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Clinical practice with anti-dementia drugs: a revised (second) consensus statement from the British Association for Psychopharmacology

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Abstract

The British Association for Psychopharmacology (BAP) coordinated a meeting of experts to review and revise its first (2006) Guidelines for clinical practice with anti-dementia drugs. As before, levels of evidence were rated using accepted standards which were then translated into grades of recommendation A to D, with A having the strongest evidence base (from randomized controlled trials) and D the weakest (case studies or expert opinion). Current clinical diagnostic criteria for dementia have sufficient accuracy to be applied in clinical practice (B) and brain imaging can improve diagnostic accuracy (B). Cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) are effective for mild to moderate Alzheimer's disease (A) and memantine for moderate to severe Alzheimer's disease (A). Until further evidence is available other drugs, including statins, anti-inflammatory drugs, vitamin E and Ginkgo biloba, cannot be recommended either for the treatment or prevention of Alzheimer's disease (A). Neither cholinesterase inhibitors nor memantine are effective in those with mild cognitive impairment (A). Cholinesterase inhibitors are not effective in frontotemporal dementia and may cause agitation (A), though selective serotonin reuptake inhibitors may help behavioural (but not cognitive) features (B). Cholinesterase inhibitors should be used for the treatment of people with Lewy body dementias (Parkinson's disease dementia and dementia with Lewy bodies (DLB)), especially for neuropsychiatric symptoms (A). Cholinesterase inhibitors and memantine can produce cognitive improvements in DLB (A). There is no clear evidence that any intervention can prevent or delay the onset of dementia. Although the consensus statement focuses on medication, psychological interventions can be effective in addition to pharmacotherapy, both for cognitive and non-cognitive symptoms. Many novel pharmacological approaches involving strategies to reduce amyloid and/or tau deposition are in progress. Although results of pivotal studies are awaited, results to date have been equivocal and no disease-modifying agents are either licensed or can be currently recommended for clinical use.

Keywords

Alzheimer's disease, dementia, guidelines, treatment

Introduction

The British Association for Psychopharmacology (BAP) produced a first edition of clinical practice guidelines for anti-dementia drugs in 2006 (Burns and O'Brien, 2006). As with other BAP guidelines, these were explicitly based on the

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published evidence available and formulated by an expert group following a face-to-face consensus meeting. Given advances in the field, a review of these guidelines was planned at that stage for 5 years later. An expert consensus group therefore reconvened to review and grade the strength of current evidence, consider its clinical implications and agree on revised guidelines for the use of anti-dementia drugs. The focus was on new evidence which had become available since the first guidelines were published. The current revised guidelines have been drawn up after extensive feedback from participants, and have undergone independent peer review prior to publication. The revised guideline covers the diagnosis of dementia, its treatment with anti-dementia drugs, its management in primary and secondary care and its prevention. The guidelines do not directly deal with drug treatments specifically for behavioural disturbances in dementia (e.g. antidepressants, antipsychotics and other agents) but do consider these symptoms when impacted upon by drugs aimed specifically at the disease process underlying the cognitive decline.

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, 15–20%), dementia with Lewy bodies (DLB, 15%), other rarer causes and occasionally reversible conditions (5%). These figures include a substantial proportion of cases where there is evidence of mixed pathology. The diagnosis of subtype of dementia is based on clinical history, physical and mental state (cognitive) 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 in predicting institutional care. Many types of BPSD, including agitation, aggression and psychosis, have traditionally been treated with neuroleptic (antipsychotic) agents. However, recent concerns over cerebrovascular adverse events and 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 VaD 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 antiparkinsonian medication where necessary (L-dopa monotherapy having the least propensity to exacerbate psychosis) and cholinesterase inhibitors. Management of BPSD is more challenging, and antipsychotic drugs should be avoided because of extrapyramidal side effects and the likelihood of prolonged and severe sensitivity reactions.

Other guidelines and guidance are available for the diagnosis and treatment of dementia, including those of the National Institute for Health and Clinical Excellence (NICE) (www.nice.org.uk), the European Federation of Neurological

Sciences (EFNS) (Hort et al., 2010; Waldemar et al., 2007), the American Academy of Neurology (Knopman et al., 2001) and the Scottish Intercollegiate Guidelines network (SIGN) (www.sign.ac.uk). Within the UK, the context where these current guidelines are primarily set, current NICE guidance for cholinesterase inhibitors and memantine has been controversial, recommending that memantine is not made available within the National Health Service (NHS) for people with AD, and that use of cholinesterase inhibitors is limited to those with moderate dementia as usually defined by mini mental state examination (MMSE) scores 10–20. NICE are currently undertaking a reappraisal of their guidance for anti-dementia drugs, though this is limited to cholinesterase inhibitors and memantine, for AD, whilst these BAP guidelines cover all forms of dementia and all putative anti-dementia medications. NICE is concerned with both clinical and cost effectiveness, whereas BAP guidelines are concerned only with clinical effectiveness. Cost effectiveness varies considerably, both between countries and over time, in regard to costs of how drugs are prescribed and monitored and the actual costs of the drugs themselves. For example, within the UK the three cholinesterase inhibitors have patents which expire in 2012, and any recommendations based on current cost effectiveness are unlikely to remain valid after that date.

Methodology

A consensus meeting was held in Manchester in January 2010. The participants were selected for their clinical and research experience in the field of dementia care, and included a person with dementia. The group arrived at its decisions totally independently and guidelines were prepared following the format of previous BAP consensus meetings, and the first consensus meeting on anti-dementia drugs. All participants provided an evidence summary based 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 December 2009 were considered. Particular emphasis was placed on reviewing the previous recommendations in the light of new evidence published since the last guidelines. The objectives of the guideline were to:

1. Review evidence for the clinical diagnosis of dementia and its subtypes and the role of investigations in improving diagnostic accuracy.
2. Assess the evidence for the efficacy of currently available anti-dementia drugs in all common types of dementia and, based on that, make clear recommendations for clinical practice.
3. Appraise the evidence for the efficacy of drugs for those with early cognitive impairments (mild cognitive impairment).
4. Appraise the evidence for drugs with potential to delay or prevent dementia, or modify its disease course.

The level of evidence was categorized according to standard criteria, and level of evidence was then translated into strength of recommendation as detailed in Table 1. A summary of all the recommendations (Tables 2–12) is provided in Table 13 for easy reference.

Table 1. Categories of evidence and strength of recommendation¹

Categories of evidence for causal relationships and treatment	
I	Evidence from meta-analysis of randomized controlled trials*, at least one large, good-quality, randomized controlled trial* or replicated, smaller, randomized controlled trials*
II	Evidence from small, non-replicated, randomized controlled trials*, at least one controlled study without randomization or evidence from at least one other type of quasi-experimental study
III	Evidence from non-experimental descriptive studies, such as uncontrolled, comparative, correlation and case-control studies
IV	Evidence from expert committee reports or opinions and/or clinical experience of respected authorities
Proposed categories of evidence for non-causal relationships	
I	Evidence from large representative population samples
II	Evidence from small, well-designed, but not necessarily representative samples
III	Evidence from non-representative surveys, case reports
IV	Evidence from expert committee reports or opinions and/or clinical experience of respected authorities
Strength of recommendation	
A	Directly based on category I evidence
B	Directly based on category II evidence or extrapolated# recommendation from category I evidence
C	Directly based on category III evidence or extrapolated# recommendation from category I or II evidence
D	Directly based on category IV evidence or extrapolated# recommendation from category I, II or III evidence

¹Anderson et al. (2008).

*Randomized controlled trials must have an appropriate control treatment arm; for primary efficacy this should include a placebo condition.

Extrapolation may be necessary because of evidence that is only indirectly related, covers only a part or the area of practice under consideration, has methodological problems or is contradictory.

Diagnosis and investigations

The criteria used to define dementia continue to cause controversy. Those of the Diagnostic and Statistical Manual (DSM) versions 3R and 4TR (American Psychiatric Association, 1994, 2000) have been most widely used within research settings, and are suitable for routine application in clinical practice. However, the reliance in these (and most other dementia criteria) on significant episodic memory disturbance as a core feature does not adequately capture the seminal features of non-Alzheimer dementia such as VaD, frontotemporal dementia (FTD) and DLB. The other issue is that dementia, by definition, is a late-stage clinical syndrome, when not only are there two or more cognitive domains affected, but the cognitive impairment has a significant impact on social and/or occupational functioning. In light of recent developments in diagnosis, this leads to some illogical incongruity, in that according to current criteria conditions such as AD can only be diagnosed once a dementia is present (McKhann et al., 1984), yet increasingly the use of clinical features and biomarkers allows recognition of the Alzheimer disease process (i.e. plaque and tangle pathology) at a stage before dementia is apparent. Thus, new criteria for very early AD have been proposed (Dubois et al., 2007), and although they remain to be validated, it is very likely that

either using these or similar criteria it will soon be possible to diagnose AD (i.e. the Alzheimer disease process in the brain) at a 'pre-dementia' stage. The advent of amyloid imaging only fuels this debate, since over 60% of subjects with mild cognitive impairment (MCI) have evidence of significantly increased amyloid binding on positron emission tomography (PET), and around 20% or more of apparently normal older people have similar burdens of amyloid (Aizenstein et al., 2008). Further follow-up of those with MCI and normal controls with increased amyloid will determine the extent to which this particular biomarker is useful for such a 'pre-dementia' diagnosis, but early indications are that, at least when symptomatic, increased brain amyloid binding increases the risk of conversion to Alzheimer's dementia (Okello et al., 2009).

As well as proposed criteria for early AD, other recent developments in relation to diagnostic criteria include a revision of the diagnostic criteria for DLB (McKeith et al., 2005). The original criteria (McKeith et al., 1996) were subject to several validation studies, which showed a universally high specificity (and therefore high positive predictive value) but a relatively low sensitivity, especially in some centres (Litvan et al., 2003). Increasing evidence suggested other features as being robustly associated with DLB, including REM sleep behaviour disorder, neuroleptic sensitivity and striatal dopamine loss on single photon emission computed tomography (SPECT) or PET imaging. These additional three features were therefore added to the original core features (fluctuation, recurrent visual hallucinations and spontaneous parkinsonism) in an attempt to increase the sensitivity of the DLB criteria without losing specificity. Whilst further validation studies are needed, initial reports suggest the new criteria detect around 25% more DLB cases than the old criteria (Aarsland et al., 2008), and a follow-up of possible DLB cases showed that those with abnormal dopamine imaging had a very high probability of becoming probable DLB cases, thus providing some validation to the addition of the imaging criteria as a suggestive feature (O'Brien et al., 2009).

The relationship between DLB and Parkinson's disease dementia (PDD) remains a subject of debate, with current consensus that they are two parts of a spectrum, but that for pragmatic reasons, not least the very different clinical presentations of DLB and PDD, that it is premature to consider them a single disorder at the current time. Consensus criteria for the diagnosis of a PDD have now been proposed (Emre et al., 2007) which should allow uniform definitions to be applied for future research studies.

Neuroimaging and cerebrospinal fluid biomarkers

There is increasing interest in the use of brain imaging and cerebrospinal fluid (CSF) biomarkers, both to assist with early and accurate differential diagnosis, and as potential markers of disease progression which may be used as surrogate outcome measures for clinical trials.

Brain imaging is extensively used to assist with diagnosis, both by excluding other causes for dementia syndrome, and by providing features to support subtype specific diagnosis

(for review see O'Brien, 2007). Evidence for its use in excluding other causes for cognitive impairment and for supporting subtype diagnosis of dementia was discussed in the first guideline. Cerebrovascular changes on imaging are necessary for the application of standard diagnostic criteria for VaD (Roman et al., 1993), and increasingly imaging changes are being incorporated into other diagnostic criteria. FTD is associated with frontal and anterior temporal lobe atrophy, together with profound hippocampal atrophy, on structural imaging and frontotemporal hypoperfusion on SPECT and hypometabolism on PET. AD is associated with medial temporal lobe atrophy, particularly of the entorhinal cortex and hippocampus, and temporoparietal hypoperfusion and SPECT and hypermetabolism on PET. Early onset AD is also associated with parietal and precuneus atrophy. DLB is associated with relative preservation of the medial temporal lobe on structural imaging (Burton et al., 2009) and hypoperfusion and hypermetabolism of posterior temporal and occipital areas on SPECT and PET (Colloby et al., 2008). Dopaminergic SPECT or PET can distinguish DLB from AD (McKeith et al., 2007). Amyloid PET imaging using PIB has shown increased uptake of ligand in most cortical areas, apart from sensorimotor cortex, occipital lobe and cerebellum, in AD compared with healthy controls and those with FTD (Rowe et al., 2007). However, increased PIB uptake is also seen in several DLB subjects, consistent with a higher burden of amyloid pathology known to occur. Decreased cardiac sympathetic uptake, as indicated by decreased MIBG-SPECT binding, has been found in Parkinson's disease and DLB in several single-centre studies, and to potentially be a helpful discriminator between DLB and other dementias, including AD (Yoshita et al., 2006).

Raised levels of CSF tau (both total and phosphorylated tau) and reduced levels of Abeta have proved, when combined in a ratio, to have reasonable diagnostic accuracy for separating AD from other dementias (mean sensitivity 72%, mean specificity 78% when comparing AD with other dementias) (Mitchell, 2009). However, multicentre studies have shown substantial inter-centre variation in biomarker levels, especially for Abeta 42 (Mattsson et al., 2009), and further standardization and investigation of the reasons for this are required before biomarkers can enter clinical practice (See Table 2 for recommendations).

Drug treatments for Alzheimer's disease

There are currently two classes of drug approved for the treatment of AD: the cholinesterase inhibitors tacrine (though not marketed in the UK), donepezil, rivastigmine and galantamine, and the NMDA receptor antagonist, memantine. Many other trials of putative disease-modifying agents are in progress. Donepezil, rivastigmine and galantamine are licensed for mild to moderate AD, memantine for moderate to severe AD, and several randomized clinical trials (RCTs) demonstrate their efficacy in these situations. However, the clinical significance of the benefits has been questioned, with some arguing the drugs are not clinically effective, others that the drugs are effective but the choice of outcome measures is flawed.

