

## Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia: EFNS guideline

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The aim of this international guideline on dementia 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 dementia. It covers major aspects of diagnostic evaluation and treatment, with particular emphasis on the type of patient often referred to the specialist physician. The main focus is Alzheimer's disease, but many of the recommendations apply to dementia disorders in general. The task force working group considered and classified evidence from original research reports, meta-analysis, and systematic reviews, published before January 2006. The evidence was classified and consensus recommendations graded according to the EFNS guidance. Where there was a lack of evidence, but clear consensus, good practice points were provided. The recommendations for clinical diagnosis, blood tests, neuroimaging, electroencephalography (EEG), cerebrospinal fluid (CSF) analysis, genetic testing, tissue biopsy, disclosure of diagnosis, treatment of Alzheimer's disease, and counselling and support for caregivers were all revised when compared with the previous EFNS guideline. New recommendations were added for the treatment of vascular dementia, Parkinson's disease dementia, and dementia with Lewy bodies, for monitoring treatment, for treatment of behavioural and psychological symptoms in dementia, and for legal issues. The specialist physician plays an important role together with primary care physicians in the multidisciplinary dementia teams, which have been established throughout Europe. This guideline may contribute to the definition of the role of the specialist physician in providing dementia health care.

### Introduction

Dementia afflicts at least 5 million people in Europe [1] and is associated with significant physical, social and psychiatric disability in the patients and with significant burden and distress in family caregivers. Furthermore, Alzheimer's disease (AD) and other dementia disorders

rank second in Western Europe when comparing the burden of brain diseases by the loss of disability adjusted life years [2]. The total health care costs in Europe related to dementia amount to at least 55 billion € per year, not including indirect costs and costs in young patients with dementia [1,3], and the majority of the costs are spent on institutional care.

Despite the fact that there is significant evidence for the benefits of early diagnostic evaluation, treatment and social support, the rate of diagnosis and treatment in people with dementia varies considerably in Europe [4]. General practitioners play a major role in the identification, diagnosis and management of patients with dementia. In many places multidisciplinary teams have been established to facilitate the management of the complex needs of patients and caregivers during the course of the dementia disease. The neurologist and other specialist physicians play a major role in these

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teams and clinics together with other professionals with special training in dementia.

In 2003, a task force was set up to develop a revision of the EFNS guideline on dementia published in 2000 [5], with the aim to provide peer-reviewed evidence-based guidance for clinical neurologists, geriatricians, old age psychiatrists, and other specialist physicians responsible for the care of patients with dementia. This guideline addresses major issues in the diagnosis and management of AD and other disorders with dementia. Since the previous guideline was published in 2000 significant evidence has accumulated, and new methods have become available for diagnosis and treatment.

The task force panel, appointed by the Scientific Committee of the EFNS, included neurologists, and representatives from geriatrics and old age psychiatry, with clinical and research expertise in dementia, and a representative from the patient organization, Alzheimer Europe. The guideline applies to patients with suspected or diagnosed dementia, and covers aspects of diagnostic evaluation, as well as treatment, with particular emphasis on the type of patient often referred to the specialist. It does not, however, include treatment of mild cognitive impairment (MCI). The main focus of the guideline is AD, but there are many other conditions, although lower in prevalence, which require specific assessment and treatment, and many of the recommendations apply to dementia disorders in general. The guideline represents the minimum desirable standards for the guidance of practice, but does not include an analysis of cost-effectiveness of the recommended diagnostic and treatment interventions.

The evidence for this guideline was collected from Cochrane Library reviews, other published meta-analyses and systematic reviews, other evidence-based management guidelines in dementia, including the practice parameters from the American Academy of Neurology (AAN) [6–8], and original scientific papers published in peer-reviewed journals before January 2006. For each topic, the evidence was sought in MEDLINE according to pre-defined search protocols. The scientific evidence for diagnostic investigations and treatments were evaluated according to pre-specified levels of certainty (class I, II, III, and IV), and the recommendations were graded according to the strength of evidence (grade A, B, or C), using the definitions given in the EFNS guidance [9]. In addressing important clinical questions, for which no evidence was available, the task force group recommended ‘good practice points’ based on the experience and consensus of the task force group. Consensus was reached by circulating drafts of the manuscript to the task force members and by discussion of the classification of evidence and recommendations at four task force meetings during 2004 and 2005.

This guideline may not be appropriate in all circumstances, and decisions to apply the recommendations must be made in the light of the clinical presentation of the individual patient and of available resources.

