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EFNS GUIDELINES/CME ARTICLE

EFNS guidelines for the diagnosis and management of Alzheimer's disease

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Background and objectives: In 2008 a task force was set up to develop a revision of the European Federation of the Neurological Societies (EFNS) guideline for the diagnosis and management of Alzheimer's disease (AD) and other disorders associated with dementia, published in early 2007. The aim of this revised international guideline was to present a peer-reviewed evidence-based statement for the guidance of practice for clinical neurologists, geriatricians, psychiatrists, and other specialist physicians responsible for the care of patients with AD. Mild cognitive impairment and non-Alzheimer dementias are not included in this guideline.

Methods: The task force working group reviewed evidence from original research articles, meta-analysis, and systematic reviews, published before May 2009. The evidence was classified and consensus recommendations graded (A, B, or C) according to the EFNS guidance. Where there was a lack of evidence, but clear consensus, good practice points were provided.

Results: The recommendations for clinical diagnosis, blood tests, neuropsychology, neuroimaging, electroencephalography, cerebrospinal fluid (CSF) analysis, genetic testing, disclosure of diagnosis, treatment of AD, behavioural and psychological symptoms in dementia, legal issues, counselling and support for caregivers were all revised as compared with the previous EFNS guideline.

Conclusion: A number of new recommendations and good practice points are made, namely in CSF, neuropsychology, neuroimaging and reviewing non-evidence based therapies. The assessment, interpretation, and treatment of symptoms, disability, needs, and caregiver stress during the course of AD require the contribution of many different professionals. These professionals should adhere to these guideline to improve the diagnosis and management of AD.

Objectives

The objective of the Task Force set up in 2008 was to revise previous European Federation of Neurological Societies (EFNS) recommendation on the diagnosis and management of Alzheimer disease (AD) [1]. The previous guideline reflected Diagnostic and Statistical Manual, 4th edition (DSM IV) and National Institute of Neurological, Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for dementia syndrome and AD. In the revised guideline special attention was given to whether further evidence had become available for biomarkers of disease like magnetic resonance imaging (MRI), positron emission tomography (PET) and cerebrospinal fluid (CSF) that have been proposed to increase the confidence of the clinical diagnosis [2]. Special attention was given to

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results of recent clinical trials in AD, both for cognitive and behavioral aspects of the disease. Because AD is the focus of this guideline, non-Alzheimer dementias such as vascular (VaD), frontotemporal (FTLD), Parkinson disease dementia, dementia with Lewy bodies (DLB), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), Creutzfeldt–Jacob (CJD) and others will be dealt with separately. This guideline represents desirable standards to guide practice, but may not be appropriate in all circumstances as clinical presentation of the individual patient and available resources should be taken into account. Cost-effectiveness is not discussed, as heterogeneity across Europe will result in different, country specific, conclusions.

Background

Dementia affects 5.4% of the over 65s and its prevalence further increases with age [3]. AD is responsible for the majority of cases. The European Collaboration on Dementia, co-ordinated by Alzheimer Europe, found there were currently 8.45 million people in Europe with AD. Dementia causes a significant financial burden to society, estimated at 141 billion Euros of annual cost for the whole of Europe, of which 56% are the costs of informal care. The costs per person with dementia was about 21 000 Euros per year, while disability caused by the illness is estimated at 350 disability adjusted life years per 100 000 persons, compared to 247 caused by diabetes [4]. With increasing longevity, numbers of people with dementia are set to double in the next 30 years [3]. AD with early onset ($<$ 65 years) merits special consideration because of its greater genetic predisposition, differing clinical and cognitive profile and course, which is characteristically more aggressive than in late onset cases. In addition subjects may still be working and of childbearing age. Early onset AD, therefore, poses particular management issues.

Clinical AD is often preceded by a phase called Mild Cognitive Impairment (MCI) in which there are complaints and objective impairments in one or more cognitive domains, but with preserved activities of daily living (ADL) [5]. The panel decided not to review MCI syndrome extensively since discussions around the nosological status of MCI and its relationship to AD are ongoing.

Search strategy

The evidence for this guideline was collected from Cochrane Library reviews, meta-analyses and systematic reviews and original scientific papers published in peer-reviewed journals before May 2009 accessed using the MEDLINE database. The scientific evidence were evaluated according to pre-specified levels of certainty (classes of evidence I, II, III, and IV) by the expert group members, and the recommendations were graded according to the strength of evidence (grade A, B, or C), using the definitions given in the EFNS guidance [6]. In addressing important clinical questions, for which no evidence was available, 'good practice points' were recommended based on the experience and consensus of the expert task force group.

Reaching of the consensus

A proposed guideline with specific recommendation was drafted for circulation to task force members and displayed on EFNS web pages for comments from all panel members. Consensus was reached at three task force meetings during 2009.

