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Clinical practice with anti-dementia drugs: a revised (third) 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 previous (2011) 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 randomised 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 both structural (CT and MRI) and functional (PET and SPECT) brain imaging can improve diagnostic accuracy in particular situations (B). Cholinesterase inhibitors (ChEI; donepezil, rivastigmine, and galantamine) are effective for cognition in mild to moderate Alzheimer's disease (AD)(A), memantine for moderate to severe AD (A) and combination therapy (ChEI and memantine) may be beneficial (B). Drugs should not be stopped just because dementia severity increases (A). Until further evidence is available other drugs, including statins, anti-inflammatory drugs, vitamin E, nutritional supplements and ginkgo biloba, cannot be recommended either for the treatment or prevention of AD (A). Neither ChEI nor memantine are effective in those with Mild Cognitive Impairment (A). ChEI are not effective in frontotemporal dementia and may cause agitation (A), though selective serotonin reuptake inhibitors may help behavioural (but not cognitive) features (B). ChEI should be used for the treatment of people with Lewy body dementias (both Parkinson's disease dementia and dementia with Lewy bodies), and memantine may be helpful (A). No drugs are clearly effective in vascular dementia, though ChEI are beneficial in mixed dementia (B). Early evidence suggests multifactorial interventions may have potential to prevent or delay the onset of dementia (B). Though 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 in those with or at high risk of AD are in progress. Though results of pivotal studies in early (prodromal/mild) AD are awaited, results to date in more established (mild to moderate) AD have been equivocal and no disease modifying agents are either licensed or can be currently recommended for clinical use.

Keywords

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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), which were subsequently revised (O'Brien and Burns, 2011). As with other BAP guidelines, these were explicitly based on the 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 five 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, third, revision of the 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 processes thought to underpin the cognitive decline.

Dementia affects around 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, 10-15%), frontotemporal dementias, other rarer causes and occasionally reversible conditions (5%). These figures include a substantial proportion of cases where there is evidence of mixed pathology, which is more common in older people. 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 (ChEI; 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. There is general agreement that anticholinergic burden should be minimised in those with dementia, especially before prescribing cholinergic medication. Anticholinergic use has been associated with poorer cognitive and functional performance, cognitive decline (Ancelin et al. 2006; Fox et al. 2011; Shah et al. 2013) and with increased risk for dementia (Gray et al. 2015). Scales to assess anticholinergic burden are available (for reviews see Salahudeen et al. 2015; Cardwell et al. 2015) and while minimising anticholinergic burden makes clinical sense, there are no definitive studies on the effects of such a reduction on cognitive and functional decline in people with dementia.

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, concerns over cerebrovascular adverse events and increased mortality has forced consideration of alternative approaches to the treatment of BPSD, including ChEI, memantine and increased the emphasis on non-pharmacological therapies including activity, music 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 ChEI and memantine. DLB is treated symptomatically with cautious use of anti-parkinsonian medication where necessary (L-dopa monotherapy having the least propensity to exacerbate psychosis) and ChEI. Management of BPSD is more challenging and antipsychotic drugs should be avoided because of parkinsonian 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 (www.nice.org.uk), the European Federation of Neurological Sciences (Hort et al., 2010; Schmidt et al., 2015; Waldemar et al., 2007), the American Academy of Neurology

(Knopman et al., 2001) and the Scottish Intercollegiate Guidelines network (SIGN) (www.sign.ac.uk). Guidelines are also available on non-pharmacological management, which is not discussed in detail here (BPS, 2014).

Methodology

We held a consensus meeting in London in March 2016. The participants were selected for their clinical and research experience in the field of dementia care, and also included a person with dementia. The group arrived at its decisions after expert papers were written independently and then presented and discussed at the meeting. Guidelines were then prepared following the format of previous BAP consensus meetings, and the first and second consensus meetings on anti-dementia drugs (Burns and O'Brien, 2006; Burns and O'Brien, 2011). 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 2015 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 pre-dementia conditions such as Mild Cognitive Impairment or prodromal/ preclinical dementia

4. Appraise the evidence for drugs with potential to delay or prevent dementia, or modify its disease course.

The level of evidence was categorised according to standard criteria, and level of evidence was then translated into strength of recommendation as detailed in Table 1.

Table 1. Categories of evidence and strength of recommendation[1]

Categories of evidence for causal relationships and treatment
I   Evidence from meta-analysis of randomised controlled trials*, at least one large, good quality, randomised controlled trial* or replicated, smaller, randomised controlled trials*
II   Evidence from small, non-replicated, randomised controlled trials*, at least one controlled study without randomisation 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

[1] (Anderson et al., 2008)

* Randomised 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 and cognitive disorders continue to cause controversy. Since the last guideline, a revision of the influential Diagnostic and Statistical Manual (DSM 5) has been published (American Psychiatric Association, 2013). Two key changes from DSM-IV TR (American Psychiatric Association, 2000) of relevance here are a) a move away from the terms of dementia and mild cognitive impairment to major and mild neurocognitive disorder respectively and b) the inclusion of Lewy body disorder (major or mild neurocognitive disorder with Lewy bodies). There have been several proposals to revise the criteria for AD, with the inclusion of biomarkers aiming to both improve the accuracy of diagnosis, and allow diagnosis at an earlier pre-dementia or prodromal stage. The International Working Group has proposed criteria for very early AD (Dubois et al., 2007), which were later expanded to include prodromal AD (Dubois et al., 2010) and further revised to include amyloid imaging (Dubois et al., 2014). The NIA-AA group has published new criteria for AD dementia (McKhann et al., 2011), mild cognitive impairment due to AD (Albert et al., 2011) and preclinical AD (Sperling et al., 2011). Within these criteria, prodromal AD or mild cognitive impairment due to AD refers to early (pre-dementia) but symptomatic disease, whilst preclinical refers to pre-symptomatic or "at risk" states. The main purpose of many of these changes has been to allow internationally agreed criteria to be used for subject selection and stratification for ongoing natural history and therapeutic studies, though the validation and clinical usefulness of these criteria remains to

be fully determined. There have been no new revisions of the criteria for DLB (McKeith et al., 2005) or Parkinson's disease dementia (Emre et al., 2007) since the last guideline, though the DLB criteria are under review at the time of writing. In keeping with the moves in the Alzheimer field towards earlier diagnosis, criteria for mild cognitive impairment in Parkinson's disease have been published (Litvan et al., 2012).