Choice of outcome measures for AD studies

Debate, largely fuelled by questions over cost effectiveness raised by NICE, has revolved around the appropriateness of outcome measures in clinical trials. Traditionally, primary outcome in regulatory trials has been on a global cognitive measure, such as the ADAS-Cog or MMSE. However, AD is a complex disorder. Cognitive symptoms include not just memory loss but impaired spatial and temporal orientation, language, praxis and other symptoms. Functional symptoms include reduced ability to carry out activities of daily living (ADL); behavioural and psychological symptoms include psychosis, mood swings, agitation and aggression, and the timing of symptom expression is highly variable between patients. The MMSE, as an endpoint in clinical trials, may therefore not capture the diversity of symptoms associated with AD in 'real life'. The MMSE has pronounced floor and ceiling effects, poor test/retest reliability (of ± 3 points at 1 month) and cannot reliably measure disability in AD. Rates of change vary depending on initial MMSE score; follow-up of the CERAD cohort showed that those with initial MMSE scores between 20 and 24 deteriorated by 1–2 points per year, but those with scores between 8 and 12 deteriorated by more than 5 points per year (Mendiondo et al., 2000). Similar findings on baseline MMSE have been shown in RCTs, and predicting response to treatment in a

Table 2. Summary box: Assessment and diagnosis

Intervention	Level of evidence	Recommendation
Making a diagnosis of dementia subtype	There is type I evidence that the clinical diagnosis of dementia subtype according to internationally agreed consensus criteria is accurate, but some of the newly proposed criteria still require validation.	A
Use of structural brain imaging for diagnosis	There is type I evidence that CT or MRI should be used to exclude other cerebral pathologies and to help establish the subtype diagnosis.	A
Use of SPECT or PET imaging	There is type I evidence that perfusion (HMPAO) SPECT or FDG PET can differentiate between AD, VaD and FTD. There is type I evidence that dopaminergic SPECT or PET imaging can help differentiate DLB from AD.	A
CSF biomarkers	There is type II evidence that CSF markers of amyloid and tau may be useful diagnostic markers for Alzheimer's disease, but further standardization and validation is required before they can be used clinically.	B

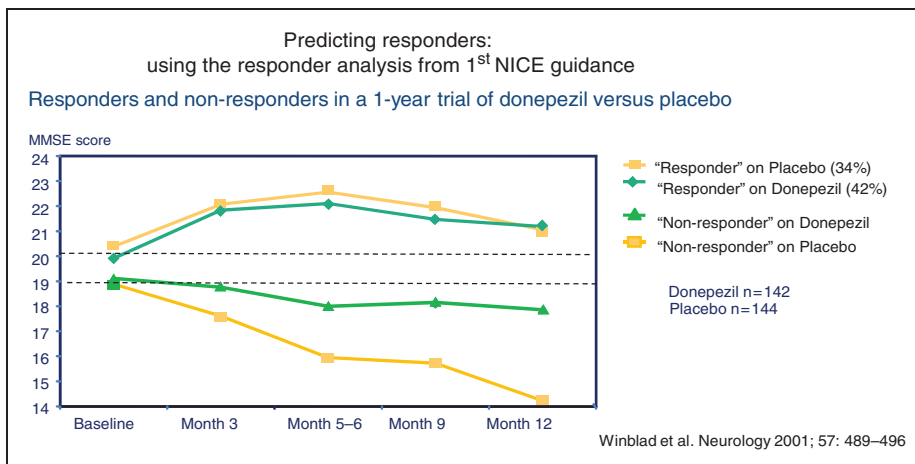


Figure 1. Patients declining according to the NICE definition of response at 3 months showed much less MMSE decline on donepezil compared with placebo, demonstrating a clear drug effect.

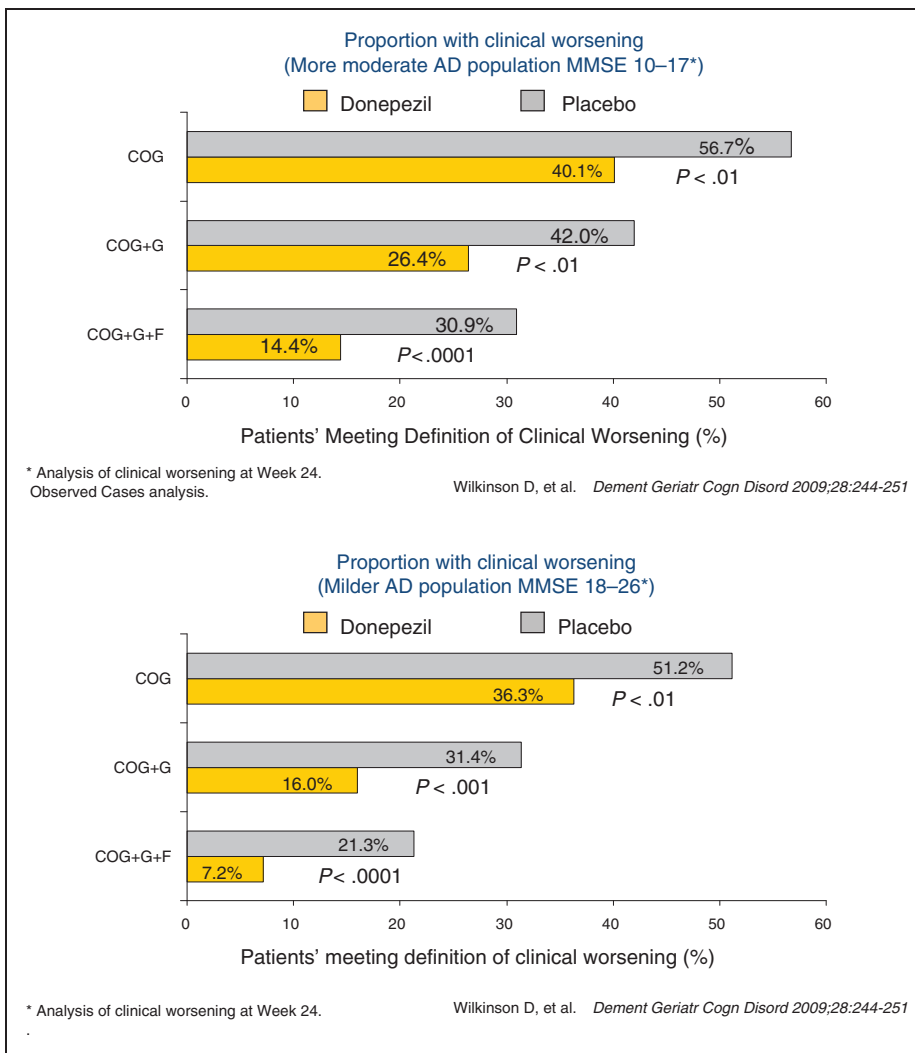


Figure 2. All patients from three trials showing clinical worsening on cognition alone (COG), cognition and a global assessment (COG +G), and on cognition on a global assessment and a functional scale (COG+G+F).

progressive condition is extremely challenging. Initial NICE guidance from 2001 recommended the use of cholinesterase inhibitors be continued for those with mild to moderate AD who 'responded' to treatment at 3 months in terms of an improvement or no change in cognition, combined with global or behaviour improvement. However, clinical use of the drugs in this way was shown to be flawed when reanalysis of placebo-controlled data from the Nordic study (Winblad et al., 2001) clearly demonstrated that even those who did not fulfil responder criteria for NICE still benefited from cholinesterase treatment. Indeed, these patients benefited to an even greater extent than those who had been classified as responders (www.nice.org.uk).

Benefit from treatment is therefore more complex than simply measuring an improvement on a cognitive measure, and really reflects the degree to which the curve of decline over time has been shifted upwards (the area under the curve) by treatment (see Figure 1). Because of this, rather than simply measuring response, prevention of clinical worsening may be a more useful outcome measure (see Figure 2). With marked clinical worsening defined as any cognitive decline, plus any decline on ADL plus any decline in global function, 30% of those on placebo but only 14% of those on donepezil showed clinical worsening (Wilkinson et al., 2009). In those people with dementia of moderate severity, who have currently fallen within NICE guidance, but in those with MMSE scores above 18, 21% deteriorated on placebo compared with only 7% on donepezil. This definition of prevention of worsening, arguably more in accord with both clinical practice and what patients and carers request, shows that those with mild AD respond equally well, if not better, than those with moderate disease. The concept of clinical worsening has also been applied to studies of memantine, with those

on placebo having significantly greater degrees of worsening than those on memantine (21% vs. 11%) (Wilkinson and Andersen, 2007).

Recent studies have investigated whether specific domains of cognitive or non-cognitive symptoms respond to different treatments. An analysis of three mild to moderate Alzheimer studies showed that memantine had particular benefits in domains of orientation, following commands, praxis and comprehension (Mecocci et al., 2009). Post-hoc analysis from Phase III studies shows particular non-cognitive benefits for delusions, agitation/aggression and irritability (Gauthier et al., 2008). Cholinesterase inhibitors can help behavioural symptoms by improving attention and concentration. Feldman et al. (2001) showed particular benefits for apathy, anxiety and depression. The CALM-AD study compared donepezil with placebo in moderate to severe AD subjects with clinically significant agitation that had not responded to a 4-week non-pharmacological intervention, so mirroring usual clinical practice. There was no significant benefit of donepezil over placebo in reducing agitation (Howard et al., 2007).

The effect of adding memantine to cholinesterase inhibitors is not clear. An initial study showed clear benefit in cognitive and non-cognitive symptoms (again agitation and irritability responding best) when memantine was added to donepezil therapy (Tariot et al., 2004). However, a more recent study investigating memantine add-on to all three cholinesterase inhibitors failed to demonstrate any clear cognitive or non-cognitive benefit (Porsteinsson et al., 2008). Open-label observational data suggest that treatment with anti-dementia drugs may slow admission to residential care (Figure 3), with the greatest benefits seen in those on combination therapy (Lopez et al., 2009).

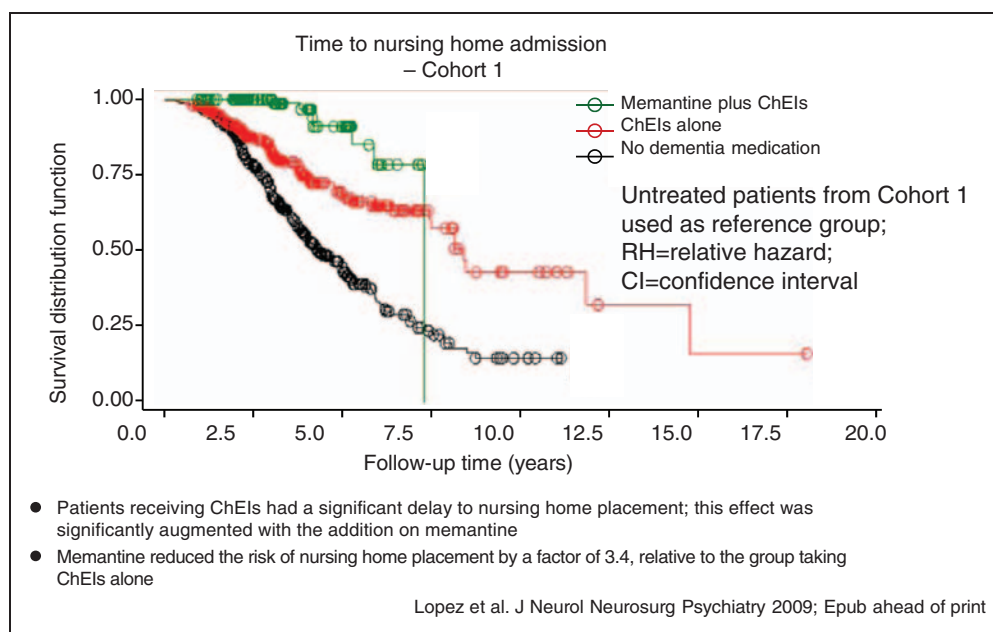


Figure 3. Long-term effects of the concomitant use of memantine with cholinesterase inhibition in AD.

Table 3. Summary box: Alzheimer's disease

Intervention	Level of evidence	Recommendation
Treatment with cholinesterase inhibitors and memantine	There is type I evidence for the efficacy of cholinesterase inhibitors in the treatment of mild to moderate Alzheimer's disease and type I evidence for memantine in moderate to severe Alzheimer's disease.	A
Switching between cholinesterase inhibitors	There is type II evidence to support the switching of one cholinesterase inhibitor to another if the first is not tolerated or effective.	B
Combination therapy	There is type II evidence for adding memantine to a cholinesterase inhibitor, but also a negative type 1b study. Until further studies are available the benefits of combination therapy is unclear.	B

Comparative trials

No new comparative trials have been published in the last 5 years. Previous comparative trials failed to consistently demonstrate any significant differences in efficacy between the three cholinesterase inhibitors, the main differences found being in frequency and type of adverse events (Burns and O'Brien, 2006).

Switching and combination therapy

The rationale for switching between cholinesterase inhibitors rests on their different chemical classes and pharmacological properties. Reasons for switching may be because of poor tolerability and/or lack of perceived efficacy. Within the UK, since a change in NICE guidance which no longer requires a patient to show a clinical improvement in order to be eligible to continue to receive medication, switching is largely because of poor tolerability. There have been few studies of switching, and none double blind. No new studies of switching were identified since the last consensus meeting so the main finding from these earlier studies, that a significant proportion (up to 50%) may respond or improve on switching medication, remains valid (See Table 3 for recommendations).

Drugs for dementia with Lewy bodies

Pharmacological management of DLB remains one of the most challenging issues facing neurologists, psychiatrists, geriatricians, primary care physicians and others. The combination of cognitive, neuropsychiatric, autonomic and motor features in DLB is, when compared with AD, much more likely to lead to greater functional impairment (McKeith et al., 2006) and poorer quality of life. Moreover, the balance between these features varies, both between individual subjects and as the disease progresses. Treatments for one aspect of the disease may exacerbate other symptoms. In particular, treatment for neuropsychiatric features may exacerbate parkinsonism, while L-dopa and other antiparkinsonian medications may exacerbate psychosis. Careful, individualized and patient-centred approaches are required to control individual symptoms, depending on the severity of symptoms and the wishes of patients and carers. Motor features are classically thought to respond poorly to antiparkinsonian medication in DLB. However, controlled randomized studies (type II) have demonstrated that around a third of subjects with DLB obtain a good

motor response to L-dopa, though side effects do require to be monitored (Bonelli et al., 2004; Goldman et al., 2008; Molloy et al., 2005). Medication should generally be introduced at low doses and increased slowly to the least dose required to minimize disability. Other antiparkinsonian medications apart from L-dopa, including selegiline, amantadine, COMT inhibitors, anti-cholinergics and dopamine agonists should be used with extreme caution in view of concerns about inducing confusion and psychosis (Goldman et al., 2008).