## Diagnostic evaluation

### Clinical diagnosis

With the remarkable exception of autosomal dominant causes of dementia, there is no specific biological marker for degenerative dementias. Therefore, in the absence of neuropathological confirmation, the aetiological diagnosis of a dementia syndrome can only be made in terms of probability. The clinical diagnosis should rely on criteria that have been proposed to increase the reliability and accuracy of the diagnosis. The accuracy of these diagnostic criteria varies as a function of the dementia. For AD, both the *Diagnostic and Statistical Manual, 3rd edn, revised* (DSM-III-R) [10] and the *National Institute of Neurologic, Communicative Disorders and Stroke – Alzheimer’s Disease and Related Disorders Association* (NINCDS-ADRDA) [11] criteria achieved a good sensitivity (up to 100%, average 81% across studies), but a low specificity (average across studies 70%) for ‘probable’ AD, based on class I–II studies with post-mortem confirmation [7]. For dementia with Lewy bodies (DLB), the Consortium for DLB diagnostic criteria from 1996 [12] showed rather low sensitivities in class I and II studies [7]. For fronto-temporal dementia (FTD) [13,14] advances in the understanding of the underlying pathophysiology and genetic mechanisms have indicated that the clinical syndromes are associated with several different neuropathological abnormalities, although generally, specific sets of pathological findings have not been associated with specific clinical syndromes. For vascular dementia (VaD), the *National Institute of Neurologic Disorders and Stroke and the Association Internationale pour la Recherche et l’Enseignement en Neurosciences* (NINDS-AIREN) diagnostic criteria [15] achieved a low sensitivity (43%), but a good specificity (95%) in the only published class I study [16]. Mixed pathologies and the prevalent findings of vascular lesions in all patients with dementia add to the complexity of the diagnosis of VaD.

### Medical history

The clinical history is a corner stone of medical practice and serves to focus the examination and investigations. The history should include the cognitive domains affected, the mode of onset, the pattern of progression and the impact on activities of daily living (ADL). Past medical history, current co-morbidities, family history and educational history are important. Due both to the

presence of cognitive deficit and to the possibility of anosognosia it is important to obtain a history from an independent informant. Several class I to II studies have confirmed the value of informant based instruments, such as the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) and the Blessed Roth Dementia Scale (BRDS) in the detection of dementia [17–22].

#### **Recommendation: medical history**

The clinical history should be supplemented by an independent informant where available (*Level A*).

#### **Neurological and physical examination**

The neurological examination in early AD is unremarkable apart from the cognitive impairment. However, for many of the other dementing disorders, for example DLB and prion diseases, the presence of additional neurological features, such as an extra pyramidal syndrome or myoclonus, is a key component of the diagnostic criteria. Moreover, many of the disorders in which dementia is part of a broader range of neurological dysfunction (the dementia plus syndromes) or in which abnormalities on physical examination such as organomegaly occur, the examination is critical in the diagnostic process. Furthermore, the general physical examination may reveal relevant comorbidities. Whilst no formal studies have addressed the issue of the added value of a neurological and physical examination this is an important part of the differential diagnosis of dementia.

#### **Recommendation: neurological and physical examination**

A general neurological and physical examination should be performed on all patients presenting with dementia (*Good Practice Point*).

#### **Assessment of cognitive functions**

Assessment of cognitive function is important for several reasons: (1) the diagnosis of dementia mainly relies on the evidence of cognitive deficits (episodic memory, instrumental and executive functions); (2) most of aetiologies of dementia (e.g. AD, FTD and DLB) can be identified by the nature of their cognitive and behavioural changes; (3) as specialist physicians increasingly see patients at early stages of the disease, it is now important to be able to identify the specific degenerative disorders at a prodromal phase before the symptoms reach the threshold of dementia. Accordingly, an

evaluation of cognitive function by a physician and/or by a clinical neuropsychologist is required for the management of patients with a prodromal, mild or moderate stage of dementia, whereas it is less essential for severely demented patients. The battery should investigate the following domains:

#### *Global cognitive functions*

The Mini-Mental State Examination (MMSE) of *Folstein et al.* [23] may help for the detection of cognitive impairment (I) and its sensitivity increases, if a decline of the score overtime is taken into account. The 7-min screen and the clinical dementia rating (CDR) (score = 1) demonstrate a specificity of 96% and 94% with sensitivity of 92% for the diagnosis of dementia [24,25] (IV) and can be useful for the detection of dementia. These two tests can be used as screening instruments for assessing general intellectual functioning. The Mattis Dementia Rating Scale [26] takes longer time and tests in addition several areas related to executive functions. It is, therefore, more appropriate for the assessment and follow up of FTD and fronto-subcortical dementias.

#### *Memory function*

Memory has to be systematically assessed. Episodic long-term memory impairment is required to fulfil the diagnosis criteria for dementia. Word recall, such as the Rey Auditory Verbal Learning Test (RAVLT), can distinguish between patients with AD and those without dementia (I) [27]. However, an effective encoding of information should be controlled to exclude the influence of depression, anxiety and other emotional states to cognitive problems. Semantic cueing may also help for separating retrieval for storage deficits [28]. For that reason, the Memory Impairment Scale (MIS) (sensitivity of 60% and specificity of 96% for identification of dementia [29]) and the '5 word' test (sensitivity of 91% and specificity of 87% for the identification of AD [30]) are short and simple memory tests that can be useful for a first-line screening tool for medical practitioners. Semantic memory should also be assessed (category fluency test, pictures naming task, word and picture definition), since deficits may be observed in AD and be prominent in Semantic Dementia (SD) [31].