Clinical criteria for Frontotemporal Dementia (FTD) have been updated (Rascovsky et al., 2011). New criteria are sensitive and specific for the diagnosis of behavioural variant FTD although the related syndromes of semantic dementia and progressive non-fluent aphasia are now classified according to new primary progressive aphasia (PPA) recommendations (Gorno-Tempini et al., 2011)(see Figure 1). The PPA classification system has lower diagnostic accuracy in terms of predicting pathological diagnosis and includes a clinical syndrome mostly associated with Alzheimer pathology (Mesulam and Weintraub, 2014). This poses further potential problems in performing and interpreting treatment trials in this disease area. There have been no internationally agreed formal revisions of criteria for VaD, but consensus groups have offered frameworks whereby some apparently contradictory concepts, such as the dimensional nature of vascular cognitive impairment (O'Brien et al., 2003) can to some extent be reconciled with the dimensional approach of major and minor neurocognitive disorder (Sachdev et al., 2014). What is clear is that in all areas, new knowledge, especially regarding genetics and biomarkers, and the

need to stratify people at an early stage in their disease, have been the driving forces behind these revisions, more of which can be expected over time as further advances are made.

Neuroimaging and CSF 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 a dementia syndrome and providing information to support a 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 and second guideline. Cerebrovascular changes on imaging are necessary for the application of standard diagnostic criteria for VaD (Román et al., 1993), and increasingly imaging changes are being incorporated into other diagnostic criteria. FTD is associated with frontal and anterior temporal lobe atrophy, with a variable extent of hippocampal atrophy depending on the subtype, on structural imaging and frontotemporal hypoperfusion on Single Photon Emission Computerised Tomography (SPECT) and hypometabolism on FDG PET (Fluoro-deoxy glucose Positron Emission Tomography). AD is associated with

medial temporal lobe atrophy, particularly of the entorhinal cortex and hippocampus, and temporoparietal hypoperfusion on SPECT and hypometabolism on FDG PET. Early onset AD is also associated with parietal and precuneus atrophy. Preservation of the medial temporal lobe in DLB has emerged as the most robust structural imaging marker separating DLB from AD and has been confirmed in studies with autopsy verification (Burton et al., 2009). DLB is associated with hypoperfusion and hypometabolism of posterior parietal and occipital areas on SPECT and FDG PET respectively (Colloby et al., 2008). A blinded study comparing FDG-PET with hexamethylpropylene amine oxime (HMPAO) SPECT in the diagnosis of degenerative (AD or DLB) dementia from controls found a clear (20%) superiority for FDG-PET over HMPAO SPECT in diagnostic accuracy (O'Brien et al., 2014). Dopaminergic SPECT or PET can distinguish DLB from AD with 80% sensitivity and 90% specificity (McKeith et al., 2007; O'Brien et al., 2014). Decreased cardiac sympathetic uptake, as indicated by decreased metaiodobenzylguanidine (MIBG) SPECT binding has been found in Parkinson's disease and DLB. MIBG imaging has now been shown in single and now multi-centre studies to distinguish DLB from AD with 70% sensitivity and 90% specificity (Yoshita et al., 2015).

Amyloid PET imaging can be undertaken with C^{11}-PIB and, since the last guideline, three fluorinated compounds which have all received a licence for demonstrating increased brain amyloid as an adjunct to diagnosing AD (florbetapir, flurbetaben and flutemetamol).

These have all been subject to autopsy validation studies, where a positive amyloid scan predicts significant plaque pathology at autopsy with >90% certainty, and clinical studies indicating good diagnostic accuracy for AD (O'Brien and Herholz, 2015). Whilst a positive amyloid scan would be expected in both early and late onset AD, some caution is necessary when interpreting results as increased brain amyloid occurs with advancing age (present in 40% of the over 80's) and possession of the ApoE4 genotype (Jansen et al., 2015), and is seen in around 50% subjects with DLB and in older subjects with other dementias (Ossenkoppele et al., 2015).

Raised levels of CSF tau (both total and phosphorylated tau) and reduced levels of A-beta 1-42 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 to other dementias) (Mitchell, 2009). However, multi-centre studies have shown substantial inter-centre variation in biomarker levels, especially for A-beta 42 (Mattsson et al., 2009), and further standardisation and investigation of the reasons for this are required before CSF biomarkers can enter clinical practice (Ritchie et al., 2014; Ritchie et al, 2015).

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
	There is type II evidence that medial temporal atrophy can be helpful in the diagnosis of Alzheimer's disease, and for distinguishing Alzheimer's disease from dementia with Lewy bodies in some cases.	B
Use of SPECT or PET imaging	There is type I evidence that perfusion (HMPAO) SPECT or FDG PET can differentiate between Alzheimer's disease, vascular dementia and frontotemporal dementia.	A
	There is type II evidence that FDG PET is superior to perfusion (HMPAO) SPECT in the diagnosis of degenerative dementia.	B
	There is type I evidence that dopaminergic SPECT or PET imaging can help differentiate dementia with Lewy bodies from Alzheimer's disease.	A

	There is type I evidence that amyloid PET imaging can identify patients with elevated amyloid burden in the brain, and so be a useful diagnostic marker for Alzheimer's disease.	A
	There is type I evidence that MIBG can differentiate dementia with Lewy bodies from Alzheimer's disease.	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 more widely used clinically.	B

Drug treatments for Alzheimer's disease

Since the previous revision of the Guideline no new drugs have been licensed for AD.

There are currently two classes of drug approved for the treatment of AD, the ChEI 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 RCTs demonstrate their efficacy in these situations. The drugs were originally marketed as Aricept tablets (donepezil), Exelon

capsules and later skin patches (rivastigmine), Reminyl tablets and later Reminyl XL

capsules (galantamine) and Ebixa tablets (memantine); all are now available as generic or

other marketed versions. A higher dose (13.3mg/24 hours) rivastigmine patch is now

available (Cummings et al., 2012).

The basic evidence to support the use of these drugs remains unchanged and, in

general, the costs of the drugs are now significantly lower, particularly for donepezil.

Combination therapy using a ChEI initially with the later addition of memantine is now

considered optimal treatment in many countries particularly as the dementia advances. A

European guideline based on systematic assessment of the quality of the evidence has been

published and is the first such review (Schmidt et al., 2015). It suggests using a

combination rather than a ChEI alone in patients with moderate to severe AD, but the

strength of the recommendation is weak (see Figure 2).

In some countries, it is recommended that ChEI treatment should stop when AD

becomes severe and reimbursement may depend on this. There have been little data to

guide the clinician and potential concerns have been raised that continuing treatment is

associated with an increase in adverse outcomes (Gill et al., 2009). The UK donepezil and

memantine in moderate to severe AD (DOMINO) study (Howard et al., 2012), which

randomized those on stable donepezil with moderate to severe dementia (standardized

MMSE score 5-13) to continuation donepezil, discontinuation, a change to memantine or

adding memantine, clearly showed that continued donepezil treatment (or a switch to memantine or combination therapy) was associated with cognitive and functional benefits over the following 12 months, compared to placebo (see Figure 3). Previous data from observational studies as well as a more recent analysis from the DOMINO study suggest that treatment with anti-dementia drugs may delay admission to residential and nursing home care (Howard et al., 2015).