RCTs of cholinesterase inhibitors have demonstrated benefit in cognitive and non-cognitive symptoms in DLB and PDD (Aarsland et al., 2002; Emre et al., 2004; Grace et al., 2001; McKeith et al., 2000; Minett et al., 2003; Samuel et al., 2000). A comparative study, based on published literature though not controlled, found evidence to support all three cholinesterase inhibitors in DLB (Bhasin et al., 2007). Cholinesterase inhibitors have also been shown to be effective for neuropsychiatric symptoms including hallucinations, apathy, anxiety and sleep disorders. Memantine has not been as well-investigated in DLB, but a RCT in subjects with either DLB or Parkinson's disease dementia showed significant cognitive benefit (1.9 difference in MMSE) of memantine compared with placebo and significant benefit on clinical global impression of change, the primary outcome, with almost 30% of patients having a moderate or substantial improvement on memantine compared with 0% on placebo (Aarsland et al., 2009). There was no benefit on non-cognitive symptoms and no evidence of either improvement or worsening of parkinsonism. Memantine was well tolerated. Treatment of other features of DLB is outwith the scope of this guideline, but is reviewed comprehensively elsewhere (McKeith et al., 2004; Thaisetthawatkul et al., 2004) (See Table 4 for recommendations).

Drugs for vascular dementia

VaD remains the second most common pathological cause of dementia. The pathologies underlying VaD are heterogeneous, ranging from large multiple infarcts caused by emboli to diffuse white matter changes associated with chronic hypoperfusion (O'Brien et al., 2003). There are no currently licensed treatments for VaD within the UK, so treatment strategies have largely focused on control of underlying cardiovascular risk factors and treatment of associated symptoms. There has been suggestion that cholinergic

dysfunction occurs in VaD, prompting interest in use of cholinesterase inhibitors for this disorder. However, an autopsy-based study showed that loss of cholinergic function was only evident in VaD patients with concurrent AD and that cholinergic activity may actually be increased in those with multi-infarct dementia (Sharp et al., 2009), confirming an earlier report of no cholinergic loss in 'pure' VaD (Perry et al., 2005). Vascular risk factors should be identified in all patients with VaD. Where prevention of recurrent stroke is necessary, use of antihypertensive therapy in the case of haemorrhagic stroke and use of antihypertensive and lipid-lowering strategies after ischaemic stroke according to national guidelines should be implemented. Specific pharmacological interventions have involved donepezil, galantamine, rivastigmine and memantine. There is also a literature on the use of the calcium channel blocker, nimodipine.

Since publication of the previous guideline, there have been additional studies with donepezil 5 mg, galantamine and rivastigmine. These have been reviewed by Baskys and Hou (2007), Bocti et al. (2007), and Rojas-Fernandez and Moorhouse (2009). In a 24-week study with galantamine there were significant improvements in ADAS-Cog and executive function (EXIT25) but no significant changes in ADL, global or behavioural scales (Auchus et al., 2007). Some 13% of galantamine and 6% of placebo patients discontinued treatment because of adverse events. In a randomized double-blind placebo-controlled trial of rivastigmine capsules, significant benefit was found on V-ADAS-Cog, ADAS-Cog and MMSE, but not other outcomes (Ballard et al., 2008). The incidence of adverse events was higher in the rivastigmine group. The previous guideline referred only to published studies with donepezil, and one review showed that donepezil produced similar changes in cognition and global function in VaD and AD but that the changes in VaD were inconsistent (Passmore et al., 2005). A meta-analysis (Kavirajan and Schneider, 2007) included all trials with donepezil, galantamine,

rivastigmine and memantine compared with placebo in VaD. Post-hoc analyses of the initial two donepezil studies and the galantamine trial suggested greater improvement in patients with cortical and multiple territorial lesions, respectively, compared with those with predominantly subcortical lesions. The authors commented that the clinical heterogeneity of VaD patients limited generalizability of the trials' outcomes because the effect of treatment on specific patients or subgroups could not be defined. The conclusion from the meta-analysis was that cholinesterase inhibitors and memantine produced small benefits in cognition of uncertain clinical significance in patients with mild to moderate VaD. Data are insufficient to support widespread use of these drugs in VaD. Individual patient analyses are needed to identify subgroups of patients with VaD who might benefit.

Nimodipine has some short-term benefits in VaD (Lopez-Arrieta and Birks, 2002) and can beneficially affect MMSE, executive function measures and global rating in subcortical ischaemic vascular dementia (SIVD) (Pantoni et al., 2005). However, there has been no update on the original Cochrane review of nimodipine (Lopez-Arrieta and Birks, 2002). In this context, rivastigmine (up to 6 mg daily) was compared with nimodipine in a single-blinded study of 14 months duration. Patients were subdivided according to whether they had multi-infarct dementia (MID) or SIVD. In the SIVD group rivastigmine did not improve MMSE but had beneficial effects upon measures of executive function, neuropsychiatric features, depression and Clinical Dementia Rating. In the MID group, rivastigmine had no effect on MMSE, but had beneficial effects on neuropsychiatric features and depression. All patients in the rivastigmine groups completed the study (Moretti et al., 2008).

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is an uncommon genetic form of SIVD. In an 18-week, placebo-controlled, double-blind, randomized parallel-group trial,

Table 4. Summary box: Dementia with Lewy bodies

Intervention	Level of evidence	Recommendation
Cholinesterase inhibitors	There is type I evidence to support treatment with cholinesterase inhibitors in Lewy body dementia, both dementia with Lewy bodies and Parkinson's disease dementia and that both cognitive and neuropsychiatric symptoms improve.	A
Memantine	There is type II evidence to support equal efficacy of all three cholinesterase inhibitors. There is type II evidence that memantine may produce cognitive and global improvements.	B

Table 5. Summary box: Vascular dementia

Intervention	Level of evidence	Recommendation
Treatment with cholinesterase inhibitors and memantine	There is type I evidence showing small cognitive improvements with both cholinesterase inhibitors and memantine in vascular dementia. However, benefits in terms of global outcome are not seen and adverse events for cholinesterase inhibitors (but not memantine) are significantly greater than placebo. Evidence indicates that neither cholinesterase inhibitors nor memantine should be prescribed to people with vascular dementia, though those with mixed VaD and Alzheimer's disease may benefit.	A

10 mg donepezil daily had no effect on V-ADAS-Cog (the primary outcome measure) but there was a significant treatment effect favouring donepezil on some measures of executive function, the clinical relevance of which was unclear (Dichgans et al., 2008).

A Cochrane review of Huperzine A (a naturally occurring cholinesterase inhibitor derived from the Chinese herb *Huperzia serrata*) concluded that there is no convincing evidence that Huperzine A is of value in VaD. This was based on one small trial and further research is needed (Hao et al., 2009). There have been no new data for memantine since the last guideline. The effects of memantine in VaD have been reviewed by Bockt et al. (2007), Kavirajan and Schneider (2007), McShane et al. (2006) and Thomas and Grossberg (2009) (See Table 5 for recommendations).

Frontotemporal and other dementias

FTD comprises a group of clinical syndromes associated with circumscribed degeneration of the prefrontal and anterior temporal lobes. These syndromes are clinically and pathologically heterogeneous. Abnormal behaviour is the dominant feature of FTD. Executive dysfunction is common in most, though not all, FTD variants, and may be well preserved with more focal orbitomedial frontal lobe involvement. NICE dementia guidelines recommend diagnosis of FTD according to Lund-Manchester or NINDS criteria (National Collaborating Centre for Mental Health, 2006). In these guidelines no evidence was found that met the eligibility criteria relating to the treatment of non-Alzheimer dementia with cholinesterase inhibitors or memantine. Indeed, worsening of behavioural symptoms by cholinesterase inhibitors has been reported (Mendez et al., 2007). Recent open-label studies of memantine suggest minimal or no improvement in neuropsychiatric symptoms (Boxer et al., 2009; Diehl-Schmid et al., 2008; Swanberg, 2007). A placebo-controlled study of three patients with FTD showed no overall benefit for the alpha(2) antagonist idazoxan, with some areas of performance improving (e.g. sustained attention) and others worsening (e.g. spatial working memory) (Coull et al., 1996). A within-subjects, double-blind, placebo-controlled study in eight patients suggested that methylphenidate may ameliorate

abnormal risk-taking behaviour in FTD (Rahman et al., 2006). Another study (double-blind, quetiapine-controlled cross-over design) showed beneficial effects upon abnormal behaviour for dextro-amphetamine in eight patients (Huey et al., 2008). Serotonergic agents including trazodone and selective reuptake inhibitors (SSRIs) have been used in FTD. In 2004 a Cochrane review (Martinon-Torres et al., 2004) found no evidence to support the use of trazodone as a treatment for behavioural and psychological symptoms in FTD, based upon a single study. A later placebo-controlled RCT of trazodone showed improvement, as evidenced by a decrease of more than 50% in neuropsychiatric inventory (NPI) score, in 10 of 26 evaluable patients (Lebert et al., 2004). A randomized, piracetam-controlled, open study of paroxetine in 16 patients indicated significant improvement in behavioural symptoms and reduced care-giver stress at 14 months in the SSRI group (Moretti et al., 2003). A more rigorous, randomized controlled cross-over trial of paroxetine in 10 subjects with FTD led to no improvement in NPI or Cambridge Behavioral Inventory (CBI) score and worsened cognition (Deakin et al., 2004). With greater understanding of the pathogenic mechanisms underpinning FTD, including microtubule-associated protein tau, progranulin and TDP-43, it should be possible to translate potential disease-modifying treatments from animal models into human trials (Vossel and Miller, 2008) (See Table 6 for recommendations).

Progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) are characterized by accumulation of hyperphosphorylated tau protein and a variable admixture of cognitive, neuropsychiatric and extrapyramidal features. Both may present with a 'frontal' syndrome. Cholinesterase inhibitors are not recommended for the treatment of the cognitive syndrome. Two trials in PSP (one Level I, one II) showed no significant cognitive benefits (Fabbrini et al., 2001; Litvan et al., 2001), while ADL/mobility scores significantly worsened in one study (Litvan et al., 2001). Riluzole did not prolong survival in PSP in a large multicentre international RCT ($n=362$), nor did it influence rate of disease progression (Bensimon et al., 2009). Coenzyme Q10, a physiological co-factor of mitochondrial complex I, led to slight improvement in the Frontal Assessment Battery in a double-blind RCT of 21 cases after 6 weeks (Stamelou et al., 2008).

Table 6. Summary box: Frontotemporal dementia

Intervention	Level of evidence	Recommendation
Cholinesterase inhibitors	There is type I evidence that cholinesterase inhibitors are not recommended for the treatment of frontotemporal dementia.	A
SSRIs	There is type II evidence that SSRIs may help some behavioural aspects of frontotemporal dementia, but do not improve cognition. Studies are mixed and further evidence is needed.	B

Table 7. Summary box: Progressive supranuclear palsy

Intervention	Level of evidence	Recommendation
Cholinesterase inhibitors	There is type II evidence that cholinesterase inhibitors are not helpful in progressive supranuclear palsy. No treatments can be recommended at the current time.	B

Disease-modifying approaches to PSP and CBD include the inhibition of glycogen synthase kinase-3 (GSK-3), a key enzyme in the hyperphosphorylation of tau protein. Other trials with putative GSK-3 inhibitors are ongoing.

Prion diseases are rapidly progressive neurodegenerative diseases caused by the accumulation of an abnormal isoform of native prion protein. Creutzfeldt-Jakob disease (CJD) is the most common prion disease in the UK. An open-label, patient-preference trial of 300 mg quinacrine daily in 107 patients with prion disease showed that the drug was reasonably tolerated but did not significantly affect disease course (Collinge et al., 2009). Intraventricular infusion of pentosan polysulphate did not lead to any obvious clinical improvement in 11 patients treated in an open-label study in Japan (Tsuboi et al., 2009) (See Table 7 for recommendations).

Numerous other conditions may present with dementia, or feature significant cognitive decline with or without neuropsychiatric features as an integral part of the disease course. These disorders include other neurodegenerative diseases (e.g. Huntington's disease), inflammatory disorders (e.g. multiple sclerosis), connective tissue diseases (e.g. systemic lupus erythematosus, Sjögren's syndrome) and vasculitic and metabolic disorders. Treatment of the underlying systemic disorder where possible (e.g. via replacement therapies, steroids, etc.) is clearly indicated, but there is generally a dearth of evidence-based recommendations for the management of dementia in these disorders, given the lack of randomized trial data.

Mild cognitive impairment

Early diagnosis of AD is challenging and indeed, under current criteria (as referred to above), AD cannot be diagnosed until a more global cognitive decline for dementia is present. Historically, this has led to difficulties in the classification and categorization of people presenting with early memory difficulties, with or without objective evidence of impairment, at a pre-dementia stage. The most widely accepted concept to date is that of MCI, defined clinically by objective impairment of memory or other cognitive domains which fall short of current criteria for dementia in that ADL are largely preserved and global dementia is not present. Most research has focused on amnesic mild cognitive impairment, which appears largely to be a pre-Alzheimer condition, once other possible causes of cognitive difficulties have been carefully excluded. Transition to dementia, usually AD, is 10–15% per year. Amnesic MCI is associated with early AD pathology. However, some caution is necessary as, if other causes of memory difficulties are not excluded, very different outcomes for MCI have been reported. For example, in community studies up to 40% of those categorized as MCI at one time point can revert to normal.

Early cognitive markers for other dementias have not been well defined. Notably, early signs of other dementias are often non-cognitive, for example fluctuating psychosis in DLB or apathy/depression in FTD. Although MCI captures those at high risk for progression to subsequent dementia, there is controversy as to how such patients should be diagnosed and managed, whether MCI is a valid diagnosis at all and whether its recognition actually confers benefit or harm to the individual. Although benefit from RCTs of cholinesterase inhibitors has been suggested in some subgroups on post-hoc analysis, primary outcomes have uniformly been negative as summarized by recent Cochrane reviews (Birks and Flicker, 2009; Loy and Schneider, 2006). Lu et al. (2009) suggested donepezil may be effective in MCI subjects with depression. A meta-analysis of piracetam revealed equivocal findings (Flicker and Grimley Evans, 2001), and there is no other evidence to support nootropics. There have been no studies of memantine in MCI. Other studies including RCTs of vitamin E and anti-inflammatory (rofecoxib) have been negative (See Table 8 for recommendations).

