recommendations
Statins	There is <b>type 1a</b> evidence of no effect of statins in the prevention of AD	A

**Table 14** Summary box

Intervention	Level of evidence	Recommendations
Mild cognitive impairment	There is <b>type 1b</b> evidence that cholinesterase inhibitors and vitamin E are <i>not</i> effective in reducing the risk of developing Alzheimer's disease	A

and intellectual problems – are common presenting features but geriatricians more commonly see acute intellectual problems (as delirium) and less commonly provide the main management of chronic intellectual problems (in the form of dementia). There are notable individual and national (for example, Sweden) exceptions to this and most of the early memory clinics in the UK were established by geriatricians. In the UK the main management of dementia is now carried out by old age psychiatrists. In many countries, neurologists provide the main dementia service but in the UK this would be rare, although younger patients with dementia are often initially referred to neurologists (particularly if hereditary dementias or conditions like Creutzfeldt-Jakob disease are suspected). What is clear is that good practice requires close working relationships between all relevant specialities to ensure that people with dementia and their families receive as seamless and effective a service as possible.

A physician or geriatrician may play a particularly important role in managing co-morbidities in dementia. This is especially true in vascular or mixed dementia where the brain is merely one of the targets of vascular disease but it appears to be increasingly important in Alzheimer's disease as well. Risk factors include diabetes, hypertension and cholesterol levels. Parkinson's disease is another common condition of older people that itself may cause or complicate dementia. Falls – with the risk of osteoporotic fractures – are especially likely in dementia with Lewy bodies but may also occur in other types of dementia. In dementia it is important not to assume that every problem that occurs is due to dementia (Jones, 2004). Reviewing, reducing or stopping unnecessary or potentially toxic drugs, treating depression or reducing excessive alcohol consumption can all be helpful.

A geriatrician may also need to decide whether anti-dementia drug treatment could significantly affect co-existing physical disease. Whilst active bleeding from an ulcer is an absolute contraindication to cholinesterase inhibitors, there are several relative contraindications. Care is necessary in the presence of significant bradycardia, sick sinus syndrome and significant atrio-ventricular conduction disorders, and in the presence of obstructive airways disease; in theory, the drugs can also worsen urinary incontinence and there is a risk in untreated closed-angle glaucoma, which is uncommon.

In addition to the efficacy data from clinical trials, additional benefits have been noted in more general clinical use. These include improvements in attention and initiative as well as behavioural improvements such as a reduction in apathy and agitation and an improvement in mood (Rockwood *et al.*, 2004). Some 61% of patients remain on anticholinesterase inhibitors after 1 year and 42% after 2y (Jones, 2005). The mean duration of therapy ( $n=188$ ) was 1.5y. In addition, where a decision was made to stop treatment, the drug needed to be restarted in 30–40% of cases, usually as a result of clinical deterioration (Jones, 2005). Similarly for memantine, the only drug currently licensed for severe AD, improvements in language and behaviour have been noted together with an improvement in performance of simple tasks such as washing and dressing.

Physicians can play an important role in the management and treatment of dementia ranging from the careful assessment of a

patient, particularly in the presence of multiple pathologies (and including a thorough review of medication); the routine treatment of people with AD with anticholinesterase inhibitors and/or memantine; and the assessment of those people where anti-dementia drug treatment might significantly worsen other medical conditions.

### **Clinical practice with anti-dementia drugs – an old age psychiatrist's perspective**

When donepezil was first licensed in 1997, Manchester had an established Memory Clinic and a prepared shared-care protocol for the use of cholinesterase inhibitors (Russell *et al.*, 1999). The protocol had been agreed before the drug was licensed so it presented a solution to the Health Authority where managers with a responsibility for medicines and guidelines were uncertain about both the costs of introducing medicines and how to optimize prescribing. This approach made it possible to introduce all other licensed anti-dementia drugs through a simple process of modification to the protocol and has also been a good model for the introduction of other medicines in Manchester.

The implementation of a prescribing protocol for anti-dementia drugs has allowed equity of access to such treatment. There is concern about access for people for black and ethnic minority groups and a recent supra-district audit supported by Greater Manchester Strategic Health Authority (Purandare *et al.*, 2005) found that, where ethnic group was recorded, less than 1% of those receiving anti-dementia medication were from black and minority ethnic groups.