No new comparative trials between the three ChEI, or of trials switching between the ChEI, have been published in the last five years. Previous comparative trials failed to consistently demonstrate any significant differences in efficacy between the three ChEI, the main differences found being in frequency and type of adverse events (O'Brien and Burns, 2011). Similarly, our previous recommendation that a significant proportion (up to 50%) appear to both tolerate and benefit from switching between ChEI if they cannot tolerate one, remains valid.

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 severe Alzheimer's disease.	A

	There is type I evidence for memantine in moderate to severe Alzheimer's disease.	A
	There is type I evidence that cholinesterase inhibitors should not be stopped just because the point of severe dementia has been reached.	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 I evidence for adding memantine to a cholinesterase inhibitor.	B

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 and poorer quality of life. Moreover, the balance between these features varies, both between individuals 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. Comprehensive reviews of the treatment of DLB (Boot, 2015) and PDD (Goldman and Weintraub, 2015) and meta-analysis of trials (Wang et al., 2015; Stinton et al, 2015) are now available. No substantial new data regarding the use of antipsychotic or anti-parkinsonian drugs have been published since the previous DLB Consensus report (McKeith et al., 2005) and the recommendations made in these areas remain unchanged.

Early RCTs of the ChEI rivastigmine demonstrated benefit in cognition in DLB (McKeith et al., 2000) and PDD (Emre et al., 2004) and also showed effects upon neuropsychiatric symptoms including hallucinations, apathy, anxiety and sleep disorders. New data have become available regarding donepezil in DLB (Ikeda et al., 2015; Mori et al., 2015) since the last BAP statement and as a result donepezil now has a marketing authorisation for DLB in Japan and the Philippines. All other ChEI prescribing in DLB remains off-label, whereas rivastigmine is licensed for use in PDD in Europe, Canada and the USA. Turning to memantine, two, 24-week RCTs in people with mixed DLB or PDD populations (Aarsland et al., 2009; Emre et al., 2010) both showed an significant benefit on clinical global impression of change, but the subtype effects were inconsistent between the two studies, with PDD but not DLB patients benefitting in one (Aarsland et al., 2009) and

DLB but not PDD in the other (Emre et al., 2010). Significant cognitive benefit (a 1.9 difference in MMSE) of memantine compared with placebo was observed in the total population at 24 weeks in the former, but with no significant benefit on non-cognitive symptoms. By contrast the latter study found cognitive improvements in only two sub-tests out of a 16 item battery in DLB, and none in PDD at 24 weeks. There were some significant improvements on the NPI, in DLB at 24 weeks but not in PDD patients (Emre et al., 2010). Memantine was well tolerated in both studies Taken collectively these results do not show a consistent pattern of treatment response which highlights the considerable variation in sensitivity to treatment effects positive and negative, in this population which is also reported by clinicians who use ChEI. Group mean scores in trials do not fully capture this variability.

After a long period without any novel pharmacological studies in patients with DLB there appears to be a resurgence in interest in trialling symptomatic neurotransmitter based compounds and it is possible that new agents will be entering the DLB armamentarium during the life of this guideline.

Table 4. Summary Box: Dementia with Lewy bodies

Intervention	Level of evidence	Recommendation
Cholinesterase inhibitors	There is type I evidence to support treatment with rivastigmine and	A

	donepezil in Lewy body dementias, both in dementia with Lewy bodies and Parkinson's disease dementia.	
Memantine	There is type I evidence that memantine produces global improvements in Lewy body dementias, both dementia with Lewy bodies and Parkinson's disease dementia, but the pattern of cognitive and neuropsychiatric responsiveness remains uncertain.	B

Drugs for vascular and mixed dementia

Cerebrovascular disease 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; O'Brien and Thomas, 2015). There are no currently licensed treatments for VaD within the UK, so treatment strategies have largely focused on control of underlying cardiovascular and cerebrovascular risk factors and treatment of associated symptoms. There has been a suggestion that cholinergic dysfunction occurs in VaD, prompting interest in the use of ChEI 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). Cerebrovascular 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 anti-platelets or anticoagulants, 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 nimodipine, ginkgo biloba and naftidrofuryl that is discussed below.

Since publication of the previous guideline, there have been no new studies with donepezil, galantamine, rivastigmine or memantine. The previous studies have been reviewed by Baskys and Hou (2007), Bocti et al. (2007), and Rojas-Fernandez and Moorhouse (2009). The studies with ChEIs show an improvement in cognition, apart from one study with galantamine (Erkinjuntti et al., 2002), but no overall effects in other measures. In one 24-week study with galantamine there were also significant improvements in executive function (EXIT25) (Auchus et al., 2007). 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). The effects of memantine in VaD have been reviewed by Bocti et al. (2007), Kavirajan and Schneider (2007), McShane et al. (2006) and Thomas and Grossberg (2009). 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 ChEIs 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 (López-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 (López-Arrieta and Birks, 2002) and there remains a need for longer duration studies. 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 a rare monogenetic form of SIVD. In an 18-week, placebo controlled double-blind, randomized parallel-group trial, 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).

There have been further studies with ginkgo biloba (EGb761®). These have been reviewed by Baskys & Cheng (2012) and Gauthier & Schlaefke (2014) and studies included patients with AD, VaD or mixed dementia (Wang et al., 2010; Weinmann et al., 2010) but no data related to VaD alone has been provided. One RCT separately analysed the efficacy of EGb761® on 71 patients with VaD (Ihl et al., 2012). EGb761® treatment was superior to placebo in patients with VaD with respect to the Short Cognitive Performance Test and Neuropsychiatric Inventory scores. In a systematic review (von Gunten et al., 2015) of patients with dementia and mild to moderate behavioural symptoms, it was reported that EGb761® at a dose of 240mg had significant benefits on cognition,

activities of daily living, behavioural symptoms, clinical global impression but not quality of life in the VaD subgroup. Further studies are recommended.

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).

In a recent Cochrane review of naftidrofuryl (Lu et al., 2011), the conclusion was that in patients with VaD or mixed dementia there were significant benefits on a number of outcomes. However the numbers were very small and did not permit an overall recommendation apart from the need for further trials in specific groups.

It is widely recognised that a good number of people diagnosed with dementia have mixed brain pathology which is predominantly due to Alzheimer's and cerebrovascular changes. One RCT with galantamine (Erkinjuntti et al., 2002) included VaD and AD patients showing radiological and historical evidence of cerebrovascular disease. A combined analysis of VaD and AD patients showed a significant treatment effect on cognition, function, behavioural symptoms and clinical global impression. The systematic review of EGb761®reported significant benefits in all outcomes tested in patients with mixed dementia. Further studies are necessary in well defined groups.

There is a rationale for study of vascular risk factor control in established mixed dementia. In a recent randomized controlled trial, multi-component vascular care that combined pharmacological and nonpharmacological interventions did not slow functional or cognitive decline in 130 patients with AD and CVD (Richard et al., 2009). However it is worth noting that some of the vascular factors, for example blood pressure, were no different between the intervention and control group.