The NICE process

In the UK, within England and Wales, recommendations on the use of licensed drugs are made by NICE. There have been two appraisals of cholinesterase inhibitors and memantine, and a third appraisal is ongoing at the time of writing. The first appraisal considered cholinesterase inhibitors and advised that donepezil, rivastigmine and galantamine should be made available in the NHS as one component of the management of people with AD of mild to moderate severity, with MMSE scores above 12. The concept of a responder was defined on the basis of improvement or no change in cognition, together with some evidence of improvement in global, functional or behavioural outcome. Recommendations were that only responders to treatment at 3 months should continue on therapy. In the first provisional revision of the NICE guidance, in March 2005, a different approach was taken based on the NICE view that the drugs were clinically efficacious but not cost effective. Provisional recommendations were that donepezil, rivastigmine and galantamine should now not be made available for new patients with mild to moderate AD. Following considerable disquiet at this provisional guidance, NICE reanalysed data from RCTs to determine whether there may be subgroups who showed good response to treatments, in whom the drugs might prove cost effective and so be permitted. The results showed that cholinesterase inhibitors appeared to be more effective for moderate AD compared with those with mild disease (Table 9). Memantine was not recommended except as part of well-designed clinical studies, because NICE criteria for cost

Table 8. Summary box: Mild cognitive impairment

Intervention	Level of evidence	Recommendation
Treatment with cholinesterase inhibitors and vitamin E	There is type I evidence that cholinesterase inhibitors are not effective in reducing the risk of developing Alzheimer's disease and type I evidence that vitamin E is not effective in reducing the risk of Alzheimer's disease.	A

Table 9. Responder analysis undertaken by NICE showing cognitive change on ADAS-Cog according to AD severity on MMSE

	Effect of dementia severity on ADAS-cog change (<i>n</i> = 5216)		
	Mild (21+) <i>n</i> = 2218	Moderate (15–20) <i>n</i> = 2163	Moderately severe (10–14) <i>n</i> = 835
Meta-analysis (all drugs)	1.86 (0.83–2.89)	3.98 (3.22–4.74)	5.44 (3.94–6.94)

MCR biostatistics analysis for NICE, January 2006, www.nice.org.uk

effectiveness were not met. The NICE decision was appealed in 2006 by pharmaceutical companies, by the Royal College of Psychiatrists, the British Geriatric Society and the Alzheimer's Society, but the appeal was rejected and final guidance issued in 2006. The main source of contention was the economic model used by NICE, which had not been fully released to interested parties. The subsequent judicial review and judgment by the court of appeal specified that NICE had to release the full economic model. Mistakes were noted in the model, but NICE felt that, despite these, the guidance would remain unchanged, but undertook a full review and reappraisal which is currently ongoing.

In contrast to NICE, other European guidelines recommend both early treatment of AD and the use of memantine. For example, EFNS guidelines specify that there is level A recommendation that in patients with AD, treatment with cholinesterase inhibitors should be considered at the time of diagnosis and that there is level A recommendation for the use of memantine. The Italian Association of Psychogeriatrics Guidelines (Caltagirone et al., 2005) specify that treatment with cholinesterase inhibitors should be started as soon as the diagnosis of AD is established. As such, current NICE guidance is not consistent with guidance and guidelines in most other European countries. This indicates the difficulties and controversies inherent when economical modelling is applied to a condition such as AD, where there are major issues about how quality of life can be measured, how to measure improvements for care givers as well as patients, and the serious chronic nature of the condition combined with the lack of any suitable alternative treatments.

Perspective from a person with dementia

Many people with dementia and their carers have been important advocates for the clinical use of anti-dementia drugs, and this should be an essential part of any decision making process. Members of patient and carer organizations like the Alzheimer's Society were consultees during the NICE process, while the NICE/SCIE Dementia Guideline Group included two carer representatives and Peter Ashley as a person with dementia. This current BAP Consensus Group invited Peter Ashley, as a person with DLB, to join the meeting.

The uniform view of people with dementia and their carers is that all the dementias are devastating illnesses to be diagnosed with, that diagnosis is followed by a period of despair and slow acceptance of the condition, and that any treatments, even those with relatively limited benefit, are highly valued and can make important individual contributions to improve quality of life that are not always reflected in average clinical measures from large trials. Individual goals and experiences are

obviously more important, and some attempts to measure or individualize goal-directed strategies have been developed. Most people with dementia and their carers strongly feel that anti-dementia drugs should be made available, where appropriate, to all people with dementia and be available as soon as possible after the diagnosis has been made. In Peter's case this fortunately happened, although under the current NICE TA111 this should not have been the case.

Peter Ashley was invited to address the members and give a brief overview of his own thoughts about his condition (also see Ashley, 2009, for further details). He explained that over the 9 years since his diagnosis he had learnt such a lot and it was through the generous welcoming of professionals that he had gained such knowledge. "There has never been the 'them and us' culture when working in concert with real professionals, unlike some, who don the mantle of dementia experts but who have knowledge that is only 'skin deep'." It was his belief that the taking of a cholinesterase inhibitor (rivastigmine) had proved highly beneficial, and his own attitude of 'use it or lose it' had led to a period of longevity where his intellectual functions had remained more or less intact.

People with dementia have a unique opportunity to express their views on dementia as they are surely experts in their own right – to have a condition does, by its very nature, confer on the person an understanding of how they feel which only they, if they are still able to express themselves, can articulate.

Management of dementia in primary care and relationship to specialist services

If policy were enough to produce changes in clinical practice, dementia care in the community would be very well organized. The proliferation of policy suggests the opposite, that the treatment of people with dementia remains stubbornly sub-optimal. Much of this low-quality care may be due to profound under-resourcing of health and social care services, but even when this is not clearly the case, as with the prescribing of cholinesterase inhibitors, there is considerable variation between Primary Care Trusts in the levels of prescribing. Variations in prescribing of cholinesterase inhibitors are likely related to several factors, including combinations of patient characteristics, practitioner attitudes and beliefs, and system performance. It has been shown that receipt of cholinesterase inhibitors is associated with being a home owner (Cooper et al., 2010) and having a higher level of education (Johnell et al., 2008). Amongst British general practitioners (GPs) who took part in the 2009 National Audit Office survey, older doctors were more confident about diagnosis and management but less certain of the benefit of early

recognition (Ahmad et al., 2010). The EVIDEM programme's study of 20 practices involved in a trial of an educational intervention to support dementia diagnosis suggests that specialist services in the UK operate largely independently of general practice, carry out almost all medication monitoring, and that GPs have little or no knowledge of shared care protocols and are uncertain about the benefits of cholinesterase inhibitors. Educational interventions have tended to concentrate on diagnosis not management, and the only convincing evidence of increased prescribing comes from a US care management trial (Vickrey et al., 2006). Modifying the care pathway and transferring management tasks (including monitoring medication) to general practice may be a more effective way of ensuring that people with AD are offered a trial of medication than any educational intervention. However, significant education and up-skilling of primary care would need to occur for this to happen.

Other putative therapies for dementia

Dimebon

Dimebon (latrepirdine) is an antihistamine identified as a weak inhibitor of cholinesterase activity with a number of other actions, including enhancing mitochondrial function. It was used as an antihistamine in Russia but is no longer licensed. It has been investigated in a 6-month randomized placebo-controlled trial followed by an open-label extension in a study undertaken in Russia of 183 people with mild to moderate AD randomized to dimebon 20 mg tds or placebo (Doody et al., 2008). Dimebon produced significant improvements in cognition (ADAS-Cog) as well as global outcome, ADL and neuropsychiatric symptoms at 26 weeks. Benefits remained at 1 year in an open-label extension. However, more recently, preliminary and unpublished data from a Phase III study were disappointing, but further Phase III trials are ongoing.

Ginkgo biloba

Many studies have reported benefits in cognition from using leaf extracts from the maidenhair tree, *Ginkgo biloba*. Different products are available but the active components are thought to be flavonoids, terpenoids and terpene lactones which are believed to exert a variety of beneficial effects on blood flow (reducing viscosity, dilating vessels) and neurotransmitter systems, as well as having anti-oxidant properties (via flavonoids) and possibly an anti-amyloid aggregation effect. The most recent Cochrane review (Birks and Grimley Evans, 2009) (last updated in March 2008) reported that early trials were typically small, of poor quality and raised concerns about publication bias. Overall they found weak evidence of benefit for cognition from *Ginkgo biloba* treatment. However, when two studies were removed because their statistical features were so different from other studies (Mazza et al., 2006; Napryeyenko and Borzenko, 2007) there was no overall benefit from *Ginkgo biloba*. Importantly, two large well-designed RCTs in dementia subjects (McCarney et al., 2008; Schneider et al., 2005) showed no benefits from *Ginkgo* on cognition. Since this review three other studies have been

reported, one examining dementia subjects and two primary prevention studies. An east European study (Yancheva et al., 2009) in dementia with neuropsychiatric features found no additional benefit with *Ginkgo* augmentation of donepezil. A primary prevention feasibility study (Dodge et al., 2008) over 42 months in 118 people over 85 at baseline found *Ginkgo biloba* did not prevent the development of dementia or decline in memory but found an increase in stroke and transient ischaemic attack cases in the *ginkgo* group. Finally, the GEM Study (DeKosky et al., 2008) assessed 3069 volunteers who had MCI or were cognitively normal, randomized to placebo or *Ginkgo biloba* over a median follow-up of 6.1 years. *Ginkgo* had no effect on reducing incident AD or all-cause dementia but was associated with a doubling in haemorrhagic stroke (16 vs. 8). Although this was non-significant and may have been a chance finding, use of warfarin was an exclusion because of existing concerns about the effect of *ginkgo* on coagulation, and together with the Dodge study findings, should remind potential users that herbal products are not without risks.

Hormone replacement therapy

Evidence from epidemiological and animal studies has suggested that using oestrogen replacement therapy (ERT) or combined oestrogen and progestagen replacement therapy (HRT) in post-menopausal women may both protect against cognitive decline and dementia and be used as a cognitive treatment in pre-existing dementia. However, a large primary prevention trial, the WHIMS trial (the Women's Health Initiative Memory Study) examined the possible benefit of HRT/ERT in reducing the frequency of or time of onset of dementia in post-menopausal women (participants were aged 65–79 at entry). Adverse outcomes led to both arms being terminated early because treatment was linked to increased rates of 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) (Shumaker et al., 2003). Combining these two groups, there was a highly clinically and statistically significant increase in dementia in women taking HRT, hazard ratio 1.76 (95%CI 1.19–2.60) (Shumaker et al., 2004). There was no evidence of any differences in risk for dementia subgroups. When the substantially increased risk of other major illnesses, e.g. ischaemic stroke was increased by 44%, is added, it is clear that the use of HRT and ERT cannot be justified in the primary prevention of dementia, at least in those over 65, or in the treatment of dementia. The termination of WHIMS led to other studies being stopped, but further evidence on HRT on cognitive function in post-menopausal women has emerged and is included in the up-to-date Cochrane review (Lethaby et al., 2008) which concluded that ERT and HRT do not protect against cognitive ageing in older post-menopausal women and may increase the risk of dementia.

Randomized trials have also failed to find any clinically meaningful and consistent evidence of benefit in treating patients with pre-existing mild-moderate AD with oestrogen. A Cochrane review (of seven trials including 251 women with AD) (Hogervorst et al., 2009) concluded HRT/ERT is not indicated in AD.

Folate and vitamin B12

Folate is an essential dietary element whose absorption is reduced by the C677T mutation in the methylenetetrahydrofolate (MTHFR) enzyme, leading to lower plasma and red cell folate levels and increases in homocysteine. Increased plasma homocysteine levels are in turn associated with vascular disease and dementia. Hence dietary supplementation using folic acid (the synthetic analogue of folate) and vitamin B12, which reduce homocysteine levels, have been proposed for both preventing dementia and in its treatment. A Cochrane review (last updated March 2008) identified six trials using folic acid alone and two using folic acid combined with vitamin B12 and concluded there was no evidence that such treatments improved cognition in unselected older people with or without dementia (Malouf and Grimley Evans, 2008). However, one large, 3-year trial of folic acid supplementation in 818 older people with high homocysteine levels reported some cognitive benefits, but did not examine dementia outcome (Durga et al., 2007). Another Cochrane review has examined the use of vitamin B12 supplementation alone and identified three studies, all in people with dementia, none of which reported benefits from this intervention but all of which were small and of poor quality (Malouf and Areosa Sastre, 2003). Since these reviews, one study of combined high-dose folic acid, vitamin B12 and vitamin B6 has been reported (Aisen et al., 2008). This study examined 409 subjects with normal homocysteine levels and with mild to moderate AD (MMSE 14–26) over 18 months and found no

benefits on cognition but an unexpected increase in depression in the intervention group.

Statins and dementia

No new randomized placebo-controlled trials in relation to dementia prevention have been published since the last guideline. The previous two large studies (heart protection study (HPS) and PROSPER) examined the effects of statins on cognitive decline and dementia as secondary study endpoints in large numbers of subjects (HPS enrolled 20,536 subjects, PROSPER 5804 subjects). Neither found a significant effect of statin treatment on cognitive function. Recent studies investigating the use of statins in established AD have shown no consistent evidence of benefit (See Table 10 for recommendations).

Disease-modifying therapies

There are several strategies currently being investigated for possible disease-modifying effects in dementia, though most studies focus on AD. These include the use of drugs that may modulate amyloid and/or tau processing, for example to decrease production of beta-amyloid or to increase its breakdown or removal, and other approaches which try to reduce the likelihood of amyloid monomers binding to produce oligomers and insoluble sheets. There have also been anti-inflammatory and neurotrophic strategies. Most of the interest has centred on anti-amyloid therapies, but other mechanisms have also been suggested. The earliest potential anti-amyloid therapies were directed at beta and gamma secretase inhibition or modulation, and this is still an active area. An alternative secretase strategy involved enhancing the alpha secretase pathway. Anti-aggregation therapy, aimed at reducing the formation of beta-amyloid, is also promising and there are also a number of molecules of potential interest aimed at reducing or inhibiting the phosphorylation of tau, including methylthioninium.