#### *Executive functions*

Executive dysfunctions are observed in several dementia conditions. This impairment results in decreased verbal fluency with speech reduction, verbal stereotypies and echolalia; perseverations of mental set; retrieval deficits; attentional disorders; concrete thinking and in some cases disinhibition, impaired

adaptation, and uncontrolled behaviours. These deficits are currently assessed by the Wisconsin card sorting test [32], the Trail Making test [33], the Stroop test [34], the verbal fluency tests [35], and the digit ordering test [36] which trigger the cognitive processes needed for executive functions. In some dementias, executive dysfunction is only an epiphenomenon, part of a more diffuse and global picture. By contrast, it can be a prominent feature and essential for the diagnosis of other dementias, such as FTD [37] and progressive supranuclear palsy (PSP) [28].

#### *Instrumental functions*

Language (comprehension and expression), reading and writing, praxis (execution and recognition), visuospatial and visuoconstructive abilities can also be more or less affected according to the type of dementia disorder. These cognitive domains, often referred to as instrumental functions, are particularly impaired in diseases with prominent cortical involvement such as AD and DLB and may be the initial domain of dysfunction in lobar atrophy [progressive aphasia syndromes, progressive apraxia, cortico-basal degeneration (CBD) or posterior cortical atrophy].

#### **Recommendations: assessment of cognitive functions**

Cognitive assessment is central to diagnosis and management of dementias and should be performed in all patients (*Level A*). Quantitative neuropsychological testing, ideally performed by someone trained in neuropsychology, should be considered in patients with questionable, prodromal, mild, or moderate dementia (*Level C*). The specialist physician should include a global cognitive measure and in addition more detailed testing of the main cognitive domains including memory, executive functions and instrumental functions (*Level C*).

#### **Assessment of behavioural and psychological symptoms**

Various terms including 'behavioural and psychological symptoms of dementia' (BPSD), 'neuropsychiatric features', and 'non-cognitive symptoms' are used to describe a range of symptoms that are common in dementia and which contribute substantially to patient distress and caregiver burden [38]. They are frequently a major factor leading to the prescription of psychotropic medications and to nursing home placement [39] (III). Their presence may contribute to the process of differential diagnosis, e.g. visual hallucinations are a prominent feature of DLB [12] (II), whereas disinhibition and lack of personal concern are characteristic of FTD [40]

(II). Their temporal course also varies, e.g. apathy, depression and anxiety tend to occur early in the course of AD with delusions, hallucinations and agitation appearing in the middle to late stages. BPSD may be worsened or caused by somatic co-morbidity. Patients with psychosis experience a more rapid cognitive decline than those without, and neuropsychiatric features may predict an increased rate of conversion to dementia in patients diagnosed with MCI [41] (II).

The accurate identification of BPSD is essential both for diagnosis and management of patients with dementia, but often such symptoms may not be disclosed by patients or caregivers, until they are intolerable or they precipitate a crisis [42]. Earlier detection can be achieved by routine and repeated enquiry. Several rating instruments have been designed for this purpose, enquiring not only about the presence or absence of different symptoms, but also about their frequency, severity and impact upon the caregiver. They usually rely upon the report of an informant who should have regular contact with the patient. Repeated use of such scales can also be useful in monitoring the effects of treatment interventions. Suitable scales include the Neuropsychiatric Inventory (NPI) [43], BEHAVE-AD [44] and the Manchester and Oxford Universities Scale for the Psychopathological Assessment of Dementia (MOUSEPAD) [45].

The most common neuropsychiatric feature of AD is apathy (72%), followed by aggression/agitation (60%), anxiety (48%) and depression (48%) [46] (II).

*Apathy and inertia* may occur independently of depressed mood and may be particularly frustrating for carers, especially in the early stages. *Agitation and aggression* may be very persistent and frequent causes of requests for institutionalization. *Anxiety* may manifest physically with tension, insomnia, palpitations and shortness of breath and also with excessive worrying and fearfulness particularly if separated from the spouse or carer. *Depressed mood* should be assessed independently of weight loss, appetite changes, sleep disturbances and retardation that may occur as features of the dementia. Core psychological manifestations of depression such as sadness, thoughts of worthlessness and hopelessness, and statements about death and suicide should be enquired about. *Delusions* are common in dementia, usually of theft, intruders or imposters, often rather vaguely expressed and transient. They are typically based in forgetfulness and misinterpretation. Hallucinations, misidentifications and illusions in dementia are usually visual, particularly in DLB, but perceptual disturbances can also be auditory, olfactory or tactile. They are more common in those with impaired vision and hearing. *Purposeless activities* such as pacing and rummaging are characteristic of AD, whilst

compulsions and stereotyped behaviours are more common in FTD as are *disinhibition and euphoria* exhibited as impulsivity, hyperorality, socially inappropriate behaviour and emotional lability. *Sleep disturbances* may be secondary to other psychiatric features, may be associated with daytime drowsiness and are particularly burdensome to carers who are also likely to be kept awake. Rapid eye movement (REM) sleep behaviour disorder is characteristic of DLB [47] (II).