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 vascular dementia and Alzheimer's disease may benefit.	A

Other dementias

This group of disorders is used here to include FTD, the Primary Progressive Aphasias, Progressive Supranuclear Palsy (PSP), Corticobasal degeneration (CBD) and prion dementias amongst others, and the overlap between some of these conditions is illustrated in Figure 4. No new evidence regarding the use of ChEI in FTD has become available since the last BAP statement. The existing evidence does not support the use of these drugs in FTD although rates of off label use remain high, despite increased agitation having been reported with their use in FTD (O'Brien et al, 2011). There have been no new trials of antidepressants in FTD, as before, evidence for the use of these drugs is mixed and largely rests on small open label studies. New randomized controlled trials of memantine in FTD report a lack of efficacy with this drug (Boxer et al., 2013; Vercelletto et al., 2011). A small trial of Souvenaid reported beneficial effects in behaviour and social cognition measures over a short time period (Pardini et al., 2015), but more studies are needed. Oxytocin administered intranasally in FTD appears safe and tolerable; larger studies are needed to assess its efficacy (Finger et al., 2015).

There are no adequately powered treatment studies in Primary Progressive Aphasia upon which to make firm recommendations. Since the last BAP statement there has been no new trial evidence for ChEI or Coenzyme Q10 in treating PSP. Existing evidence does not support their use. The largest PSP trial to date found that davunetide (proposed to decrease

tau phosphorylation and stabilize microtubules) was not an effective treatment (Boxer et al., 2014).

Since the last BAP statement a trial demonstrated no survival benefit in Creutzfeldt-Jakob disease (CJD) patients treated with quinacrine (an antimalarial drug that reduces abnormal prion protein deposits *in vitro*) (Geschwind et al., 2013). Doxycycline was not effective in treating CJD (Haïk et al., 2014).

There are no adequately powered studies of ChEI to support the use of these drugs for cognitive impairment in Huntington's disease. There is no evidence to support the use of other medications to treat dementia associated with Huntington's disease though several disease modifying avenues are being pursued, including compounds to reduce metal induced aggregation of the Huntingtin protein (Angus et al., 2015).

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	B

	mixed and further evidence is needed.	
Memantine	There is type I evidence that memantine is not recommended for frontotemporal dementia.	A

Table 7. Summary Box: Progressive Supranuclear Palsy

Intervention	Level of evidence	Recommendation
Progressive supranuclear palsy	Type II evidence indicates that no treatments can be recommended at the current time.	B

Mild cognitive impairment, MCI due to AD and Prodromal Alzheimer's disease

There have been no new positive studies to inform prescribing in prodromal conditions such as mild cognitive impairment (MCI). Cochrane and other reviews show lack of efficacy of ChEI (Birks and Flicker, 2006; Loy and Schneider, 2006), equivocal findings with piracetam (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 drugs (rofecoxib) have been negative. There have been numerous trials conducted and ongoing in MCI due to AD or prodromal AD though none have been successful and progressed beyond Phase 3.

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
	There is type 1 evidence that cholinesterase inhibitors are not effective in those with Mild Cognitive Impairment	A

Other relevant issues in management

The NICE process

In the UK, within England and Wales, recommendations on the use of licensed drugs are made by the National institute for Health and Clinical Excellence (NICE). NICE was established in 1999 as a NHS Special health Authority and changed in 2013 to an arm's length non-departmental government body. This reflected an extension of its remit to also include social care. It is contained within the Department of Health but outside the NHS and it is accountable to parliament through the Secretary of State for Health. It has

several remits, including the production of focussed technology appraisal, mostly on drugs, and broader guidelines which can cover clinical care, public health and social care. With regard to dementia, there have been several technology appraisals on anti-dementia drugs, the most recent (TA 217) on ChEI and memantine for AD, published in 2011 and updated 2016. Unlike earlier technology appraisals of these drugs, which had limited use of these agents to either those who were deemed to respond to the drug or to those with moderate disease, TA 217 recommends the use of donepezil, galantamine and rivastigmine as treatment options for all patients with mild to moderate AD, and memantine for moderate to severe AD. No recommendations are made either for or against combined therapy. Recommendations for severe disease or for non-Alzheimer dementia are not contained within TA 217, since technology appraisals are limited to the licence of the drug.

There is also a NICE dementia guideline, GD42 (NICE, 2006), which was in the process of being fully revised at the time of the publication of this BAP guideline. The current guideline recommends the use of ChEI for Lewy body dementia, but not for FTD, VaD or MCI.

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. As with previous guidelines, for this revision we invited Peter Mittler as a

person with dementia to join the meeting. His insights were invaluable and very much

accorded with experience of the clinicians on the panel. Peter reflected on the wider

contexts in which the first prescription can be considered. These range from the patient's

initial interpretation of the significance of medication to the ethical imperative for

professionals to strike a balance between the global quest for cure and the fundamental

human rights of people with dementia for care and support[i]. This is consistent with the bio-

psychosocial model of impairment which includes quality of life indicators.

Accounts provided by people living with dementia reflect strong dissatisfaction with the

complex journey to diagnosis and also with the lack of post-diagnostic support (Schalock et

al., 2016). These suggest that the time is ripe for clear guidance on good and bad practice in

diagnosis and its aftermath. The medical profession carries the main responsibility for

timely diagnosis and for maintaining the health and well-being of each person in their own

homes for as long as possible. It is well placed to use its prestige with the public to

emphasise that disability is part of the human experience and that it is possible to live well

with dementia. It could also influence public opinion, politicians and the media by avoiding

the use of degrading language involving time-bombs and tsunamis. In our quest for

prevention and cure, we have lost sight of the uniqueness of the individual highlighted by

Tom Kitwood and more recently by Steven Sabat who focuses on the maintenance of a

sense of self and personal identity from first diagnosis to the end of life (Schalock et al.,

2016). We need to provide services based on the needs and wishes of the individual and

their principal care partner by providing tailor-made support and rehabilitation comparable

to that received by people who sustain brain injury as a result of stroke or road traffic

accident. A visiting dementia adviser should be able to access the additional supports that

are or may become necessary – e.g. an occupational therapist to suggest adaptations to the

home and to appliances such as personal computers. A dementia-friendly community

should include children, young people and students, who as future leaders need to be aware

that each person with dementia is a unique individual with the right to be supported as a

member of their local community.