Table 10. Summary box: Other treatments for dementia

Intervention	Level of evidence	Recommendation
Dimebon for AD	There is preliminary level II evidence of a benefit of dimebon in AD, but further studies are awaited. Dimebon should not be prescribed for AD until further studies report.	B
Ginkgo biloba for dementia	There is level I evidence that Ginkgo biloba is not beneficial in improving cognitive symptoms in dementia.	A
Ginkgo biloba for prevention of dementia	There is level I evidence that Ginkgo biloba is not effective in the primary prevention of either all-cause dementia or Alzheimer's disease.	A
Hormone Replacement Therapy (HRT) in prevention and treatment of Alzheimer's disease in post-menopausal women	There is level I evidence that HRT is not effective either in treating cognition in Alzheimer's disease, or for the primary prevention of all-cause dementia or Alzheimer's disease.	A
Folate and vitamin B12 for dementia	There is level I evidence that HRT is harmful. HRT should not be prescribed either as a prevention or treatment for dementia, including Alzheimer's disease.	A
Statins for the treatment or prevention of dementia	There is type I evidence that supplementation with folic acid with or without vitamin B12 does not benefit cognition in people with dementia. On current evidence, neither vitamin B12 nor folate, either singly or in combination, can be recommended as treatments for dementia, or for dementia prevention.	A
	There is level I evidence that statins do not prevent dementia.	A
	There is level II evidence that statins do not produce cognitive benefits in AD.	B

Secretase inhibition

The most widely studied gamma secretase inhibitor to date has been tarenflurbil, a gamma secretase modulator which showed some limited evidence of efficacy of high dose (800 mg bd) compared with low dose (400 mg bd) and placebo in a Phase II study (Wilcock et al., 2008). Phase III studies over 18 months have shown no difference between tarenflurbil and placebo in cognition, global outcome or ADL (Green et al., 2009; Wilcock et al., 2009). Other studies of BACE (beta secretase) inhibitors are ongoing. Phase II studies of tramiprosate, which binds to soluble A beta reducing the production of the fibrillar form, have been undertaken in mild to moderate AD and proved negative.

Anti-neurofibrillary tangle strategies have included studies of methylthioninium which are ongoing as described earlier. An established treatment for bipolar disorder and depression, lithium, has also been explored, as it is able to regulate GSK-3 and potentially reduce tau phosphorylation. MacDonald et al. (2008) undertook a low-dose study for up to a year of treatment in AD. The side-effect profile was reasonable, though more lithium-treatment subjects dropped out earlier compared with controls, and although not powered for cognition, there was no difference between lithium treatment and placebo in cognition. Hampel et al. (2009) also undertook a trial of lithium which involved 71 mild AD subjects in a 10-week single-blind placebo-controlled study. There was no benefit of lithium on cognition (ADAS-COG) and no effect on CSF phosphorylated tau, GSK activity in lymphocytes or other biomarkers, and this approach is probably not worth further exploration.

Neurotrophic factors may also be beneficial, and Nerve Growth Factor (NGF) is the most studied of these in AD. The major challenge in studies of NGF is the delivery of the

drug to the target sites, which needs to be surgical (e.g. intracerebroventricular injection or stereotactical placement at an appropriate site) until other methods can be developed. Phase I studies of implants with fibroblasts modified to produce NGF have been reported, and in one study eight subjects with early AD showed both clinical and imaging evidence of increased brain activity. Phase II studies are ongoing and will determine whether it is worth developing NGF analogues that may be given less invasively.

Cholinesterase inhibitors have been shown to stabilize disease processes by modifying amyloid precursor protein (APP) processing via nicotinic receptors and other pathways in experimental animals, but convincing data from either clinical trials or routine clinical use are lacking. Similarly, memantine treatment of transgenic mice has suggested effects both on reduced amyloid and reduced tau phosphorylation, but once again clinical trial evidence is lacking. One major difficulty in studies is separating clinical symptomatic from disease-modifying effects in the absence of well-established biomarkers. Further development of brain imaging, whether serial MRI or amyloid PET, together with CSF markers should lead to future study designs that can tease out symptomatic from disease-modifying effects.

Metal-attenuating compounds

In the Alzheimer brain, A beta interacts with copper and zinc to form aggregates, including the neuro and synaptotoxic oligomers which aggregate further to form plaques. Compounds such as clioquinol and PBT2, a metal-protein-attenuating compound, prevent the interaction between A beta and these metals and so have been investigated as putative disease-modifying agents through a reduction in the formation of oligomers (Adlard et al., 2008). In a Phase IIa study

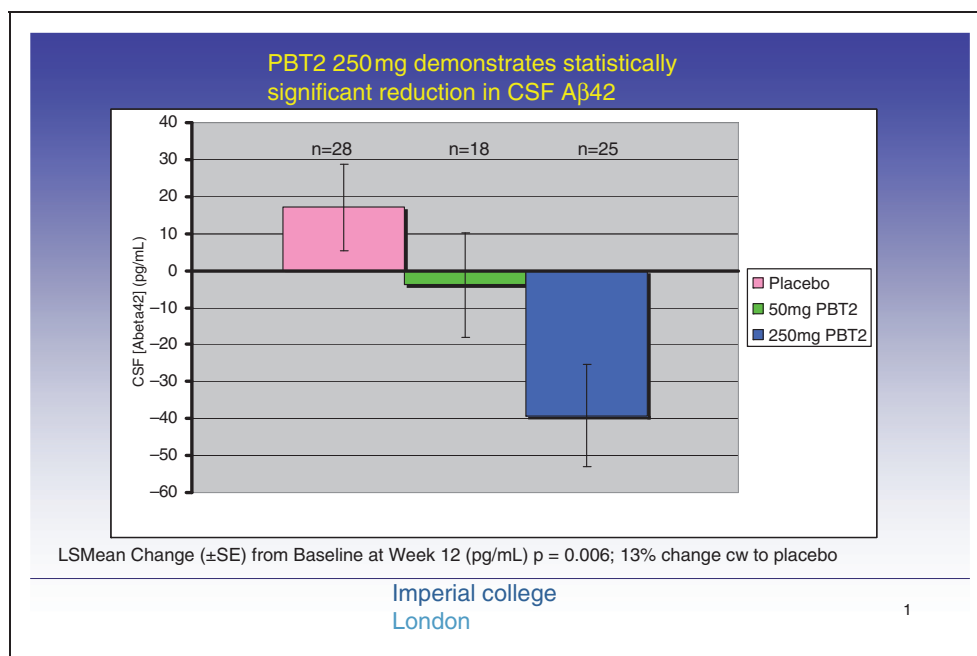


Figure 4. Effects of PBT2 on CSF biomarkers.

clioquinol showed promise and the need for further studies. However, manufacturing difficulties led to the cessation of further trials for clioquinol and the subsequent study of PBT2 (an 8-hydroxyquinoline derivative). A European and Australian study investigated the safety, efficacy and biomarker findings of PBT2 as a potential Abeta-modifying therapy for AD (Lannfelt et al., 2008). Some 78 subjects with mild AD (MMSE 20–26) on stable cholinesterase therapy were randomized to placebo, 50 mg PBT2 or 250 mg PBT2 taken once daily for 12 weeks. Both doses of PBT2 were well tolerated, with treatment-emerging events present in 48% of placebo, 50% of low dose and 62% of higher dose PBT2. Main side effects were headache, dizziness and back or neck pain. A significant change in CSF biomarkers of Abeta-42, and trend for Abeta-40 was seen when comparing high-dose PBT2 with placebo, and although no significant difference was seen in composite Z-score on neuropsychological test battery, executive function significantly improved. Further PBT2 studies are planned (see Figure 4).

Vaccination and immunization programmes

Early pioneering studies by Schenk et al. showed that vaccination of transgenic mice that over-expressed human APP with Abeta₁₋₄₂ reduced Abeta deposition (Schenk et al., 1999). The mice produced high titres of antibodies directed against Abeta following vaccination. In a separate experiment, passive immunization with monoclonal antibodies to Abeta similarly reduced cerebral amyloid deposits, implying that the beneficial effects of the vaccine were due to the generation of Abeta-specific antibodies (Bard et al., 2000).

The success of the initial mouse vaccine studies led to human trials of AN1792, an Abeta₁₋₄₂ vaccine, in 2001. In total, 80 patients were enrolled in the UK initial Phase I trial. An extension of the trial to 80 weeks included the addition of the emulsifier polysorbate 80, and was used in the subsequent larger Phase II trial that enrolled 372 patients (Gilman et al., 2005). This second trial was halted after 18 out of 298 (6%) immunized patients developed symptoms of meningo-encephalitis (Orgogozo et al., 2003). Post-mortem examination of the Phase I vaccine-treated patients revealed extensive plaque clearance from the cerebral cortex (Nicoll et al., 2003). Microglia contained Abeta particles, implying phagocytosis as the method of clearance (Nicoll et al., 2006). The degree of plaque removal was correlated with mean antibody response (Holmes et al., 2008).

Although post-mortem examination of AN1792-treated patients showed sustained and significant reductions in amyloid deposits within the brain, there was no convincing beneficial therapeutic effect. Long-term clinical follow-up and post-mortem neuropathological examination of patients from the original Phase I trial reported (Holmes et al., 2008) that even in immunized patients with almost complete plaque removal there was no evidence of a difference in time to severe dementia, with all but one case having severe dementia immediately prior to death (see Figure 5). In addition, while an analysis of a small subset of the Phase II patients ($n = 30$) found that antibody responders had a significantly slower rate of cognitive decline over 12 months (Hock et al., 2003), a full analysis of the trial data, including the placebo group, showed no therapeutic effect on cognitive decline (Gilman et al., 2005).

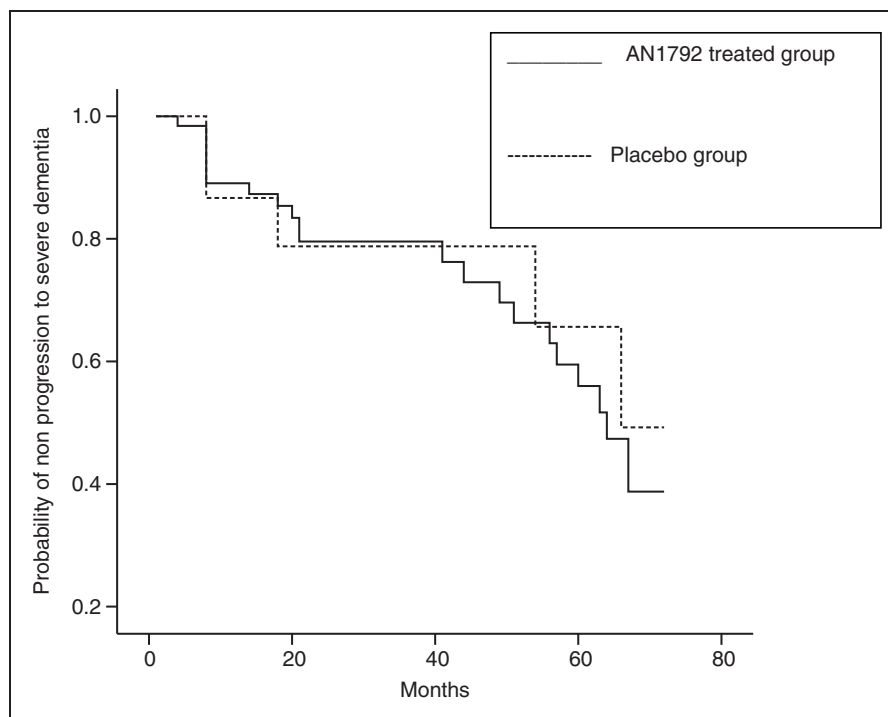


Figure 5. Kaplan-Meier estimates of survival time to severe dementia by treatment group.

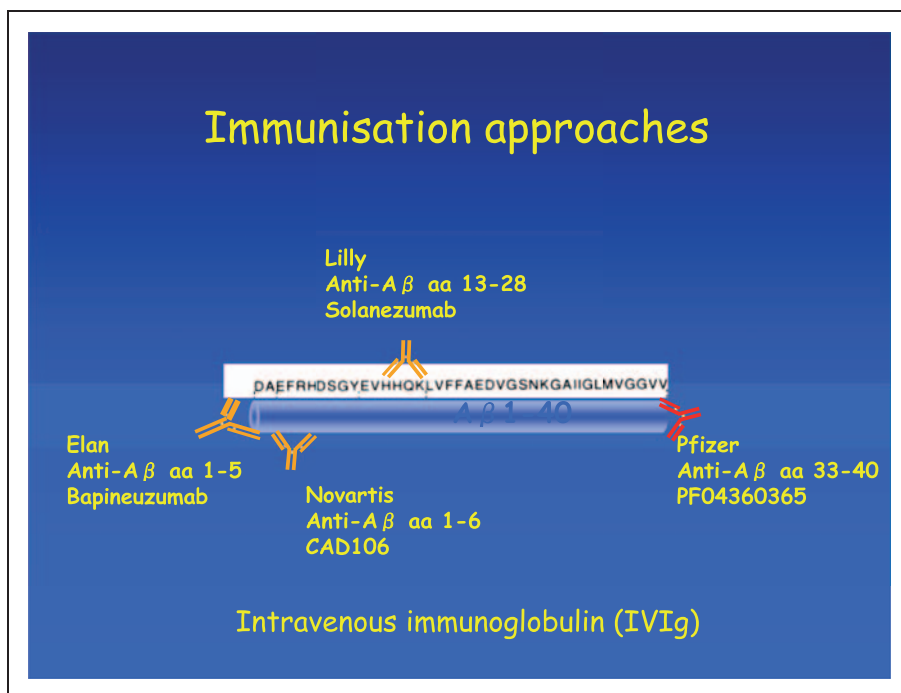


Figure 6. Approaches to develop immunization therapies for Alzheimer's disease.