Results

Clinical diagnosis: medical history, laboratory, neurological and physical examination

The history, from the patient and a close informant, should focus on the affected cognitive domains, the course of the illness, and the impact on ADL and any associated non-cognitive symptoms. Past medical history, co-morbidities, family and educational history are important. The neurological and general physical examination is particularly important in distinguishing AD from other primary degenerative and secondary dementias and co-morbidities [1]. There exist no evidence-based data to support the usefulness of specific routine blood tests for evaluation of those with dementia but these are useful in excluding co-morbidities. Most expert opinion advises to screen for vitamin B12, folate, thyroid stimulating hormone, calcium, glucose, complete blood cell count, renal and liver function abnormalities. Serological tests for syphilis, Borrelia and HIV should be considered in individual cases at high risk or where there are suggestive clinical features.

Assessment of cognitive functions

There are two main reasons for neuropsychological assessment in AD: (i) the diagnosis of dementia requires evidence of multiple cognitive defects; and (ii) initial stages of all principal forms of dementia have a selective anatomical localisation reflected by typical patterns of neuropsychological impairment. Screening tests are used to assess cognitive functions globally to identify patients who require more detailed investigation. This is then undertaken with a battery of neuropsychological tests which should evaluate memory, executive

functions, language, praxis and visual-spatial abilities. The most widely used *screening test* (I) is the Mini-Mental State Examination (MMSE), which standard cut-off score (24) should be increased to 27 in highly educated individuals [7] and lowered in patients whose native tongue is another language or with low education. Patients with early AD fail mainly in orientation and memory tasks, whereas fronto-temporal dementia (FTD) individuals exhibit early impairment in speech and DLB patients may be affected in visuospatial components (pentagons) [8]. Other neuropsychological or clinical screening instruments reported in Table 1 provide an equal or greater accuracy in the diagnosis of AD (III).

Memory functions

Memory, especially episodic memory, should be systematically assessed (I), because it is the function most commonly impaired early in AD as consequence of mesial temporal lobe atrophy (entorhinal cortex, hippocampus) which disables consolidation. Retrieval, which depends on frontal lobe and subcortical structures, is less affected. This can be clarified by cuing as applied in California Verbal Learning Test [9] or Buschke Free and Cued Selective Reminding test, to distinguish patients at an early stage of AD from other subjects [10]. The Rey Auditory Verbal Learning Test (RAVLT) can distinguish between patients with AD and those without dementia or between AD and other forms of dementia with a diagnostic accuracy of 83–86% [11]. In particular, a very severe impairment (0 score) on RAVLT delayed free recall has a very high (97%) specificity for AD (I) [11]. A less severe score can raise diagnostic problems, since it can be due to defective encoding resulting from depression, anxiety or attentional deficit. A comparison between free recall and cued recall revealed different results in mild AD patients. Vogel *et al.* [12] found that cued and free recall

Table 1 Assessment of cognitive functions in AD

Screening tests	Sensitivity	Specificity	References
Neuropsychological instruments			
MMSE	80–85% (Demented versus non-demented very old patients)	76–80%	[94]
7 min	93%	93% (AD versus various forms of depression and dementia)	[95]
ACE	94%	89% (AD versus NC and other forms of dementia)	[96]
MOCA	90%	90% (Mild AD versus MCI and NC)	[97]
Mattis D.R.S.	85%	85% (AD versus FTD)	[98]
Clock drawing 67%	97%	(very mild AD versus NC)	[99]
CERAD battery 80%	81%	(Mild AD versus MCI and NC)	[100]
5 words test	91%	87% (AD versus functional memory disorders)	[15]
Assessment of specific cognitive domain			
Episodic memory			
Logical memory	89% (free recall)	87% (very mild AD versus NC)	[14]
FCSRT	80% (free and cued recall)	90% (MCI converters versus non-converters)	[10]
CVLT	50% (free and cued recall)	98% (Mild AD versus MCI and NC)	[9]
Category cued recall	88%	89% (very mild AD versus NC)	[12]
RAVLT	50% (0 score) (free recall and recognition)	97% (AD versus other forms of dementia)	[11]
Semantic memory (category fluency)			[16]
Language (naming)			
Graded naming			[21]
Boston naming	Overall accuracy: 77% (AD versus NC)		[20]
Visual-spatial abilities			
BVRT			[22]
Executive functions			
Verbal fluency tests			[16]
WCST			[17]
TMT			[18]
Stroop test			[19]

MMSE, Mini-Mental State Examination; ACE, Addenbrooke's cognitive examination; MOCA, Montreal Cognitive Assessment; FCSRT, Free and Cued Selective Reminding test; CVLT, California Verbal Learning Test; RAVLT, Rey Auditory Verbal Learning Test; BVRT, Benton Visual Retention Test; CST, Wisconsin Card Sorting test; TMT, Trail Making Test; AD, Alzheimer's disease; MCI, mild cognitive impairment; FTD, fronto-temporal dementia; NC, normal controls.

had the same values of sensitivity and specificity whereas Ivanoiu *et al*. [13] found that cued recall test was the best predictor of mild AD. High values of sensitivity and specificity have also been obtained by Salmon *et al*. [14] with the delayed recall from the 'Logical Memory' test or in the '5 word' test [15]. *Semantic memory* (category fluency test, pictures naming task, word and picture definition) testing may confirm deficits in AD or more prominently in Semantic Dementia [16].