The role of Primary Care in the management of dementia

Primary care general practitioners (GPs) increasingly work in larger

multidisciplinary teams. This expansion has been influenced by a national policy of *care

closer to home*, greater focus on preventative care and the transfer of primary clinical

responsibility for chronic disease management from secondary to primary care. Most

common chronic illnesses (e.g. diabetes, asthma, hypertension) are largely managed by the

GP with the aid of shared care pathways, prescribing protocols and specialist nurses. A

new General Medical Services (GMS) Contract in 2004 fundamentally changed the way

GPs in England work through the introduction of 'core services' with 'optional enhanced services'. The Contract links achievements in care quality, with a major focus on chronic illness care, properly funded through an evidence-based Quality and Outcomes Framework (QOF). QOF criteria for dementia exist and comprise: i). establishing and maintaining a register of patients with diagnosed dementia and ii) undertaking an annual review on patients' on the register.

The majority of people with dementia live in the community with their GP the primary health care provider most of the time. The GP can have an extensive range of post diagnostic responsibilities including: information provision; access to other services; carer support; management of co-morbid conditions and behavioural problems; future care planning and end of life care (Robinson et al., 2010). As our populations rapidly age and the demand on specialist old age psychiatry services increases, primary care may need to undertake a more formalised shared care approach to dementia care as has existed in diabetic care for the last twenty years. A recent RCT comparing the effectiveness of memory clinics and GPs for delivery of post diagnostic care found no significant differences between the two services (Meeuwsen et al., 2012).

In some European countries GPs can initiate anti-dementia drugs; the current evidence base for the initiation, and review, of anti-dementia drugs by non-specialists is very limited and restricted to low quality, observational studies (Aupperle and Coyne,

2000; Aupperle et al., 2003; Watanabe et al., 2012). In the UK existing NICE guidelines (2006) stipulates drug initiation should be on the advice of a specialist, with shared care prescribing supported for maintenance treatment. A UK pilot trial of a GP educational prescription to support dementia diagnosis and improve quality of care found that GPs had little knowledge of shared care protocols for anti-dementia drugs, with specialists still largely responsible for monitoring (Wilcock et al., 2013). However a US based trial of a care manager intervention, combined with a quality improvement/professional education component, found increased anti-dementia drug prescribing in primary care (Vickrey et al., 2006). With specialist disease nurses, key to the success in chronic illness management in primary care, the role of a nurse dementia case manager affords considerable potential for person-centred post diagnostic care. The evidence base however is mixed with a recent UK pilot trial struggling to successfully integrate dementia case managers into existing NHS primary and community care services (Bamford et al., 2014). New alternative primary care models with GP-led memory clinics and attached nurse facilitators have been established in some areas.

In summary, the current system of shared care prescribing of anti-dementia drugs in the UK requires further evaluation in order to identify facilitators to improve care quality. With regard to GP-led prescribing, this will be influenced by the revised NICE guidelines (due 2017); such a change in practice would however require upskilling of GPs, prescribing

protocols and the development of a shared care, integrated system co-ordinated by possibly

specialist nurses.

Table 9. Summary Box: Primary care

Intervention	Level of evidence	Recommendation
Initiation and prescription of anti-dementia drugs	There is type IV evidence to support the current practice of non-specialist initiation of these drugs, following a specialist diagnosis.	D
	There is type II evidence indicating no significance differences between the ongoing prescription and monitoring of the drugs between memory clinic and GP-led services.	B

End of life Care

One third of older people will die with some form of cognitive impairment or

dementia (Brayne et al., 2006). There are two populations of people with dementia for

whom end of life care needs to be considered, those who have dementia in the in early-

moderate stages but are dying from other disease such as cancer or organ failure or those

who have advanced dementia where the commonest cause of death is pneumonia or other

infection. They may experience poor end of life care because they are often not perceived

to have a terminal illness and health and social care services may not be optimally configured to meet their complex needs (Sampson et al., 2011).

In people with advanced dementia the main prescribing decisions are related to considering the "ceiling of care". Thus stopping medications which may have no longer term benefit i.e. statins, low dose aspirin or anti-hypertensives may be appropriate (Holmes et al., 2008).

There is little evidence available on how best to prescribe for people with severe dementia, particularly when to stop drugs which are no longer necessary or beneficial. There is a lack of RCT data for anti-dementia drugs in this population. Trials tend to be for short periods of 3-12 months with open-label extension studies after this and there is little evidence for continuing treatment when people reach this stage. It has been argued that the prescription of ChEI or memantine is "never appropriate" towards the end of life although their use remains common in care home residents (Holmes et al., 2008). However, in patients with moderate or severe Alzheimer's disease, continued treatment with donepezil is associated with significant functional benefits over 12 months; thus continuing a cholinesterase inhibitor may be in-keeping with a palliative approach (level I evidence)(Howard et al., 2012)(see Figure 2). There is uncertainty over the efficacy of memantine in end-stage dementia and the most appropriate time to discontinue this.

Different formulations and modes of administration, for example ChEI delivered as patches should be considered. The use of anti-dementia drugs should be balanced with the risk of side effects, for example Memantine may worsen constipation associated with analgesics; polypharmacy is a key issue. Covert medication may be in the person's best interests if conducted within the correct ethical and legal frameworks.

Analgesics tend to be under prescribed in people with advanced dementia but concerns about polypharmacy, interactions and side effects can be addressed. The most commonly used analgesic is paracetamol although studies using the WHO analgesic ladder which advances to NSAIDS and opioids show this approach improves pain and neuropsychiatric symptoms (level II evidence)(Husebo et al., 2011).

There is little strong evidence on prescribing in people with dementia who are reaching the end of life (level III only). Clinicians should take into account individual preferences of the person with dementia, if known, and their families, and aim to achieve the best symptom control and quality of life.

Table 10. Summary Box: End of Life Care

Intervention	Level of evidence	Recommendation
Withdrawal of anti-dementia drugs	There is type I evidence that continuing donepezil may decrease the rate of functional decline in moderate/severe dementia. There	C

is type III evidence that it may be inappropriate to prescribe memantine and cholinesterase inhibitors in advanced dementia towards the end of life.

Other putative therapies for dementia

Dimebon (latrepirdine) is an antihistamine identified as a weak inhibitor of cholinesterase activity with a number of other actions, including enhancing mitochondrial function. At the time of the previous guideline, a single randomised placebo controlled trial of 183 people in Russia showed benefits of dimebon treatment over placebo (Doody et al., 2008). Unfortunately other studies have not been able to replicate these findings and a recent Cochrane review (Chau et al., 2015) concluded there was no beneficial effect of dimebon on cognition in AD, though did not rule out a possible benefit on behaviour.

Gingko biloba

Early trials were small, of poor quality and raised concerns about publication bias but two large well designed RCTs in dementia subjects (McCarney et al., 2008; Schneider et al., 2005) showed no benefits from Gingko on cognition. A primary prevention feasibility study (Dodge et al., 2008) over 42 months in 118 people over 85 at baseline found gingko biloba did not prevent the development of dementia or decline in memory but

found an increase in stroke and TIA cases in the gingko group and the GEM Study

(DeKosky et al., 2008) assessed 3069 volunteers who had MCI or were cognitively normal

randomised to placebo or ginkgo biloba over a median follow-up of 6.1 years. Gingko had

no effect on reducing incident Alzheimer's disease or all-cause dementia but was associated

with a non-significant doubling in haemorrhagic stroke (16 vs 8). However, a meta-analysis

(N=1985, mainly people with dementia) of the effect of gingko on coagulation found only

small and clinically insignificant changes (Kellermann and Kloft, 2011).