Table 11. Summary box: Disease-modifying therapies

Intervention	Level of evidence	Recommendation
Metal protein attenuating compounds	There is level II evidence of their effect on Alzheimer's disease. These agents should not be prescribed until more data on safety and efficacy are available.	B
Gamma secretase inhibition	There is level I evidence that tarenfluril is not effective in Alzheimer's disease.	A
Vaccination and immunization studies	There is preliminary level II evidence of their effect in Alzheimer's disease on some endpoints, but also level II evidence that amyloid lowering does not affect clinical course. Amyloid-lowering agents should not be prescribed until more data on safety and efficacy are available.	B

Other therapeutic approaches that have now advanced to Phase III clinical trials include the use of passive immunization to the N terminus of Abeta (Bapineuzumab); Solanezumab (LY2062430),¹ a passive immunization approach considered to bind specifically to soluble Abeta, and the use of natural anti-amyloid antibodies (IVIg; Gammagard) (see Figure 6).

An 18-month randomized placebo-controlled Phase II study of Bapineuzumab in 234 patients with AD showed no significant difference in the primary outcome measures of the ADAS-COG and the Disability Assessment for Dementia (Gelinas et al., 1999). However, exploratory analysis did show significant differences for most of the clinical outcomes for non-carriers of ApoE E4. Side effects included reversible vasogenic oedema that was present in 10% of treated subjects and which was more frequent in ApoE E4 carriers (Salloway et al., 2009). Solanezumab (LY2062430) is considered to bind specifically to soluble Abeta. In short-term clinical studies, solanezumab appeared to have dose-dependent effects,

suggesting that this antibody may mobilize Abeta₁₋₄₂ in AD plaque, and normalize soluble CSF Abeta₁₋₄₂ in patients with AD. However, the clinical studies to date have been too short to evaluate any potential delay in the progress of AD. Notably, however, there have been reports of infusion reactions. Another approach is to use intravenous immunoglobulin (IVIg), obtained from the pooled plasma of healthy human blood donors, and which contains natural anti-amyloid antibodies. In a Phase I safety and preliminary efficacy clinical trial (US), eight patients with AD were treated with IVIg (Gammagard) for 6 months of therapy. Cognitive function stopped declining in all seven patients and improved in six of the seven patients (Relkin, et al., 2009). In another Phase I safety and preliminary efficacy clinical trial (Germany) five 'clinically probable or possible' AD patients were treated with IVIg and a slight improvement was observed on neuropsychological testing at 6 months in all patients except one, where the score did not change between baseline and at 6 months (Dodel et al., 2004). Other less

advanced studies include a Phase II passive immunization approach to the C terminus of Aβ (PF0436035; Pfizer) and a Phase I active immunization approach to the N terminus (CAD 106; Novartis) (Figure 6) (See Table 11 for recommendations).

Prospects for prevention

Preventing dementia, or delaying the onset by a few years, can have a major impact on its prevalence: delaying onset by 5 years would have the effect of halving the current prevalence (Jorm et al., 2005). Epidemiological evidence has identified a number of strategies that could potentially reduce the risk of dementia, both AD and VaD. These include interventions to reduce vascular risk, reducing the impact of other pathologies on the brain (for example the use of anti-inflammatories and antioxidants) and increasing neuronal reserve through, for example, non-pharmacological strategies such as cognitive training (Purandare et al., 2005). Unfortunately, the evidence from the secondary analyses of RCTs with cardiovascular outcomes as primary outcomes is mainly negative, except for the reduced risk of incident dementia observed in the Syst-Eur trial of antihypertensive nitrendipine (Forette et al., 1998). There is Level I evidence to show that statins, non-steroidal anti-inflammatories, vitamin E and Ginkgo do not prevent dementia in those with MCI (Purandare et al., 2005).

Treatments for reducing vascular risk and dementia

It is still not clear whether treatment of vascular risk factors decreases the risk of dementia and cognitive decline. Observational studies constantly show a lower risk for dementia, including AD, in individuals on antihypertensive treatment (Khachaturian et al., 2006), and some studies report similar findings in individuals on statins. Six RCTs with antihypertensive agents, and two with lipid-lowering agents, with dementia as a secondary endpoint have been conducted (Applegate et al., 1994; Beckett et al., 2008; Forette et al., 1998; McGuinness et al., 2009; Peters et al., 2008; Skoog and Gustafson, 2006; Skoog et al., 2005; Tzourio et al., 2003). All these trials observed significant reductions in the primary cardiovascular outcomes, but only the Syst-Eur trial (Forette et al., 1998) reported a reduction in the incidence of dementia in the treatment group. The first trials were mainly conducted among individuals below age 80, where risk for dementia is low (Skoog and Gustafson, 2006). The Hypertension in the Very Elderly Trial (HYVET-COG) was conducted on patients aged 80 and above who had systolic hypertension (Beckett et al., 2008). The HYVET trial had to terminate early as interim analyses showed reduction in both stroke and total mortality in actively treated patients. However, the cognitive function sub-study (Peters et al., 2008) found no statistical differences between treatment and placebo groups regarding dementia incidence or

Table 12. Summary box: Prevention of dementia

Intervention	Level of evidence	Recommendation
Prevention of dementia	There is no evidence at present to support any intervention to prevent dementia. There is type II evidence that antihypertensive therapy may be helpful, but further studies are required.	B
Treatment of vascular risk factors	There is level III and IV evidence that vascular risk factors are inadequately recognized and managed in people with dementia, and that recognition and management should be as active as in those without dementia.	D

Table 13. Summary of all recommendations

Intervention	Level of evidence	Recommendation
Assessment and diagnosis		
Making a diagnosis of dementia subtype	There is type I evidence that the clinical diagnosis of dementia subtype according to internationally agreed consensus criteria is accurate, but some of the newly proposed criteria still require validation.	A
Use of structural brain imaging for diagnosis	There is type I evidence that CT or MRI should be used to exclude other cerebral pathologies and to help establish the subtype diagnosis.	A
Use of SPECT or PET imaging	There is type I evidence that perfusion (HMPAO) SPECT or FDG PET can differentiate between AD, VaD and FTD.	A
	There is type I evidence that dopaminergic SPECT or PET imaging can help differentiate DLB from AD.	A
CSF biomarkers	There is type II evidence that CSF markers of amyloid and tau may be useful diagnostic markers for Alzheimer's disease, but further standardization and validation is required before they can be used clinically.	B

(continued)

Table 13. Continued

Intervention	Level of evidence	Recommendation
Alzheimer's disease		
Treatment with cholinesterase inhibitors and memantine	There is type I evidence for the efficacy of cholinesterase inhibitors in the treatment of mild to moderate Alzheimer's disease and type I evidence for memantine in moderate to severe Alzheimer's disease.	A
Switching between cholinesterase inhibitors.	There is type II evidence to support the switching of one cholinesterase inhibitor to another if the first is not tolerated or effective.	B
Combination therapy	There is type II evidence for adding memantine to a cholinesterase inhibitor, but also a negative type 1b study. Until further studies are available the benefits of combination therapy is unclear.	B
Dementia with Lewy bodies		
Cholinesterase inhibitors	There is type I evidence to support treatment with cholinesterase inhibitors in Lewy body dementia, both dementia with Lewy bodies and Parkinson's disease dementia and that both cognitive and neuropsychiatric symptoms improve.	A
Memantine	There is type II evidence to support equal efficacy of all three cholinesterase inhibitors. There is type II evidence that memantine may produce cognitive and global improvements.	B B
Vascular dementia		
Treatment with cholinesterase inhibitors and memantine	There is type I evidence showing small cognitive improvements with both cholinesterase inhibitors and memantine in vascular dementia. However, benefits in terms of global outcome are not seen and adverse events for cholinesterase inhibitors (but not memantine) are significantly greater than placebo. Evidence indicates that neither cholinesterase inhibitors nor memantine should be prescribed to people with vascular dementia, though those with mixed VaD and Alzheimer's disease may benefit.	A
Frontotemporal dementia		
Cholinesterase inhibitors	There is type I evidence that cholinesterase inhibitors are not recommended for the treatment of frontotemporal dementia.	A
SSRIs	There is type II evidence that SSRIs may help some behavioural aspects of FTD, but do not improve cognition. Studies are mixed and further evidence is needed.	B
Progressive supranuclear palsy		
Cholinesterase inhibitors	There is type II evidence that cholinesterase inhibitors are not helpful in progressive supranuclear palsy. No treatments can be recommended at the current time.	B
Mild cognitive impairment		
Treatment with cholinesterase inhibitors and vitamin E	There is type I evidence that cholinesterase inhibitors are not effective in reducing the risk of developing Alzheimer's disease and type I evidence that vitamin E is not effective in reducing the risk of Alzheimer's disease.	A
Other treatments for dementia		
Dimebon for AD	There is preliminary level II evidence of a benefit of dimebon in AD, but further studies are awaited. Dimebon should not be prescribed for AD until further studies report.	B
Ginkgo biloba for dementia	There is level I evidence that Ginkgo biloba is not beneficial in improving cognitive symptoms in dementia.	A
Ginkgo biloba for prevention of dementia	There is level I evidence that Ginkgo biloba is not effective in the primary prevention of either all-cause dementia or Alzheimer's disease.	A
Hormone Replacement Therapy (HRT) in prevention and treatment of Alzheimer's disease in post-menopausal women	There is level I evidence that HRT is not effective either in treating cognition in Alzheimer's disease, or for the primary prevention of all-cause dementia or Alzheimer's disease. There is level I evidence that HRT is harmful. HRT should not be prescribed either as a prevention or treatment for dementia, including Alzheimer's disease.	A A
Folate and vitamin B12 for dementia	There is type I evidence that supplementation with folic acid with or without vitamin B12 does not benefit cognition in people with dementia. On current evidence, neither vitamin B12 nor folate, either singly or in combination, can be recommended as treatments for dementia, or for dementia prevention.	A
Statins for the treatment or prevention of dementia	There is level I evidence that statins do not prevent dementia. There is level II evidence that statins do not produce cognitive benefits in AD	A B

(continued)

Table 13. Continued

Intervention	Level of evidence	Recommendation
Disease modifying therapies		
Metal protein attenuating compounds	There is level II evidence of their effect on Alzheimer's disease. These agents should not be prescribed until more data on safety and efficacy are available.	B
Gamma secretase inhibition	There is level I evidence that tarenflurbil is not effective in Alzheimer's disease.	A
Vaccination and immunization studies	There is preliminary level II evidence of their effect in Alzheimer's disease on some endpoints, but also level II evidence that amyloid lowering does not affect clinical course. Amyloid-lowering agents should not be prescribed until more data on safety and efficacy are available.	B
Prevention of dementia		
Prevention of dementia	There is no evidence at present to support any intervention to prevent dementia. There is type II evidence that antihypertensive therapy may be helpful, but further studies are required.	B
Treatment of vascular risk factors	There is level III and IV evidence that vascular risk factors are inadequately recognized and managed in people with dementia, and that recognition and management should be as active as in those without dementia.	D

cognitive decline. Thus, the results of the HYVET trial suggest that treatment of systolic hypertension is indicated also in very elderly individuals to decrease the risk of stroke and total mortality, while short-term treatment show no effect on the incidence of dementia. It is noteworthy that no study showed increased risk for dementia in the treatment groups. There are many possible explanations for the negative results on cognitive function, including short time of follow-up, inclusion of mentally healthy participants at baseline, practice or learning effects, selective drop-out in relation to dementia, and difficulties in diagnosing dementia in large trials (Skoog and Gustafson, 2006).

So far, no large RCT has evaluated the effect of antihypertensive treatment or cholesterol lowering on cognitive symptom in individuals with MCI or dementia. In the SCOPE trial, a secondary analysis showed that the treatment group had less cognitive decline than the placebo group among those with MCI at baseline (Skoog et al., 2005). Observational studies indicate that Alzheimer patients on antihypertensive drugs (Mielke et al., 2007) or treatment for vascular risk factors (Deschaintre et al., 2009) have a slower decline in cognitive function than those not on treatment. One small RCT suggested that treatment of vascular risk factors did not affect progression of AD (Richard et al., 2009). In the future, it could be discussed whether RCTs are ethical in demented individuals with hypertension or other vascular risk factors, due to the beneficial effect on cardiovascular outcomes of treatment shown in large trials on mainly non-demented individuals.

Most individuals with hypertension and other vascular risk factors are not detected by the health care system. The same is true for dementia and cognitive impairment, and this can impact on compliance with treatment. It is noteworthy that a recent meta-analysis showed that only a minority of guidelines for treatment of vascular disease in the elderly mention the importance of detecting cognitive impairment (Rockwood et al., 2009).

In summary, no RCT has shown that treatment of vascular risk factors decreases the risk of developing dementia, or slows

progression of cognitive symptoms in individuals with MCI or dementia. However, there is a lack of long-term studies and also of RCTs investigating the effect on cognitive function of treatment of vascular risk factors in individuals with MCI or dementia. Irrespective of the effect on cognitive function, vascular risk factors should be treated due to the effect on cardiovascular and cerebrovascular disease (See Table 12 for recommendations).

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Conflict of interest

Expenses associated with the meeting were in part defrayed by charges relating to pharmaceutical companies who sent representatives to the meeting and had the opportunity to comment on the evidence presented but who were not part of the writing group (Lundbeck, Pfizer, Eisai). Contributors at the consensus meeting each provided a declaration of interest of potential conflict in line with BAP and Journal of Psychopharmacology policy. These are held on file at the BAP Office. BAP Executive Officer, Susan Chandler, BAP Office, Cambridge, UK (susan@bap.org.uk).

Note

1. Since the consensus meeting was held Lilly have stopped all trials of their gamma secretase inhibitor because of lack of efficacy and increased side effects (risk of skin cancer) (see <http://newsroom.lilly.com/releasedetail.cfm?releaseid=499794>).