Executive functions

A predominance of executive dysfunction over episodic memory impairment is typical for FTLD and VaD (III) and is more frequent in early onset AD. Decreased fluency on verbal fluency tests, perseverations on the Wisconsin card sorting test (WCST) [17]; reduced speed of processing on the Trail Making test [18] and defects in inhibiting automatic responses on the Stroop test [19], may be caused by subcortical or frontal lesions [18,19].

Language (speech comprehension and production, reading and writing) *praxis and visual-spatial abilities* can be variably affected according to type and stage of dementia suggesting for prominent cortical involvement. Boston Naming test [20] or the Graded Naming test [21] are frequently impaired in the earliest stages of AD. High number of errors on the Benton visual retention test can predict the development of AD more than a decade before diagnosis [22].

Studies of apraxia are remarkably few in AD, but a significant relationship has been found between apraxia severity and dependency in ADL [23].

The ADAS cog is a 11-item cognitive test battery that has been particularly useful to detect changes in severity of AD, mainly in clinical trials, but it is not useful for diagnostic purposes.

Assessment of ADL

Functional decline is required for the diagnosis of dementia. It also allows evaluation of the need for personal and institutional care. ADL's are divided into Basic (e.g. bathing, toileting) and Instrumental (e.g. shopping, handling finances), the latter being more vulnerable to cognitive decline early in the course of the disease. There is no 'gold standard' available for ADL assessment. Out of 12 systematically reviewed scales the informant-based questionnaires the Disability Assessment for Dementia and the Bristol ADL are among the most useful, though their overall psychometric properties were still only of moderate quality [24]. ADL are reflected in the clinical dementia rating scale which is widely used for rating of dementia severity. The Blessed Roth Dementia Scale and the Informant Questionnaire on Cognitive Decline in the Elderly are also helpful in detection of dementia [1]. The AD8 is a brief, sensitive informant-based questionnaire that reliably differentiates between non-demented and demented individuals. The respondent rates change (yes versus no) in memory, problem-solving abilities, orientation, and ADL [25].

Assessment of behavioural and psychological symptoms

The term 'behavioral and psychological symptoms of dementia' (BPSD) is used to describe the spectrum of non-cognitive symptoms of dementia (apathy, psychosis, affective and hyperactive behaviors) [26] Identification of neuropsychiatric symptoms is essential since BPSD occur in the majority of persons with dementia over the course of the disease, and in 35–75% of MCI patients [27] (I). BPSD are associated with declining cognitive and functional ability [27], decreased quality of life and increased institutionalization. Somatic co-morbidity and environmental triggers should be ruled out as a possible cause. Several global reliable and validated scales are used to assess BPSD and their change as a result of treatment [28]. They rely upon the report of an informant and include the neuropsychiatric inventory, and the behavior rating scale for dementia of the CERAD (CERAD-BRSD) [29]. For assessing treatment effects the change in scales representing a clinically meaningful improvement has not been established. More focused scales evaluating agitation or depression in dementia are also available [29]. The Cornell scale for depression in dementia (CSDD) is based on combined caregiver and patient interviews. The 15-item geriatric depression scale has also been validated for use in AD but the CSDD appears to be a more sensitive and specific tool for detecting depression independently of the severity of dementia [30].

Assessment of co-morbidity

AD patients commonly have co-morbid medical conditions such as depression, cardiovascular and pulmonary diseases, infections, arthritis, other neurological disorders, sleep disturbances, falls and incontinence, and drug-related adverse effects, especially in older patients. There is a strong association between medical conditions and impaired cognitive status in AD and the prompt identification and treatment of the associated medical illnesses at the time of diagnosis and throughout the disease evolution may improve cognition in AD patients [31].

Neuroimaging

Structural imaging in the diagnostic work up of AD serves two purposes: exclude other, potentially surgically treatable diseases and include specific findings for AD.