Hormone replacement therapy

A large primary prevention trial, the WHIMS trial (the Women's Health Initiative

Memory Study) examined the possible benefit of HRT/ERT in reducing dementia in post-

menopausal women (participants were 65-79 at entry). Adverse outcomes led to both arms

being terminated early. 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). Following WHIMS the critical window hypothesis emerged claiming use of ERT in younger women might be beneficial but a recent review has questioned this and there is no good quality data to support this (Maki and Henderson, 2012).

Folate and vitamin B12

Dietary supplementation using folic acid (synthetic analogue of folate) and vitamin B12, which reduce homocysteine levels, have been proposed for preventing and treating dementia. Whilst cross-sectional studies have generally supported this view (Ho et al., 2011), prospective studies have not found a relationship between dementia and high homocysteine (Ho et al., 2011) and a systematic review of randomised clinical trials of B vitamin and folate supplementation found no beneficial effects on cognition in people with or without cognitive impairment (Ford and Almeida, 2012).

Statins and dementia

No new randomised placebo controlled trials in relation to dementia prevention have been published since the last guideline. Neither of the previous two large studies (heart protection study and PROSPER) found an effect of statins on ameliorating cognitive decline or dementia.

Souvenaid

Three double blind RCTs with a medical food (nutritional combination Fortasyn Connect) in AD have been reported. Souvenir I and II were in people with mild AD (MMSE ≥20) not on AD medication. Souvenir I (Scheltens et al., 2010), in 212 subjects randomised to active drink or control drink, found a small improvement in a categorical analysis of the WMS-R delayed recall at 12 weeks but not in overall change in WMS-R delayed recall or in ADAS-Cog or other outcomes or in any measures at 24 week extension. Souvenir II (Scheltens et al., 2012) found a small improvement at 24 weeks in the Neuropsychological Test Battery memory composite score in 209 subjects but not in overall score or in any other outcome measures. The S-Connect study (Shah et al., 2013) in 527 people with mild to moderate AD (MMSE ≥14) on AD medication found no improvements in the active group in the primary outcome (ADAS-Cog) at 24 weeks or in any other clinical measures. The drink was well tolerated in all studies. The absence of any evidence of benefits on global outcomes and only patchy modest effects on memory scores do not provide evidence to support its use in AD.

Therapeutic non-invasive brain stimulation

Interest in the use of non-invasive stimulation approaches such as transcranial direct current stimulation (tDCS) and rapid rate transcranial magnetic stimulation (rTMS) has gained significant traction over the past number of years. The use of such approaches is appealing in dementia given their low predilection to side effects and evidence across multiple investigative platforms (e.g. young healthy controls, ageing studies, pathological groups etc.) has suggested that non-invasive stimulation techniques can have effects which are sustained beyond the period of the stimulation and this clearly has important therapeutic ramifications (Elder and Taylor, 2014; Hsu et al., 2015; Kuo et al., 2014).

rTMS, in particular, is now used for a wide array of neurological and mental health symptoms; for example rTMS is now a US Food and Drug Administration (FDA) approved treatment for Major Depressive Disorder in patients who have not responded to prior antidepressants (US Food and Drug Administration, 2011) and guidance on its use for conditions such as depression and migraine have been issued by the UK National Institute for Clinical Excellence (NICE, 2014, 2015).

Mechanistically both tDCS and rTMS modulate cortical activity non-invasively. rTMS does so by the delivery, through the scalp, of a high intensity time-varying magnetic pulse which causes current flow within the brain. By varying the stimulation parameters such as the stimulation intensity, frequency of pulsing and duration, rTMS can either enhance or suppress cortical activity in target brain regions. tDCS delivers a low intensity

electrical current, typically between two scalp pads (positive polarity= anode; negative polarity = cathode) and has been postulated to modulate neuronal transmembrane potential toward hyperpolarization or depolarization in brain tissues underlying the anode or cathode scalp pads, respectively.

Non-invasive brain stimulation techniques have been applied in healthy older adults to enhance cognition and importantly, also in patients with dementia (Boggio et al., 2011; Hsu et al., 2015) but the data are not as comprehensive as that for the treatment of depression with rTMS. A recent systematic review and meta-analysis identified 11 studies with a total of 200 Alzheimer's disease patients and found a significant effect size of 1.35 for cognitive outcomes with subgroup analyses suggesting more pronounced effects for studies applying the stimulation during the execution of a cognitive task compared with studies delivering the stimulation before the task (Hsu et al., 2015). However there was very little data to indicate whether any cognitive benefits are sustained. In addition, it was noted in the meta-analysis by Hsu et al. (2015) that individual trial sizes were small and protocol designs heterogeneous; furthermore in the studies examined there was also evidence of positive publication although notably across the dementia studies which examined rTMS or tDCS there was a lack of any serious adverse events.

Quality trial data for the use of rTMS or tDCS in other dementias is even more scant (Elder and Taylor, 2014). Similarly extension of the use of these non-invasive

approaches to ameliorate neuropsychiatric symptoms in dementia is very limited and

positive outcomes uncertain; for example, one double blind RCT of tDCS for the treatment

of apathy in 40 AD subjects did not demonstrate any positive effect (Suemoto et al., 2014).

There are also controversies about the efficacy of tDCS and general issues of

concerning the design of tDCS protocols which have hampered development of robust and

well powered trials (Elder and Taylor, 2014; Horvath et al., 2014, 2015).

Therefore, it is too soon to formally recommend these approaches in their

application to the treatment of dementia and its associated symptoms although the existing

data may suggest that there may be a potential future role for these agents but further larger

scale and well-designed trials are needed.

Table 11. Summary Box: Other treatments for dementia

Intervention	Level of evidence	Recommendation
Hormone Replacement Therapy (HRT) in prevention and treatment of Alzheimer's disease in post-menopausal women	There is type 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
	There is type I evidence that HRT is harmful. HRT should not be prescribed either as a prevention or	A

	treatment for dementia, including Alzheimer's disease.	
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 type I evidence that statins do not prevent dementia.	A
	There is type II evidence that statins do not produce cognitive benefits in Alzheimer's disease.	B
Souvenaid	There is type II evidence indicating possible benefits of Souvenaid on cognition but effects are variable between studies and no effect on global outcomes has been shown. Souvenaid is not recommended until further evidence becomes available.	B
rTMS and tDCS	There is type II evidence indicating benefit of rTMS and tDCS on cognition but effects may not be sustained. These treatments are not recommended until further evidence becomes available.	B

Disease modifying therapies

There are several strategies currently being investigated for possible disease modifying effects in people at high risk of progression to dementia, though most studies focus on AD and include subjects with prodromal AD or preclinical AD. These include the use of drugs that may modulate amyloid and/or tau processing, e.g. 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.