The successful introduction of anti-dementia drugs has been accompanied by other changes in the practice, some of these brought about by the opportunity to treat people at an earlier stage of their illness. These changes have included the development of a post-diagnostic group (Page and Hope, 2005) and the introduction of supplementary prescribing (Page, *In press*; Department of Health, 2005). The use of these medicines are also promoted through local dementia and depression protocols.

### **Clinical practice with anti-dementia drugs – a general practitioner's perspective**

In England the National Service Framework for Older People is unequivocal in identifying early diagnosis of dementia as beneficial (Department of Health, 2001). Following this, the Audit Commission reiterated that a priority for services was to diagnose mental health problems in older people 'as early as possible' (Audit Commission, 2002).

The opportunities that early diagnosis provides include access to medical treatment with the cholinesterase inhibitors, and facilitating people with dementia and their relatives to come to terms with dementia and its prognosis, and planning for life changes. However, these opportunities are not perceived as being unequivocally good by some general practitioners, who remain sceptical about the benefits of early recognition and early intervention in dementia, and say so forcefully (Logan, 2005). This section

explores this scepticism, examining the arguments around medication effectiveness in the wider context of risk judgements about dementia diagnosis and management.

All medical interventions require a risk assessment of the benefits and hazards of treatment compared with inaction. Risk is managed with a socio-political context (Lupton, 1993) as well as with professional and care-giving domains (Manthorpe, 2003). Essentially risk involves uncertainty of outcome and this may be positive or negative. Combined with judgements of the outcome's importance are assessments of likelihood or probability. In all risk assessments, subjective perceptions or judgements are involved, overtly or otherwise (Cabinet Office, 2002). In dementia the use of medication is only one of a series of risk judgements that practitioners have to make, and there is much evidence that the wider risk assessments are experienced as problematic.

In the Audit Commission's survey of 8051 general practitioners in 73 areas in England, 60% agreed that an early diagnosis of dementia was important (Renshaw *et al.*, 2001). This figure is essentially the same as that from the Audit Commission's pilot data from 12 areas, collected in 1999, suggesting that a significant minority of general practitioners remain unconvinced about the benefits of early treatment of people with dementia (Audit Commission, 2002). Even after diagnosis has been made and disclosed (by specialists) general practitioners may be reluctant to prescribe these forms of medication (Iliffe and Wilcock, 2005).

A range of factors are likely to be important in impeding the recognition of and response to dementia in primary care, which have been discussed in reviews by De Lepeleire and Heyrman (1999), Iliffe *et al.* (2000) and van Hout *et al.* (2000). In summary we should note that:

- General practitioners consistently say that they feel inadequately trained to respond to the needs of people with dementia and their families (Alzheimer's Disease Society, 1995; Audit Commission, 2002; Downs *et al.*, 2000).
- Negative attitudes towards the diagnosis and assessment tasks in dementia are widespread (Boise *et al.*, 1999), with general practitioners being embarrassed or anxious about carrying out cognitive function tests (van Hout *et al.*, 2000).
- Practitioners who have most difficulty in making the diagnosis of dementia also have more problems in disclosing the diagnosis, particularly to the person with dementia (Cody *et al.*, 2002). Nevertheless general practitioners are being encouraged to undertake activities that they find particularly difficult, but are urgently needed, like providing education, offering psychological support for carers and mobilizing carer social support.
- Resistance to the potential for early recognition and early intervention in dementia amongst general practitioners also arises from fears of making diagnostic errors, and of precipitating depressive responses in people with dementia and in their carers (Iliffe and Manthorpe, 2004).

However, the overall pattern of practitioner behaviour towards dementia is changing, with the development and implementation of shared care protocols for medication management, reports of strong local working relationships between general practitioners

and specialists (Iliffe and Wilcock, 2005), and growing interest in early psychosocial intervention (Woods *et al.*, 2003).