For the former CT and MRI perform as well and most current guidelines agree that such an imaging procedure should be carried out once in every patient. However, MRI is more sensitive to subtle vascular changes (strategic infarcts for instance) and to changes that may indicate specific conditions such as multiple sclerosis, PSP, multiple-system atrophy, CBD, prion disease, FTLD (for review see [32]). For practice purposes a standard MR protocol involving at least coronal T1 and axial T2 or fluid-attenuated inversion recovery sequences should be used. Contrast is not indicated. Of note, vascular changes seen on CT or MRI need not preclude a diagnosis of AD, especially in older age, but should prompt adequate evaluation and treatment of cardiovascular risk factors.

Hippocampal atrophy is best seen on MRI but may also be visualized on the more modern type CT scanner [33] and yields sensitivity and specificity values between 80 and 90% in most studies [32–34] (II). Since the previous guideline only one prospective study has been performed examining the added value of hippocampal atrophy on MRI in the diagnosis of AD with post-mortem verification [35]. However, being a single center, small study, in a selected population, it just fails class I evidence.

AD patients with early age of onset often present with complaints and cognitive deficits other than memory impairment [36]. Several structural MRI studies localize the pattern of the atrophy in early-onset AD to more posterior regions with prominent involvement of the precuneus and posterior cingulate cortex [37].

In addition, MRI may also be useful to monitor changes over time and may aid the clinician in following the disease process and explaining it to the patient (good practice point).

Functional neuroimaging [i.e., fluorodeoxy-glucose-(FDG-) PET and single photon emission computed tomography (SPECT)] may increase diagnostic confidence in the evaluation of dementia. In a clinical-pathological study, a positive perfusion SPECT scan raised the likelihood of AD to 92%, whereas a negative SPECT scan lowered the likelihood to 70%. SPECT was more useful when the clinical diagnosis was 'possible' AD, with the likelihood of 84% with a positive SPECT, and 52% with a negative SPECT [38]. Dopaminergic SPECT imaging (FP-CIT or DATScan™; GE Healthcare, Amersham, UK) is useful to differentiate AD from DLB with sensitivity and specificity around 85% (I). Care should be taken that standardized acquisition and analysis methods are used since results and interpretation of DATScans may otherwise vary [39]. FDG-PET has become a practically applicable tool since the wide distribution of PET CT machines. It may reveal specific abnormalities in AD by showing reduced glucose metabolism in the parietal and superior/posterior temporal regions, posterior cingulate cortex, and precuneus. In advanced stages of AD, frontal lobe defects are also seen. ^{18}FDG-PET has been reported to have a sensitivity of 93% and a specificity of 63% in predicting a pathological diagnosis of AD (II) [40]. FDG-PET is particularly useful in the differential diagnosis of AD towards other dementias with specificity higher than 95% in early onset cases [41]. Based on the study by Foster *et al.* [42] FDG-PET is reimbursed in the USA for the distinction between AD and FTD only. A very promising development is the possibility of imaging amyloid with new PET ligands. As of yet these are not available for routine use.

Electroencephalography (EEG)

The EEG may help to differentiate between AD, subjective complains and psychiatric diagnoses. EEG is recommended in differential diagnosis of atypical clinical presentations of AD. It can also provide early evidence for CJD or suggest the possibility of a toxic-metabolic disorder, transient epileptic amnesia or other previously unrecognized seizure disorder. Even though reduced alpha power, increased theta power and lower mean frequency are characteristic for AD patients, EEG can be normal early in the course of the disease in up to 14% of cases. In different studies, the diagnosis accuracy of EEG for AD patients versus healthy control subjects with similar demographic characteristics varied widely, with diagnosis odds ratios between 7 and 219 [43]. EEG with only diffuse abnormalities argues for AD, EEG with both diffuse and focal changes suggests AD or other forms of dementia [44].

CSF analysis

Routine CSF cell count, protein, glucose and protein electrophoresis assessment is mandatory when vasculitis, inflammatory, hematologic or demyelinating disease is suspected and in cases of suspected CJD in differentiation with AD.

The elevation of the 14-3-3 protein reflects acute neuronal loss and supports diagnosis of CJD [45] (II) while high to very high levels of total tau yield high specificity for CJD [46,47]. In AD decreased levels of beta-amyloid 42 (Aβ42) and increased total-tau or phospho-tau in CSF are frequently found. The pooled

sensitivity and specificity for Aβ42 in AD versus controls from 13 studies involving 600 patients and 450 controls were 86% and 90% [48]. For total-tau, the sensitivity was 81% and the specificity 90%, pooled from 36 studies with 2500 patients and 1400 controls. Across 11 studies with a total of 800 patients and 370 controls, phospho-tau had a mean sensitivity of 80% and specificity was set at 92% but sensitivities varied widely among studies using different methods. Combined assessment of Aβ42 and total-tau revealed sensitivities (85–94%) and specificities (83–100%) in AD versus controls [48] (I).