Immunisation

The success of mouse vaccine studies led to the first human trials of an active Aβ 1-42 vaccine (AN1792) in people with AD. Neuropathological examination of subjects from a phase I RPCT of AN1792 showed variable removal of amyloid plaques and no impact on long term clinical outcomes. A large phase II RPCT also failed to show clinical efficacy. In addition, 6% subjects developed meningo-encephalitis. More recently, the development of another active immunisation approach, CAD106 (Aβ 1-6), has shown sustained Aβ response and long term safety in AD but clinical data have not been fully reported.

A number of passive immunisation approaches have been tried in AD (see Figure 5). Bapineuzumab (anti Aβ 1-5) showed no evidence of clinical efficacy in phase II studies and around 10% subjects developed vasogenic oedema. An exploratory analysis showed better clinical outcomes in patients who did not carry the APOE e4 allele which led to two large RPCT's of Bapineuzumab in APOE e4 positive and negative AD subjects (Salloway et al., 2014). Neither study showed beneficial clinical effects. Solanezumab (anti Aβ 13-28), aimed at soluble monomeric Aβ, failed to show overall clinical benefit in two large phase III studies of AD. Likewise, Crenezumab (anti Aβ 12-23), aimed at aggregated Aβ, failed to show clinical benefit in a large phase II study. Retrospective analysis of the Solanezumab and Crenezumab data has led to larger studies aimed at the mild AD cohort. Aducanumab (anti Aβ 3-6) has shown effective amyloid removal but with mixed clinical outcomes and marked side effects with increasing dose. Gantenerumab (anti Aβ 1-11), has specifically *a priori* examined very early AD (cognitively normal but amyloid positive PET). Unfortunately this 2 year RPCT study showed no efficacy on primary or secondary outcomes.

A number of these active or passive immunisation approaches are now being tested in long term preventative RPCT studies of APOE e4 positive, cognitively normal subjects (CAD106) or presymptomatic carriers of early onset AD mutations (Solanezumab, Crenezumab and Gantenerumab). Finally the use of pooled human plasma antibodies

Gammagard™ has been examined in a phase III RPCT trial of AD patients with no differences found on primary outcomes. It is worth noting that of the other anti-amyloid approaches the use of β secretase inhibitors are still in active development and there is increasing interest in immunisation approaches aimed at the prevention of tangle propagation.

Anti-inflammatory approaches

A large number of RCT's of anti-inflammatory agents in AD have failed to reach primary outcomes (Heneka et al., 2015). Large scale studies of NSAIDs including indomethacin, naproxen and rofecoxib in AD have been unsuccessful. RPCT's with a range of other anti-inflammatory drugs, including prednisone, hydroxychloroquine, simvastatin, atorvastatin, aspirin and rosiglitazone have also shown no clinically significant changes in primary cognitive outcomes in patients with AD. A small RPCT of etanercept showed some evidence of a reduction of clinical decline but it has yet to be replicated in a large scale study (Butchart et al., 2015). Epidemiological studies of the protective effects of NSAID's are generally more positive. However, RPCT's examining the possible protective effects seen in these studies are mixed. Thus a large trial of rofecoxib found an increased risk of conversion to AD in the MCI treated group (Thal et al., 2005). Likewise a

large randomised study of the NSAIDs naproxen and celecoxib in asymptomatic

individuals with a family history of AD initially reported an increased risk of increased

cognitive decline for both drugs. However, a longer-term follow-up of these patients

suggests that the early detrimental effects were mostly in a small group of patients with

early cognitive impairment and naproxen seemed to be protective in patients for up to 4

years in those who had been asymptomatic at baseline (Alzheimer's Disease Anti-

inflammatory Prevention Trial Research Group, 2013).

Table 12. Summary Box: Disease modifying therapies

Intervention	Level of evidence	Recommendation
Gamma secretase inhibition	There is type I evidence that gamma secretase inhibitors are not effective in Alzheimer's disease.	A
	There is type I evidence that tarenflurbil is not effective in Alzheimer's disease.	A
Vaccination and immunization studies	There is preliminary type II evidence of their effect in Alzheimer's disease on some endpoints, but also type II evidence that amyloid lowering does not affect clinical course. Amyloid-lowering agents should not be prescribed until the optimal disease stage, safety and efficacy data are available.	B

Optimising outcome measures for trials

Following the expansion of NHS Memory Services, the number of people diagnosed with dementia in the UK has increased hugely (Mukadam et al., 2014), so that around 100,000 people per year receive a diagnosis of AD within the NHS. There have been huge strides forward in managing dementia. These include early diagnosis, information, advance decision making, cognitive stimulation therapy, management of neuropsychiatric symptoms, strategies for family carers, ChEI in Alzheimer's disease (AD) and changes in attitudes, including highlighting personhood and living well with dementia, but there is no cure or disease modifying treatment for the common dementias (Prince et al., 2011).

Currently trials of drugs for disease-modification in AD use different outcomes eg MRI brain volume change or change in cognition or function. They also use differing measures of the same outcome. Use of an agreed set of the most valid trials' outcome measures for disease modification studies would improve efficiency and enhance interpretation of data across studies (Ghezzi et al., 2013). This would allow the comparison of the efficacy of both drugs and non-pharmacological interventions, for example, exercise, cognitive stimulation and new drugs. Standardised core outcomes would also aid meta-analysis and enable small data sets to be combined and inform practice. These may include

quality of life and related outcomes, that people with dementia and their families report as being important to them, and can also inform cost-effectiveness analysis.

In the HTA funded Core Outcomes in Dementia study (COD dementia), we have brought together a wide body of NIHR dementia researchers to debate and agree on the best outcome measures for future clinical trials in mild and moderate dementia and expect our conclusions will have international impact and shape and optimise the design of future dementia trials.

Prospects for prevention

Prevention is typically considered in three main subdivisions. Primary prevention is where the onset of disease is prevented. Secondary prevention is where clinical symptoms are prevented in people with evidence of disease and tertiary prevention is where a later stage of clinical progression is prevented in people with both disease and symptoms. As can be seen from this general description, the terms are dependent upon the definitions of 'disease' and 'symptoms'. When we refer this to the case of AD, it is therefore critical to draw a distinction between AD and AD dementia.

In this regards, the secondary prevention is 'of' a clinical condition so – for instance in the EPAD (European Prevention of Alzheimer's Dementia) Project (Ritchie et al., 2015),

the title implies that the project is seeking to prevent dementia and hence encompasses (in the case of secondary prevention) intervening in populations who have evidence of AD and are either preclinical (disease and no symptoms) or prodromal (disease and symptoms but not satisfying criteria for dementia).