References

- Aarsland D, Ballard C, Walker Z, et al. (2009) Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies; a double-blind, placebo-controlled, multicentre trial. *Lancet Neurol* 8: 613–618.
- Aarsland D, Laake K, Larsen JP and Janvin C (2002) Donepezil for cognitive impairment in Parkinson's disease: a randomized controlled study. *J Neurol Neurosurg Psychiatry* 72: 708–712.
- Aarsland D, Rongve A, Nore SP, et al. (2008) Frequency and case identification of dementia with Lewy bodies using the revised consensus criteria. *Dement Geriatr Cogn Disord* 26: 445–452.
- Adlard PA, Cherny RA, Finkelstein DI, et al. (2008) Rapid restoration of cognition in Alzheimer's transgenic mice with 8-hydroxy quinoline analogs is associated with ionophoric activity. *Neuron* 59: 43–55.
- Ahmad S, Orrell M, Iliffe S and Gracie A (2010) GPs' attitudes, awareness, and practice regarding early diagnosis of dementia. *Br J Gen Pract* 60(578): 360–365.
- Aisen PS, Schneider LS, Sano M, et al. (2008) High-dose B vitamin supplementation and cognitive decline in Alzheimer disease: a randomized controlled trial. *JAMA* 300(15): 1774–1783.
- Aizenstein HJ, Nebes RD, Saxton JA, et al. (2008) Frequent amyloid deposition without significant cognitive impairment among the elderly. *Arch Neurol* 65: 1509–1517.
- American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders, 4th edn (DSM-IV)*. Arlington, VA: American Psychiatric Publishing Inc.
- American Psychiatric Association (2000) *DSM-III*. Arlington, VA: American Psychiatric Publishing Inc.
- Anderson IM, Ferrier IN, Baldwin RC, et al. (2008) Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2000 British Association for Psychopharmacology guidelines. *J Psychopharmacol* 22: 343–396.
- Applegate WB, Pressel S, Wittes J, et al. (1994) Impact of the treatment of isolated systolic hypertension on behavioral variables. Results from the Systolic Hypertension in the Elderly Program. *Arch Intern Med* 154: 2154–2160.
- Ashley PJS (2009) Clinical aspects of living with dementia. In: Jacoby R, Oppenheimer C, Denning T and Thomas A (eds) *Oxford Textbook of Old Age Psychiatry*. Oxford: Oxford University Press.
- Auchus AP, Brashear HR, Salloway S, Korczyn AD, De Deyn PP and Gassmann-Mayer C (2007) Galantamine treatment of vascular dementia: a randomized trial. *Neurology* 69: 448–458.
- Ballard C, Sauter M, Scheltens P, et al. (2008) Efficacy, safety and tolerability of rivastigmine capsules in patients with probable vascular dementia: the VantageE study. *Curr Med Res Opin* 24: 2561–2574.
- Bard F, Cannon C, Barbour R, et al. (2000) Peripherally administered antibodies against amyloid beta-peptide enter the central nervous system and reduce pathology in a mouse model of Alzheimer disease. *Nat Med* 6: 916–919.
- Baskys A and Hou AC (2007) Vascular dementia: pharmacological treatment approaches and perspectives. *Clin Interv Aging* 2(3): 327–335.
- Beckett N, Peters R, Fletcher A, et al. (2008) Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 358: 1887–1898.
- Bensimon G, Ludolph A, Agid Y, et al. (2009) Riluzole treatment, survival and diagnostic criteria in Parkinson plus disorders: the NNIPPS study. *Brain* 132: 156–171.
- Bhasin M, Rowan E, Edwards K and McKeith I (2007) Cholinesterase inhibitors in Dementia with Lewy Bodies – which one to use? *Int J Geriatr Psychiatry* 22: 890–895.
- Birks J and Flicker L (2009) Donepezil for mild cognitive impairment. *Cochrane Database Syst Rev* Art. No.: CD006104, DOI: 10.1002/14651858.
- Birks J and Grimley Evans J (2009) Ginkgo biloba for cognitive impairment and dementia. *Cochrane Database Syst Rev* Art. No.: CD003120, DOI: 10.1002/14651858.
- Bocti C, Black S and Frank C (2007) Management of dementia with a cerebrovascular component. *Alzheimers Dement* 3: 398–403.
- Bonelli SB, Ransmayr G, Steffelbauer M, Lukas T, Lampl C and Deibl M (2004) L-dopa responsiveness in dementia with Lewy bodies, Parkinson disease with and without dementia. *Neurology* 63: 376–378.
- Boxer AL, Lipton AM, Womack K, et al. (2009) An open-label study of memantine treatment in 3 subtypes of frontotemporal lobar degeneration. *Alzheimer Dis Assoc Disord* 23: 211–217.
- Burns A and O'Brien J (2006) Clinical practice with anti-dementia drugs: a consensus statement from British Association for Psychopharmacology. *J Psychopharmacol* 20: 732–755.
- Burton EJ, Barber R, Mukaetova-Ladinska EB, et al. (2009) Medial temporal lobe atrophy on MRI differentiates Alzheimer's disease from dementia with Lewy bodies and vascular cognitive impairment: a prospective study with pathological verification of diagnosis. *Brain* 132: 195–203.
- Caltagirone C, Bianchetti A, Di Luca M, et al. (2005) Guidelines for the treatment of Alzheimer's disease from the Italian Association of Psychogeriatrics. *Drugs Aging* 22(Suppl 1): 1–26.
- Collinge J, Gorham M, Hudson F, et al. (2009) Safety and efficacy of quinacrine in human prion disease (PRION-1 study): a patient-preference trial. *Lancet Neurol* 8: 334–344.
- Colloby SJ, Firbank MJ, Pakrasi S, et al. (2008) A comparison of 99mTc-exametazime and 123I-FP-CIT SPECT imaging in the differential diagnosis of Alzheimer's disease and dementia with Lewy bodies. *Int Psychogeriatrics* 20: 1124–1140.
- Cooper C, Blanchard M, Selwood A and Livingston G (2010) Antidementia drugs: prescription by level of cognitive impairment or by socio-economic group? *Aging Ment Health* 14: 85–89.
- Coull JT, Sahakian BJ and Hodges JR (1996) The alpha(2) antagonist idazoxan remediates certain attentional and executive dysfunction in patients with dementia of frontal type. *Psychopharmacology* 123: 239–249.
- Deakin JB, Rahman S, Nestor PJ, Hodges JR and Sahakian BJ (2004) Paroxetine does not improve symptoms and impairs cognition in frontotemporal dementia: a double-blind randomized controlled trial. *Psychopharmacology* 172: 400–408.
- DeKosky ST, Williamson JD, Fitzpatrick AL, et al. (2008) Ginkgo biloba for prevention of dementia: a randomized controlled trial. *JAMA* 300: 2253–2262.
- Deschaintre Y, Richard F, Leys D and Pasquier F (2009) Treatment of vascular risk factors is associated with slower decline in Alzheimer disease. *Neurology* 73: 674–680.
- Dichgans M, Markus HS, Salloway S, et al. (2008) Donepezil in patients with subcortical vascular cognitive impairment: a randomised double-blind trial in CADASIL. *Lancet Neurol* 7: 310–318.
- Diehl-Schmid J, Förstl H, Perneczky R, Pohl C and Kurz A (2008) A 6-month, open-label study of memantine in patients with frontotemporal dementia. *Int J Geriatr Psychiatry* 23: 754–759.
- Dodel RC, Du Y, Depboylu C, et al. (2004) Intravenous immunoglobulins containing antibodies against beta-amyloid for the treatment of Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 75: 1472–1474.
- Dodge HH, Zitzelberger T, Oken BS, Howieson D and Kaye J (2008) A randomized placebo-controlled trial of Ginkgo biloba for the prevention of cognitive decline. *Neurology* 70(19 Pt 2): 1809–1817.
- Doody RS, Gavrilova SI, Sano M, et al. (2008) Effect of dimebon on cognition, activities of daily living, behaviour, and global function

- in patients with mild-to-moderate Alzheimer's disease: a randomised, double-blind, placebo-controlled study. *Lancet* 372(9634): 207–215.
- Dubois B, Feldman HH, Jacova C, et al. (2007) Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol* 6: 734–746.
- Durga J, van Boxtel MP, Schouten EG, et al. (2007) Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double-blind, controlled trial. [see comment]. *Lancet* 369(9557): 208–216.
- Emre M, Aarsland D, Albanese A, et al. (2004) Rivastigmine for dementia associated with Parkinson's disease. *New Eng J Med* 351: 2509–2518.
- Emre M, Aarsland D, Brown R, et al. (2007) Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord* 22: 1689–1707; quiz 1837.
- Fabbrini G, Barbanti P, Bonifati V, et al. (2001) Donepezil in the treatment of progressive supranuclear palsy. *Acta Neurol Scand* 103: 123–125.
- Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P and Whalen E (2001) A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. *Neurology* 57: 613–620.
- Flicker L and Grimley Evans J (2001) Piracetam for dementia or cognitive impairment. *Cochrane Database Syst Rev* Art. No. CD001011, DOI: 10.1002/14651858.
- Forette F, Seux M-L, Staessen J, et al. (1998) Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (syst-Eur) trial. *Lancet* 352: 1347–1351.
- Gauthier S, Loft H and Cummings J (2008) Improvement in behavioural symptoms in patients with moderate to severe Alzheimer's disease by memantine: a pooled data analysis. *Int J Geriatr Psychiatry* 23: 537–545.
- Gelinas I, Gauthier L, McIntyre M and Gauthier S (1999) Development of a functional measure for persons with Alzheimer's Disease: The Disability Assessment for Dementia. *Am J Occup Therapy* 53: 471–481.
- Gilman S, Koller M, Black RS, et al. (2005) Clinical effects of Abeta immunization (AN1792) in patients with AD in an interrupted trial. *Neurology* 64: 1553–1562.
- Goldman JG, Goetz CG, Brandabur M, Sanfilippo M and Stebbins GT (2008) Effects of dopaminergic medications on psychosis and motor function in dementia with Lewy bodies. *Mov Disord* 23: 2248–2250.
- Grace J, Daniel S, Stevens T, et al. (2001) Long-term use of rivastigmine in patients with dementia with Lewy bodies: an open-label trial. *Int Psychogeriatr* 13: 199–205.
- Green RC, Schneider LS, Amato DA, et al. (2009) Effect of Tarenflurbil on cognitive decline and activities of daily living in patients with mild Alzheimer's disease. A randomized controlled trial. *JAMA* 302: 2557–2564.
- Hampel H, Ewers M, Burger K, et al. (2009) Lithium trial in Alzheimer's disease: a randomised, single blind, placebo controlled, multicenter 10-week study. *J Clin Psychiatry* 70: 922–931.
- Hao Z, Liu M, Liu Z and Lv D (2009) Huperzine A for vascular dementia. *Cochrane Database Syst Rev* Art. No. CD007365, DOI: 10.1002/14651858.
- Hock C, Konietzko U, Streffer JR, et al. (2003) Antibodies against beta-amyloid slow cognitive decline in Alzheimer's disease. *Neuron* 38: 547–554.
- Hogervorst E, Yaffe K, Richards M and Huppert FAH (2009) Hormone replacement therapy to maintain cognitive function in women with dementia. *Cochrane Database Syst Rev* Art. No. CD003799, DOI: 10.1002/14651858.
- Holmes C, Boche D, Wilkinson D, et al. (2008) Long-term effects of Abeta42 immunisation in Alzheimer's disease: follow-up of a randomised, placebo-controlled phase I trial. *Lancet* 372(9634): 216–223.
- Hort J, O'Brien JT, Gainotti G, et al., on behalf of the EFNS Scientist Panel on Dementia (2010) EFNS guidelines for the diagnosis and management of Alzheimer's disease. *Eur J Neurol* 17(10): 1236–1248.
- Howard RJ, Juszcak E, Ballard CG, et al. (2007) Donepezil for the treatment of agitation in Alzheimer's disease. *New Eng J Med* 357: 1382–1392.
- Huey ED, Garcia C, Wassermann EM, Tierney MC and Grafman J (2008) Stimulant treatment of frontotemporal dementia in 8 patients. *J Clin Psychiatry* 69: 1981–1982.
- Johnell K, Weitof GR and Fastbom J (2008) Education and use of dementia drugs: a register-based study of over 600,000 older people. *Dement Geriatr Cogn Disord* 25: 54–59.
- Jorm AF, Dear KB and Burgess NM (2005) Projections of future numbers of dementia cases in Australia with and without prevention. *Aust N Z J Psychiatry* 39: 959–963.
- Kavirajan H and Schneider LS (2007) Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomised controlled trials. *Lancet Neurol* 6: 782–792.
- Khachaturian AS, Zandi PP, Lyketsos CG, et al. (2006) Anti-hypertensive medication use and incident Alzheimer's disease. The Cache County Study. *Arch Neurol* 63: 686–692.
- Knopman DS, DeKosky ST, Cummings JL, et al. (2001) Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 56: 1143–1153.
- Lannfelt L, Blennow K, Zetterberg H, et al. (2008) Targeting A β as a modifying therapy of Alzheimer's disease: safety, efficacy and biomarker findings of a Phase IIa Randomised, Double-Blind Placebo-Controlled trial of PBT2. *Lancet Neurol* 7: 779–786.
- Lebert F, Stekke W, Hasenbroekx C and Pasquier F (2004) Frontotemporal dementia: a randomised, controlled trial with trazodone. *Dement Geriatr Cogn Disord* 17: 355–359.
- Lethaby A, Hogervorst E, Richards M, Yesufu A and Yaffe K (2008) Hormone replacement therapy for cognitive function in postmenopausal women. *Cochrane Database Syst Rev* Art. No. CD003122, DOI: 10.1002/14651858.
- Litvan I, Phipps M, Pharr VL, Hallett M, Grafman J and Salazar A (2001) Randomized placebo-controlled trial of donepezil in patients with progressive supranuclear palsy. *Neurology* 57: 467–473.
- Litvan I, Bhatia KP, Burn DJ, et al. (2003) Movement Disorders Society Scientific Issues Committee report: SIC Task Force appraisal of clinical diagnostic criteria for Parkinsonian disorders. *Mov Disord* 18: 467–486.
- Lopez OL, Becker JT, Wahed AS, et al. (2009) Long-term effects of the concomitant use of memantine with cholinesterase inhibition in Alzheimer disease. *J Neurol Neurosurg Psychiatry* 80: 600–607.
- Lopez-Arrieta JM and Birks J (2002) Nimodipine for primary degenerative, mixed and vascular dementia. *Cochrane Database Syst Rev* Art. No. CD000147, DOI: 10.1002/14651858.
- Loy C and Schneider L (2006) Galantamine for Alzheimer's disease and mild cognitive impairment. *Cochrane Database System Rev* Art. No. CD001747, DOI: 10.1002/14651858.
- Lu PH, Edland SD, Teng E, et al. (2009) Donepezil delays progression to AD in MCI subjects with depressive symptoms. *Neurology* 72: 2115–2121.
- McCarney R, Fisher P, Iliffe S, et al. (2008) Ginkgo biloba for mild to moderate dementia in a community setting: a pragmatic, randomised, parallel-group, double-blind, placebo-controlled trial. *Int J Geriatr Psychiatry* 23: 1222–1230.