Specificity of these markers for AD has been lower (39–90%) in differential to the other dementias in clinic-based series [49] which may relate to the presence of co-morbid AD pathology [50] (III).

There are considerable differences in absolute concentrations of these markers between laboratories, even when the same kit is used [51,52]. Before CSF can be widely accepted as a reliable tool a consensus for processing and handling of the samples is needed [51].

Genetic testing

The genetics of dementia is complex and genetic testing is associated with many ethical concerns. APP, PS1 and PS2 gene mutations explain 50% of the familial form of early-onset AD [53]. The ApoE ϵ4 allele is the only genetic factor consistently implicated in late-onset AD, but it is neither necessary nor sufficient for development of the disease [54]. Hence, there is no evidence to suggest ApoE testing is useful in a diagnostic setting. Autopsy diagnosis in familial dementias can be valuable for subsequent diagnosis and counselling. Testing of patients with familial dementia and of unaffected at-risk-relatives should be accompanied by neurogenetic counselling and undertaken only after full consent and by specialist centres. Pre-symptomatic testing may be performed in at risk member of family-carrying mutation. It is recommended that the Huntington's disease protocol is followed for pre-symptomatic testing [55].

Other investigations

A number of non-nervous tissue specimens (mostly fibroblasts, platelets, olfactory and vascular epithelium) have been investigated in AD, including analysis of DNA damage and repair, autophagy, proteomic analysis, oxidative processes, ionic channels and transduction, APP levels and intracellular calcium regulation. However these studies, while potentially informative about the disease process, are presently not of clinical use. Skin and muscle biopsy are used in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy diagnosis. Brain biopsy may have a role in the diagnosis of dementia where a treatable disease cannot be excluded by other means. However, it has been shown that information obtained at biopsy affected treatment in only 11% of cases biopsied for the suspicion of an infectious or inflammatory etiology, though the role of brain biopsy may increase as disease-modifying therapies become available [56].

Recommendations for diagnosis

Clinical history should be supplemented by an informant (Level A). A neurological and physical examination should be performed in all patients with dementia (good practice point). ADL impairment due to cognitive decline is an essential part of the diagnostic criteria for dementia and should be assessed in the diagnostic evaluation (Level A).

Several informant based questionnaires are available and should be used where possible (good practice point).

Cognitive assessment should be performed in all patients (Level A). Quantitative neuropsychological testing should be made in patients with questionable or very early AD (Level B). The assessment of cognitive functions should include a general cognitive measure and more detailed testing of the main cognitive domains, and in particular an assessment of delayed recall (Level A). In patients with moderate memory impairment cued recall could be more appropriate than free recall (Level B).

Assessment of BPSD should be performed in each patient (Level A). Information should be gathered from an informant using an appropriate rating scale (good practice point).

Assessment of co-morbidity is important in AD patients, both at the time of diagnosis and throughout the course of the illness (good practice point) and should always be considered as a possible cause of BPSD (Level C). Blood levels of folate, vitamin B12, thyroid stimulating hormone, calcium, glucose, complete blood cell count, renal and liver function tests should be evaluated at the time of diagnosis and serological tests for syphilis, Borelia and HIV might also be needed in cases with atypical presentation or clinical features suggestive of these disorders (good practice point).

CT and MRI may be used to exclude treatable causes of dementia. Multislice CT and coronal MRI may be used to assess hippocampal atrophy to support a clinical diagnosis of AD (Level B). FDG PET and perfusion SPECT are useful adjuncts when diagnosis remains in doubt (level B). Dopaminergic SPECT is useful to differentiate AD from DLB (level A). Follow up with serial MRI is useful in a clinical setting to document disease progression (good practice point).

EEG is recommended in differential diagnosis of atypical clinical presentations of AD (good practice point) and when CJD or transient epileptic amnesia is suspected (Level B).

Routine CSF analysis is recommended in differential diagnosis for atypical clinical presentations of AD (good practice point). CSF 14-3-3 or total tau measurement are recommended for the identification of CJD in patients with rapidly progressive dementia (Level B). Alterations in CSF total tau, phospho-tau and Aβ42 support diagnosis of AD (Level B).

Screening for known pathogenic mutations can be undertaken in patients with appropriate phenotype or a family history of an autosomal dominant dementia. Routine Apo E genotyping is not recommended.