Despite billions of dollars of effort, there are no drugs available that achieve secondary prevention of dementia (Schneider et al., 2014). Non-pharmacological, multi-modal interventions have shown better evidence of success than any drug to date e.g. the FINGER study (Ngandu et al., 2015). Pharmaceutical interventions have been hampered by poor definitions of the target population with inadequate stratification of risk and sample heterogeneity, inadequate psychometric properties of outcome measures, interventions being applied at a very late stage of the disease process, absence of surrogate biomarker changes for clinical changes and sub-optimal study prosecution. Moreover, in a complex disorder like Alzheimer's disease, specific interventions against single disease processes are unlikely to yield benefit if multiple pathological processes contribute to the clinical phenotype.

The basis therefore for successful secondary prevention of Alzheimer's dementia therefore needs all these historical shortcomings to be addressed. That is we need to develop much better disease models in preclinical and prodromal dementia that will underpin stratification of populations into more predictable groups for progression and we

need to map onto this population clinical outcomes. These outcomes need to reflect changes to the underlying disease process from an experimental neuropsychology perspective forwards rather than a dementia outcomes foundation backwards. We need to intervene as early as possible on the basis of these disease models and accept outcomes that are surrogates for incident dementia. We also need mechanisms to undertake combinatorial trials of agents with different pathological or mechanistic targets. Finally, the trials themselves need to be conducted in a limited number of centres with access to the target populations to run at scale and maintain data quality and reduce sample heterogeneity. The EPAD program concurrently addresses all these elements.

In conclusion, the secondary prevention of dementia is reliant heavily on a more complete understanding of the neurodegenerative disease processes, which lead to clinical symptoms and eventually dementia. This means we need to undertake projects (e.g. EPAD and PREVENT (Ritchie and Ritchie, 2012) which can measure brain changes through biomarker development of disease processes in mid-life beyond amyloid and tau pathology to be able to incorporate (for example) inflammatory, cerebrovascular, HPA Axis and other protein mis-folding (e.g. Prion and α-synuclein disease). Until such models are developed and used, we will be continuing to run trials that are making too many assumptions and therefore taking too much risk and may only succeed through serendipity rather than by design. Because of this, it may be that multimodal interventions that include interventions

that target broad risk factor modification e.g. diet and optimised cardiovascular health may prove more successful.

Currently, there is no evidence for pharmacological intervention to prevent dementia. There is Level 1 evidence from an RCT that met its primary outcome that a combination of diet, cognitive training, cardiovascular health optimisation and exercise can slow cognitive decline in an at-risk elderly population (Ngandu et al., 2015), though the contribution of each factor within the FINGER multi-modal intervention to benefit is not known.

Table 13. Summary Box: Prevention of dementia

Intervention	Level of evidence	Recommendation
Prevention of dementia	There is no evidence at present to support any drug 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 type 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 14. Summary Box: 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
	There is type II evidence that medial temporal atrophy can be helpful in the diagnosis of Alzheimer's disease, and for distinguishing Alzheimer's disease from dementia with Lewy bodies in some cases.	B
Use of SPECT or PET imaging	There is type I evidence that perfusion (HMPAO) SPECT or FDG PET can differentiate between Alzheimer's disease, vascular dementia and frontotemporal dementia.	A

	There is type II evidence that FDG PET is superior to perfusion (HMPAO) SPECT in the diagnosis of dementia.	B
	There is type I evidence that dopaminergic SPECT or PET imaging can help differentiate dementia with Lewy bodies from Alzheimer's disease.	A
	There is type I evidence that amyloid PET imaging can identify patients with elevated amyloid burden in the brain, and so be a useful diagnostic marker for Alzheimer's disease.	A
	There is type I evidence that MIBG can differentiate dementia with Lewy bodies from Alzheimer's disease.	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

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	A

	Alzheimer's disease and of severe dementia.	
	There is type I evidence for memantine in moderate to severe Alzheimer's disease.	
	There is type I evidence that cholinesterase inhibitors should not be stopped just because the point of severe dementia has been reached.	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 I evidence for adding memantine to a cholinesterase inhibitor.	B
Dementia with Lewy bodies		
Cholinesterase inhibitors	There is type I evidence to support treatment with rivastigmine and donepezil in Lewy body dementia, both dementia with Lewy bodies and Parkinson's disease dementia.	A
Memantine	There is type I evidence that memantine produces global improvements in Lewy body dementia, both dementia with Lewy	B

bodies and Parkinson's disease dementia, but the pattern of cognitive and neuropsychiatric responsiveness remains uncertain.

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 vascular dementia 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 frontotemporal dementia, but do not improve cognition. Studies are mixed and further evidence is needed.	B

Memantine	There is type I evidence that memantine is not recommended for frontotemporal dementia.	A
Progressive supranuclear palsy	Type II evidence indicates that 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
Primary care		
initiation and prescription of anti-dementia drugs	There is type IV evidence to support the current practice of non-specialist initiation of these drugs.	D
	There is type II evidence indicating no significance differences between the ongoing prescription and monitoring of the drugs between memory clinic and GP-led services.	B
End of life care		
Withdrawal of anti-dementia drugs	There is type I evidence that continuing donepezil may decrease the rate of functional decline in	C

	moderate/severe dementia. There is type III evidence that it may be inappropriate to prescribe memantine and cholinesterase inhibitors in advanced dementia towards the end of life.	
Other treatments for dementia		
Hormone Replacement Therapy (HRT) in prevention and treatment of Alzheimer's disease in post-menopausal women	There is type 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
	There is type I evidence that HRT is harmful. HRT should not be prescribed either as a prevention or treatment for dementia, including Alzheimer's disease.	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 type I evidence that statins do not prevent dementia.	A
	There is type II evidence that statins do not produce cognitive benefits in Alzheimer's disease.	B
Souvenaid	There is type II evidence indicating possible benefits of Souvenaid on cognition but effects are variable between studies and no effect on global outcomes has been shown. Souvenaid is not recommended until further evidence becomes available.	B
rTMS and tDCS	There is type II evidence indicating benefit of rTMS and tDCS on cognition but effects may not be sustained. These treatments are not recommended until further evidence becomes available.	B
Disease modifying therapies		
Gamma secretase inhibition	There is type I evidence that gamma secretase inhibitors are not effective in Alzheimer's disease.	A
	There is type I evidence that tarenflurbil is not effective in Alzheimer's disease.	A

Vaccination and immunization studies	There is preliminary type II evidence of their effect in Alzheimer's disease on some endpoints, but also type II evidence that amyloid lowering does not affect clinical course. Amyloid-lowering agents should not be prescribed until the optimal disease stage, safety and efficacy data are available.	B
Prevention of dementia		
Prevention of dementia	There is no evidence at present to support any drug 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 type 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

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

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