- MacDonald A, Briggs K, Poppe M, Higgins A, Velayudhan L and Lovestone S (2008) A feasibility and tolerability study of lithium in Alzheimer's disease. *Int J Geriatr Psychiatry* 23: 704–711.
- Malouf R and Areosa Sastre A (2003) Vitamin B12 for cognition. *Cochrane Database Syst Rev* Art. No. CD004394, DOI: 10.1002/14651858.
- Malouf R and Grimley Evans J (2008) Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people. *Cochrane Database Syst Rev* Art. No. CD004514, DOI: 10.1002/14651858.
- Martinon-Torres G, Fioravanti M and Grimley EJ (2004) Trazodone for agitation in dementia. *Cochrane Database Syst Rev* Art. No. CD004990, DOI: 10.1002/14651858.
- Mattsson N, Zetterberg H, Hansson O, et al. (2009) CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. *JAMA* 302: 385–393.
- Mazza M, Capuano A, Bria P and Mazza S (2006) Ginkgo biloba and donepezil: a comparison in the treatment of Alzheimer's dementia in a randomized placebo-controlled double-blind study. *Eur J Neurol* 13: 981–985.
- McGuinness B, Todd S, Passmore P and Bullock R (2009) Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia. *Cochrane Database Syst Rev* Art. No. CD004034, DOI: 10.1002/14651858.
- McKeith I, Del Ser T, Spano P, et al. (2000) Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. *Lancet* 356: 2031–2036.
- McKeith IG, Dickson DW, Lowe J, et al., Consortium on DLB (2005) Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology* 65: 1863–1872.
- McKeith IG, Galasko D, Kosaka K, et al. (1996) Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology* 47: 1113–1124.
- McKeith I, Mintzer J, Aarsland D, et al. (2004) International Psychogeriatric Association Expert Meeting on DLB. Dementia with Lewy bodies. *Lancet Neurol* 3: 19–28.
- McKeith IG, Rowan E, Askew K, et al. (2006) More severe functional impairment in dementia with Lewy bodies than Alzheimer disease is related to extrapyramidal motor dysfunction. *Am J Geriatr Psychiatry* 14: 582–588.
- McKeith I, O'Brien J, Walker Z, et al. (2007) Sensitivity and specificity of dopamine transporter imaging with 123I-FP-CIT SPECT in dementia with Lewy bodies: a phase III, multicentre study. *Lancet Neurol* 6: 305–313.
- McKhann G, Drachman D, Folstein M, Katzman R, Price D and Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 34: 939–944.
- McShane R, Areosa Sastre A and Minakaran N (2006) Memantine for dementia. *Cochrane Database Syst Rev* Art. No. CD003154, DOI: 10.1002/14651858.
- Meocci P, Bladström A and Stender K (2009) Effects of memantine on cognition in patients with moderate to severe Alzheimer's disease: post-hoc analyses of ADAS-cog and SIB total and single-item scores from six randomized, double-blind, placebo-controlled studies. *Int J Geriatr Psychiatry* 24: 532–538.
- Mendez MF, Shapira JS, McMurtray A and Licht E (2007) Preliminary findings: behavioral worsening on donepezil in patients with frontotemporal dementia. *Am J Geriatr Psychiatry* 15: 84–87.
- Mendiondo MS, Ashford JW, Kryscio RJ and Schmitt FA (2000) Modelling mini mental state examination changes in Alzheimer's disease. *Stat Med* 19: 1607–1616.
- Mielke MM, Rosenberg PB, Tschanz J, et al. (2007) Vascular factors predict rate of progression in Alzheimer disease. *Neurology* 69: 1850–1858.
- Minett TSC, Thomas A, Wilkinson LM, et al. (2003) What happens when donepezil is suddenly withdrawn? An open-label trial in dementia with Lewy bodies and Parkinson's disease with dementia. *Int J Geriatr Psychiatry* 18: 988–993.
- Mitchell AJ (2009) CSF phosphorylated tau in the diagnosis and prognosis of mild cognitive impairment and Alzheimer's disease: a meta-analysis of 51 studies. *J Neurol Neurosurg Psychiatry* 80: 966–975.
- Molloy S, McKeith I, O'Brien JT and Burn D (2005) The role of levodopa in the management of dementia with Lewy bodies. *J Neurol Neurosurg Psychiatry* 76: 1200–1203.
- Moretti R, Torre P, Antonello RM, Cazzato G and Bava A (2003) Frontotemporal dementia: paroxetine as a possible treatment of behavior symptoms. A randomized, controlled, open 14-month study. *Eur Neurol* 49: 13–19.
- Moretti R, Torre P, Antonello RM, Cazzato G and Pizzolato G (2008) Different responses to rivastigmine in subcortical vascular dementia and multi-infarct dementia. *Am J Alzheimers Dis Other Dement* 23: 167–176.
- Napryeyenko O and Borzenko I (2007) Ginkgo biloba special extract in dementia with neuropsychiatric features. A randomised, placebo-controlled, double-blind clinical trial. *Arzneimittelforschung* 57: 4–11.
- National Collaborating Centre for Mental Health (2006) *Dementia: Supporting people with dementia and their carers in health and social care*. London: NICE.
- Nicoll JA, Barton E, Boche D, et al. (2006) Abeta species removal after abeta42 immunization. *J Neuropathol Exp Neurol* 65: 1040–1048.
- Nicoll JA, Wilkinson D, Holmes C, et al. (2003) Neuropathology of human Alzheimer disease after immunization with amyloid-beta peptide: a case report. *Nat Med* 9: 448–452.
- O'Brien JT (2007) Role of imaging techniques in the diagnosis of dementia. *Br J Radiology* 80(Spec No 2): S71–77.
- O'Brien JT, Erkinjuntti T, Reisberg B, et al. (2003) Vascular cognitive impairment. *Lancet Neurol* 2: 89–98.
- O'Brien JT, McKeith IG, Walker Z, et al. (2009) Diagnostic accuracy of 123I-FP-CIT SPECT in possible dementia with Lewy bodies. *Br J Psychiatry* 194: 34–39.
- Okello A, Koivunen J, Edison P, et al. (2009) Conversion of amyloid positive and negative MCI to AD over 3 years: an 11C-PIB PET study. *Neurology* 73: 754–760.
- Orgogozo JM, Gilman S, Dartigues JF, et al. (2003) Subacute meningoencephalitis in a subset of patients with AD after Abeta42 immunization. *Neurology* 61: 46–54.
- Pantoni L, del Ser T, Soglian AG, et al. (2005) Efficacy and safety of nimodipine in subcortical vascular dementia: a randomized placebo-controlled trial. *Stroke* 36: 619–624.
- Passmore AP, Bayer AJ and Steinhagen-Thiessen E (2005) Cognitive, global, and functional benefits of donepezil in Alzheimer's disease and vascular dementia: results from large-scale clinical trials. *J Neurol Sci* 229–230: 141–146.
- Perry E, Ziabreva I, Perry R, Aarsland D and Ballard C (2005) Absence of cholinergic deficits in "pure" vascular dementia. *Neurology* 64: 132–133.
- Peters R, Beckett N, Forette F, et al. (2008) Incident dementia and blood pressure lowering, the results of the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG). A double-blind, placebo controlled trial. *Lancet Neurol* 7: 683–689.

- Porsteinsson AP, Grossberg GT, Mintzer J and Olin JT (2008) Memantine treatment in patients with mild to moderate Alzheimer's disease already receiving a cholinesterase inhibitor: A randomized, double-blind, placebo-controlled trial. *Curr Alzheimer Res* 5: 83–89.
- Purandare N, Ballard C and Burns A (2005) Prevention of Alzheimer's disease. In: Burns A, O'Brien J and Ames D (eds) *Dementia (3rd Edition)*. London: Edward Arnold, 515–521.
- Rahman S, Robbins TW, Hodges JR, et al. (2006) Methylphenidate ('Ritalin') can ameliorate abnormal risk-taking behavior in the frontal variant of frontotemporal dementia. *Neuropsychopharmacology* 31: 651–658.
- Relkin NR, Szabo P, Adamiak B, et al. (2009) 18-Month study of intravenous immunoglobulin for treatment of mild Alzheimer disease. *Neurobiol Aging* 30: 1728–1736.
- Richard E, Kuiper R, Dijkgraaf MG and Van Gool WA (2009) Evaluation of vascular care in Alzheimer's disease. Vascular care in patients with Alzheimer's disease with cerebrovascular lesions – a randomized clinical trial. *J Am Geriatr Soc* 57: 797–805.
- Rockwood K, Middleton LE, Moorhouse PK, Skoog I and Black SE (2009) The inclusion of cognition in vascular risk factor clinical practice guidelines. *Clin Interv Aging* 4: 425–433.
- Rojas-Fernandez CH and Moorhouse P (2009) Current concepts in vascular cognitive impairment and pharmacotherapeutic implications. *Ann Pharmacother* 43(7): 1310–1323.
- Roman GC, Tatemichi TK, Erkinjuntti T, et al. (1993) Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology* 43: 250–260.
- Rowe CC, Ng S, Ackermann U, et al. (2007) Imaging beta-amyloid burden in aging and dementia. *Neurology* 68: 1718–1725.
- Salloway S, Sperling R, Gilman S, et al. (2009) A phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer disease. *Neurology* 73: 2061–2070.
- Samuel W, Caligiuri M, Galasko D, et al. (2000) Better cognitive and psychopathologic response to donepezil in patients prospectively diagnosed as dementia with Lewy bodies: a preliminary study. *Int J Geriatr Psychiatry* 15: 794–802.
- Schenk D, Barbour R, Dunn W, et al. (1999) Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse. *Nature* 400(6740): 173–177.
- Schneider LS, DeKosky ST, Farlow MR, et al. (2005) A randomized, double-blind, placebo-controlled trial of two doses of Ginkgo biloba extract in dementia of the Alzheimer's type. *Curr Alzheimer Res* 2: 541–551.
- Sharp SI, Francis PT, Elliott MS, et al. (2009) Choline acetyltransferase activity in vascular dementia and stroke. *Dement Geriatr Cogn Disord* 28: 233–238.
- Shumaker SA, Legault C, Kuller L, et al. (2004) Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* 291(24): 2947–2958.
- Shumaker SA, Legault C, Rapp SR, et al. (2003) Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial.[see comment]. *JAMA* 289(20): 2651–2662.
- Skoog I, Lithell H, Hansson L, et al. (2005) Effect of baseline cognitive function on cognitive and cardiovascular outcomes: Study on COgnition and Prognosis in the Elderly (SCOPE) – a randomized double-blind trial. *Am J Hypertens* 18: 1052–1059.
- Skoog I and Gustafson D (2006) Lessons learned from primary prevention trials in dementia. In: Rockwood K and Gauthier S (eds) *Trial Designs and Outcomes in Dementia Therapeutic Research*. Abingdon: Taylor & Francis, 189–211.
- Stamelou M, Reuss A, Pilatus U, et al. (2008) Short-term effects of coenzyme Q10 in progressive supranuclear palsy: a randomized, placebo-controlled trial. *Mov Disord* 23: 942–949.
- Swanberg MM (2007) Memantine for behavioral disturbances in frontotemporal dementia: a case series. *Alzheimer Dis Assoc Disord* 21: 164–166.
- Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S and Gergel I (2004) Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *JAMA* 291: 317–324.
- Thaisethawatkul P, Boeve BF, Benarroch EE, et al. (2004) Autonomic dysfunction in dementia with Lewy bodies. *Neurology* 62: 1804–1809.
- Thomas SJ and Grossberg GT (2009) Memantine: a review of studies into its safety and efficacy in treating Alzheimer's disease and other dementias. *Clin Interv Aging* 4: 367–377.
- Tsuboi Y, Doh-Ura K and Yamada T (2009) Continuous intraventricular infusion of pentosan polysulfate: clinical trial against prion diseases. *Neuropathology* 29: 632–636.
- Tzourio C, Anderson C, Chapman N, et al. (2003) Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Arch Intern Med* 163: 1069–1075.
- Vickrey BG, Mittman BS, Connor KI, et al. (2006) The effect of a disease management intervention on quality and outcomes of dementia care: a randomized, controlled trial. *Ann Intern Med* 145: 713–726.
- Vossel KA and Miller BL (2008) New approaches to the treatment of frontotemporal lobar degeneration. *Curr Opin Neurol* 21: 708–716.
- Waldemar G, Dubois B, Emre M, et al. (2007) Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia: EFNS guideline. *Eur J Neurol* 14: e1–26.
- Wilcock GK, Black SE, Hendrix SB, Zavitz KH, Swabb EA and Laughlin MA (2008) Efficacy and safety of tarenflurbil in mild to moderate Alzheimer's disease: a randomised phase II trial. *Lancet Neurol* 7: 483–493.
- Wilcock GK, Black SE, Balch AH, et al. (2009) *Safety and efficacy of tarenflurbil in subjects with mild Alzheimer's disease: Results from an 18-month international multi-center phase 3 trial*. International Conference on Alzheimer's Disease: Vienna.
- Wilkinson D and Andersen HF (2007) Analysis of the effect of memantine in reducing the worsening of clinical symptoms in patients with moderate to severe Alzheimer's disease. *Dement Geriatr Cogn Disord* 24: 138–145.
- Wilkinson D, Schindler R, Schwam E, et al. (2009) Effectiveness of donepezil in reducing clinical worsening in patients with mild to moderate Alzheimer's disease. *Dement Geriatr Cogn Disord* 28: 244–251.
- Winblad B, Engedal K, Soininen H, et al. (2001) A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. *Neurology* 57: 489–495.
- Yancheva S, Ihl R, Nikolova G, et al. (2009) Ginkgo biloba extract EGb 761(R), donepezil or both combined in the treatment of Alzheimer's disease with neuropsychiatric features: a randomized, double-blind, exploratory trial. *Aging Ment Health* 13: 183–190.
- Yoshita M, Taki J, Yokoyama K, et al. (2006) Value of 123I-MIBG radioactivity in the differential diagnosis of DLB from AD. *Neurology* 66: 1850–1854.