## Prospects for prevention of dementia

The prevalence of dementia would be reduced by 50% if risk reduction strategies were successful in delaying the onset of dementia by 5 years (Jorm *et al.*, 1987). So far, results from trials of cholinesterase inhibitors (donepezil, galantamine and rivastigmine) in patients with mild cognitive impairment to prevent conversion to dementia have been negative. Hence, it is crucial to explore alternative strategies.

Epidemiological evidence has identified key strategies that may be used in prevention of dementia, both Alzheimer's disease and vascular dementia. The preventative strategies could be loosely divided into: treatment of vascular risk factors (hypertension, high cholesterol, diabetes, carotid atherosclerosis, heart disease and smoking); neuroprotection (lowering homocysteine, oxidative stress and inflammation); and increasing neuronal reserve (cognitive, physical and social activities).

Several large epidemiological studies have now established hypertension in midlife, both systolic and diastolic, as a risk factor for both Alzheimer's disease and vascular dementia in later life (Launer *et al.*, 2000; Murray *et al.*, 2002). The results from randomised controlled trials have been somewhat variable. Earlier trials did not identify any significant impact on cognition or incident dementia. A more recent Syst-Eur trial (Forette *et al.*, 2003) reported that nitrendipine (calcium channel blocker) reduced the risk of Alzheimer's disease by 50% over 2 years. The results of RCTs involving patients with multiple vascular risk factors in addition to hypertension have been more consistently encouraging. For example, the PROGRESS (2003) trial found a significant reduction of incident dementia in stroke patients treated with an angiotensin converting enzyme (ACE) inhibitor. The statistical power of these studies is limited by the low incident risk of dementia in the study populations. In all RCTs, incident dementia has been a secondary outcome, heart disease or stroke being the primary outcomes. The time lapse between the diagnosis of hypertension and onset of dementia can be over 15 years, and it is not known whether the protective effect of starting antihypertensives on incident dementia extends throughout this period. In this respect, it is interesting to note that blood pressure drops just before or at the onset of dementia. Epidemiological studies also suggest high cholesterol in midlife to be an independent risk factor for dementia (Kivipelto *et al.*, 2002) and use of lipid lowering drugs, specifically statins to reduce this risk (Etminan *et al.*, 2003). Unfortunately, the Heart Protection Study (2002) and the PROSPER (2003) study, did not find any positive effect on cognitive decline. Early results in MCI are not very encouraging. For other risk prevention strategies epidemiological evidence is strong but RCT evidence is lacking (see Purandare *et al.*, 2005).

Most intervention trials, currently in progress, focus on one or two risk factors and include cognition or dementia only as a secondary outcome. There is a need for RCTs which will target multiple risk factors in 'at risk' people with mild cognitive impairment

**Table 15** Summary box

Intervention	Level of evidence	Recommendations
Prevention of dementia	There is no evidence to support, at present, any intervention to prevent dementia	B

with incident dementia as a primary outcome. The sample size required for such trials could be reduced by better identification of pre-clinical dementia and surrogate markers for its progression.

## Health economics

The economics evidence base in relation to anti-dementia drugs is modest, both in quantity and certainly in quality. The earliest evidence, generated largely by the pharmaceutical industry, was based on decision models that aimed to mimic the care pathways (and their associated outcomes and costs) experienced by patients in the absence of adequate observational or trial-based data. Those models are easy to criticize with hindsight, although at the time were constructed with the best data and assumptions available. Decision modelling (of various kinds) remains the mainstay of decision making in some domains, most notably (and, as it turned out controversially) when used by NICE in their review and recommendation concerning the use of anti-dementia drugs in the English and Welsh NHS. The preliminary NICE conclusion that the medications demonstrated superior effectiveness to placebo or usual care, but were not cost effective by the wider standards required in the NHS, generated an enormous volume of discussion. The NICE model has a number of methodological features that have attracted comment, including: the computation of, and reliance on QALYs; reliance on a US equation for predicting full-time care in England; utility scores devised from proxy informants on a scale not validated for use in older people; use of quite old British data on service use patterns; a simple model of care pathways; neglect of outcomes and economic benefits for people who do not get full-time care; and limited attention to the impact of AD on family carers. The validity of the NICE model for informing such a major resource allocation decision has therefore been questioned.

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