Management of Alzheimer's disease

The first step in AD management is accurate recognition and diagnosis of the disorder, and then disclosing that diagnosis in a sensitive and timely way to the patient and others as appropriate. Disclosure of diagnosis is not harmful, and actually decreases depression and anxiety in patients and their care-givers [57] (II). The vast majority of patients with mild dementia wish to be fully informed and 75% of caregivers wish their relative to be informed [58]. Differences among ethnic, cultural, and religious groups may influence how and what disclosure occurs. It offers the patient opportunity to pursue desired activities and maximizes individual autonomy and choice by providing information necessary for decision making and advance planning, including the decision to give informed consent to research projects and autopsy. At time of diagnosis several issues need to be addressed, including the provision of high quality understandable information about the illness and its course to patient and caregiver, a careful assessment for any co-morbidities and consideration given to other services that may be required including social services, mental stimulation, occupational therapy, physiotherapy, speech and language therapy (IV). Occupational therapy can benefit patients' daily functioning and reduce the need for informal care [59] (II). Medico-legal issues need to be addressed, with driving often needing prompt attention and action taken according to the legal framework operating in that particular country. Care-giver support should consist of education about AD, and attending peer support groups may be helpful. Care-giver stress and depression are common and, if present, more intensive care-giver support and counselling and/or specific treatment for depression may be needed. The provision of a standard education and support package to caregivers has been shown in randomized controlled trials (RCT) to decrease psychiatric symptoms in caregivers and lead to delays in institutionalisation for patient [60,61] (I). Management should include clear arrangements for follow-up, as regular monitoring of medication response and adverse effects as well as changes in the severity of dementia (using scales like the MMSE) should be undertaken. Reassessment for development of co-morbidity (including carer stress) should be an integral part of management.

Primary prevention of AD

This refers to the prevention of subsequent dementia in cognitively normal subjects and is the ultimate goal for AD management. Several risk factors have been well established for AD, though some (such as age, sex and genotype) are not modifiable. Potentially modifiable risk factors which have been established through several epidemiological studies include vascular risk factors (hypertension, smoking, diabetes, atrial fibrillation and obesity) and head injury while protective factors described include use of antihypertensives, non-steroidal anti-inflammatories, statins and hormone replacement therapy, high education, diet, physical activity and engagement in social and intellectual activities. However, whether modifying these factors will reduce risk of dementia is not yet known. A meta-analysis concluded that there is no good evidence to recommend statins for reducing the risk of AD [62] while results of the large, prospective, placebo-controlled 'Women's Health Initiative Memory Study' showed that the use of estrogen plus progestin in post-menopausal women was actually associated with a significantly increased risk of dementia [63] (I).

Treatment of hypertension for prevention of dementia, including AD, has been the best studied risk factor to date. However, most RCTs have been stopped early because cardiovascular endpoints were reached, meaning they were underpowered to detect differences in rates of dementia. A study of treating hypertension in the very old reached similar conclusions, and contained a meta-analysis of all studies supporting a significant risk reduction [64] (I). However, the period over which treatment needs to be given is not known, nor has it been established whether treating vascular risk factors, including hypertension, in those with established AD affects disease progression. Currently, no clear recommendations about dementia prevention can be made.

Secondary prevention of AD

This refers to the prevention of development of AD in non-demented subjects with some evidence of cognitive impairment. The groups most often studied in this

regard are those with MCI and several RCTs of cholinesterase inhibitors (ChEIs) have been undertaken in MCI, most using 'conversion' to dementia as the primary outcome. A meta-analysis included eight studies involving all three ChEIs, with duration of treatment ranging from 16 weeks to 3 years [65]. There were no differences in rate of conversion to AD between active and placebo groups, and most secondary outcomes were also negative (I). There have also been negative studies of aspirin in primary prevention of cognitive decline and of anti-inflammatories and vitamin E in MCI (I). A large study showed no effect of Gingko on preventing AD [66] (I). Therefore, no treatments have demonstrated efficacy for preventing or delaying development of AD in MCI subjects until now, while evidence exists that ChEIs, Vitamin E, Gingko Biloba and anti-inflammatories are not substantively helpful.

Treatment of established AD

Cholinesterase inhibitors

There have been several well conducted placebo-controlled, large scale RCTs with the three ChEIs, donepezil, rivastigmine and galantamine, which have shown efficacy on cognitive function, global outcome and ADL in patients with mild to moderate AD(I), usually defined as MMSE between 16 and 26. Mean global improvement over placebo is 3–4 points on the ADAS-Cog, a level of improvement roughly equivalent to the naturalistic decline expected over a 6 month period. Most studies have been over relatively short duration (6 months), though 1 and 3 year studies have been reported with donepezil which suggest the benefits of ChEIs continue in the longer long (I). Retrospective analysis and some long term open studies suggest a possible effect of ChEI on disease modification, but more data are needed before this can be confirmed [67]. RCTs of ChEIs in more severe AD (MMSE < 10) have also shown positive results [68,69] and a Cochrane review concluded that trials supported evidence of benefit in mild, moderate and severe AD [70]. In light of current evidence, limiting prescribing of ChEIs to only some AD subjects according to certain cut-offs on a measure such as the MMSE, as operated in many countries, does not seem justified. Although a point will be reached in severe AD when ChEI are unlikely to continue to have benefit, it is currently unclear at what point in the disease process ChEI should be withdrawn.

Cholinesterase inhibitors (ChEIs) are generally well tolerated, although common gastrointestinal adverse effects such as nausea, diarrhea, and vomiting may sometimes lead to discontinuation of treatment in some patients. There have been few direct comparisons between ChEIs, and those which have been undertaken have been small in size and not produced consistent evidence of better efficacy of one drug over another (II). There is some evidence from open-label studies that patients who do not tolerate or do not seem to benefit from one ChEI may tolerate or draw benefit from the other (III). One of the ChEIs, rivastigmine, is now available in a transdermal (patch) formulation which appears to have lower incidence of side effects than oral administration but equal efficacy [71] (I).

A disease modifying effect of ChEIs has been proposed, and has some basic scientific support, but no convincing clinical data, either from trials of clinical endpoints or of those using biomarkers, has yet been forthcoming to support these claims (IV).

Effects on non-cognitive BPSD have also been shown, though as with cognition effect sizes are modest (I). There remains uncertainty as to which particular non-cognitive symptoms may respond best, though effects on psychosis and apathy are consistently reported (II). Effects on agitation are less clear, and a large placebo-controlled RCT in moderate to severe AD failed to show an effect of donepezil on patients with clinically significant agitation [72] (I).

Memantine

Memantine, a non-competitive *N*-methyl-D-aspartate receptor antagonist, also has been subject to several RCTs in AD. Studies in moderate to severe AD have been more consistently positive than those in mild to moderate AD, previous reviews of the literature have concluded that while there is a significant effect in cognition at all severities, but effects on global outcome, ADL and behaviour were only apparent in the moderate to severe studies [73] (I). Once daily dosing has been shown to be as effective as the original recommendation of administration twice daily (I) [74]. Modest effects on behaviour were also found in a pooled analysis of six studies which included all those with MMSE < 20, with delusions, agitation/aggression and irritability being the most responsive symptoms [75] (II), though studies of subjects primarily selected for the presence of these behavioural features have not yet been reported.

The benefits of adding memantine to ChEIs are not clear, an early study of adding memantine to donepezil was positive, but a recent study of over 400 subjects which added the drug or placebo to those stable on any of the three ChEIs showed no evidence of benefit in either cognitive or non-cognitive symptoms [76] (I). Further studies are needed before clear recommendations can be made about the benefits of adding memantine to ChEIs.

Other drugs and interventions

Several other treatments have been suggested as potentially beneficial for AD, including non-steroidal anti-inflammatory drugs, oestrogens and statins. A large, placebo-controlled RCT of vitamin E (1000 IU, twice a day over 2 years) in moderate AD, was found to significantly delay the time to a composite outcome of primary outcome measures, but a study in MCI has been negative and the conclusion of a Cochrane review is that there is insufficient evidence for the efficacy of vitamin E in the treatment of AD or MCI [77] (I). Studies of steroidal, non-steroidal and cyclo-oxygenase-2 inhibitors in AD and MCI have been negative yet have had potentially serious side effects (I). Evidence – based data report studies of Ginkgo biloba extract (explicitly EGb 761), but there remains controversy about the role of the EGb 761 as studies to date have included mixed populations and have not been consistent in results. A meta-analysis concluded that the evidence that Ginkgo Biloba has predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent and unreliable [78] (I). However two class I studies [79,80] demonstrating positive effects were omitted because of significant heterogeneity between the trials. Further evidence is needed before efficacy for Gingko can be clearly established.

Many other compounds, such as piracetam, nicergoline, selegiline, vinpocetine, pentoxyphylins and Cerebrolysin are prescribed in some countries as treatments for AD. For example, a recent Cochrane review of piracetam, one of the most widely studied drugs to date, found poor study design, possible publication bias and that overall the evidence from trials did not support the use of piracetam in people with dementia or cognitive impairment [81]. A review of 6 Cerebrolysin trials [82] found an effect on global outcome but no consistent effect on other scales. Further evidence is therefore required before its use can be recommended. Similarly, a Cochrane review of selegiline found no evidence for its efficacy in AD [83]. At present, therefore, there is no convincing evidence for efficacy of any of these drugs for AD.

There is much interest in the use of cognitive therapies in AD. Preliminary studies seem to suggest a beneficial effect of cognitive stimulation, also known as Reality Orientation (see http://www.nice.org.uk, dementia guideline (no 42) for comprehensive review). More studies are needed before it can be classified as class I evidence, but in individual cases the clinician may decide to try this form of therapy (good practice point).

There are many ongoing clinical studies aimed at modifying the underlying disease process, including international trials of passive and active amyloid immunisation [84] and of the drug Dimebon [85]. However, recommendations about the usefulness of these and other agents must await final results from rigorous Phase III studies.

Treatment of behavioural and psychological symptoms

Management of BPSD begins with careful search for trigger and/or exacerbating factors including environmental cues, physical problems (infections, constipation), medication and depression or psychosis. As studies of BPSD indicate a high placebo response, safe non-pharmacological management (education, exercise, aromatherapy, sensory stimulation, personalised music) should be tried wherever possible in the first instance as symptoms may naturally resolve within a short time. The beneficial effects of ChEIs and memantine for mild BPSD have been described above, but a recent RCT found donepezil did not help clinically significant agitation in those with moderate to severe AD [72]. Both conventional and atypical antipsychotics reduce BPSD, with particular effects demonstrated for risperidone for agitation/aggression and psychosis [86,87] (I). However, antipsychotics have important and potentially serious side effects, most especially increased stroke risk, increased mortality, parkinsonism and cognitive impairment [88]. They should be used with caution, at low dose, and for the shortest period needed only for those with moderate to severe symptoms causing distress and after careful assessment of risk and benefit and after discussion with care-giver and, where possible, patient. There is no evidence that conventional agents are any safer in regard to risk of stroke or mortality than atypical agents [89] and they have a less established evidence base and greater side effects. Low doses of antipsychotics should be used with careful monitoring, and drugs prescribed for the minimum period required. When BPSD have settled, antipsychotics can be withdrawn in most cases without re-emergence of BPSD, unless behavioural disturbance is still present [90]. Evidence for other drugs is limited, carbamazepine may help aggression [91] (II), though most studies of valproate have been negative [92] (II). Antidepressants, especially Selective serotonin reuptake inhibitors (SSRIs), may be useful for depression in dementia and do not have the adverse anticholinergic effects of older tricyclics [93] (II).

Recommendations on management

Diagnosis of AD should be disclosed to patient (and caregivers as appropriate) (Level B). Disclosure of diagnosis should be individually tailored. It should be

accompanied by information and counseling, as well as useful contacts such as Alzheimer's patient organizations. Patients and caregivers should be provided with education and support (Level A). Driving, medico-legal issues and the need for other support services should be considered (good practice point). If possible physicians may encourage patients to draw up advance directives containing future treatment and care preferences (good practice point).

There is insufficient evidence to support the use of any drugs purely for the primary prevention of dementia. ChEIs, vitamin E, gingko and oestrogens should not be used as treatments for those with MCI (Level A).

In patients with AD, treatment with ChEIs (donepezil, galantamine, or rivastigmine) should be considered at the time of diagnosis, taking into account expected therapeutic benefits and potential safety issues (Level A). Benefits on cognitive and non-cognitive symptoms have been demonstrated in those with mild, moderate and severe disease (Level A). Realistic expectations for treatment effects and potential side effects should be discussed with the patient and caregivers (good practice point).

In patients with moderate to severe AD, treatment with memantine should be considered taking into account expected therapeutic benefits and potential safety issues (Level A). Benefits on cognitive and non-cognitive symptoms are apparent, some non-cognitive symptoms (agitation, delusions) may respond better than others (Level B). Realistic expectations for treatment effects and potential side effects should be discussed with the patient and caregivers (good practice point).

Regular patient follow-up, which should include scales like the MMSE to monitor response to treatment and disease progression, should be an integral part of management (good practice point).

Aspirin should not be used as a treatment for AD (Level A), though it can be used in those with AD who also have other indications for its use (e.g. to prevent cardiovascular events). Vitamin E should not be used as a treatment for AD (Level A).

Currently, there is insufficient evidence to support the use of other agents including, anti-inflammatory drugs, nootropics (including piracetam, nicergoline), selegiline, oestrogens, pentoxyphylin, or statins and inconsistent evidence for EGb 761 and Cerebrolysin in the treatment or prevention of AD (Level A).

Cognitive stimulation or rehabilitation may be considered in patients with mild to moderate AD (good practice point). Occupational therapy can improve patients' functioning and reduce need for informal care (Level B).

Management of BPSD should begin with a careful search for triggers and causative factors (i.e. physical illness). Where possible, initial treatment should be non-pharmacological (Level C).

Antipsychotics should only be used for moderate or severe BPSD symptoms causing significant distress which have either not responded to other treatments (like non-pharmacological measures or ChEIs) or when other treatments are not appropriate (Level A). Low dose of atypical agents should be used only after assessment of risk benefit and full discussion with patient (when capacity allows) and caregiver (good practice point).

Atypical agents have fewer side effects and do not confer a greater risk of stroke or mortality than conventional drugs (Level B).

Selective serotonin reuptake inhibitors rather than tricyclic antidepressants should be used to treat depression in AD (Level B).

Scheduled update

2012.

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