#### **Recommendations: assessment of behavioural and psychological symptoms**

Assessment of behavioural and psychological symptoms of dementia is essential for both diagnosis and management, and should be performed in all patients (*Level A*). Symptoms should be actively enquired about from the patient and a closely involved carer using appropriate rating scales (*Good Practice Point*). Co-morbidity should always be considered as a possible cause (*Level C*).

#### **Assessment of activities of daily living**

Decline in every day functional abilities is a major component of the dementia syndrome. It has a great influence on the quantity and quality of care and its level is extremely important for the caregiver. Assessment of function in daily life is part of diagnostic process and allows clinicians to evaluate the need for personal and institutional care. Different scales are used to objectively measure these abilities. These are based mainly on the interview with the patient and his/her caregiver. Two classical fields measured are basic, or general (such as eating, dressing, etc.) and instrumental activities (such as the use of devices, shopping). Frequently used scales include the Alzheimer Disease Cooperative Study (ADCS) ADL Scale [48], Functional Activities Questionnaire (FAQ) [49]; the Progressive Deterioration Scale (PDS) [50], and the Disability Assessment for Dementia (DAD) [51].

#### **Recommendations: assessment of activities of daily living**

Impairment of activities of daily living due to cognitive impairment is an essential part of the criteria for dementia and should be assessed in the diagnostic evaluation (*Level A*). A semi-structured interview from the caregiver is the most practical way to obtain relevant information, and a panel of validated scales are available (*Good Practice Point*).

#### **Assessment of co-morbidity**

Co-morbidities are frequent, particularly in elderly patients (IV), and may rapidly worsen the cognitive and functional status of the patient. There is a strong association between medical co-morbidity and cognitive status in AD (IV), and optimal management of medical illnesses may offer potential to improve cognition [52]. Depression, cardiovascular disease, infections, adverse effects of drugs, delirium, falls, incontinence, and anorexia are frequently observed co-morbidities or complications. Some of the co-morbid conditions which were identified in a large postmortem study of patients with dementia would have affected the clinical management of the patient, had they been known antemortem (IV) [53].

#### **Recommendation: assessment of co-morbidity**

Assessment of co-morbidity is important in the evaluation of the patient with dementia, and should be performed not only at the time of diagnosis, but throughout the course of the disease, with particular attention to episodes of sudden worsening of cognitive or behavioural symptoms (*Good Practice Point*).

#### **Blood tests**

Laboratory screening with blood tests is recognized as an important integral part of the general screening of a patient presenting with cognitive disturbances. The aims of blood tests include (1) to identify co-morbidity and/or complications; (2) to reveal potential risk factors; (3) to explore the background of frequently associated confusional states; and (4) more rarely to identify the primary cause of dementia. Cognitive disturbances may be associated with a wide range of metabolic, infectious, and toxic conditions, which should be identified and treated. For most of these conditions, there is no specific evidence from randomized controlled trials that treatment will reverse cognitive symptoms. Yet, the specialist physician is often dealing with patients with confusional states, rapid progression or atypical presentation, in whom blood tests may be of diagnostic value.

#### **Recommendations: blood tests**

The following blood tests are generally proposed as mandatory tests for all patients at first evaluation, both as a potential cause of cognitive impairment or as co-morbidity: blood sedimentation rate, complete blood cell count, electrolytes, calcium, glucose, renal and liver function tests, and thyroid stimulating

hormone. More extensive tests will often be required, e.g. vitamin B12 and serological tests for syphilis, HIV, and Borrelia, in individual cases (*Good Practice Point*).

### Neuroimaging

Traditionally, imaging was considered important solely as a means of excluding treatable causes of dementia. These conditions account for a small proportion of all causes of dementia with far more common causes being AD, VaD, DLB, and FTD [54]. Neuroimaging is now the most important ancillary investigation in the work-up of dementia to aid in differential diagnosis and management decisions.

#### *Computed tomography*

Computed tomography (CT) is mostly used to exclude other illnesses that are potentially amenable to (surgical) treatment, e.g. tumours, haematomata, and hydrocephalus. The yield of such a procedure has been debated but probably lies somewhere between 1% and 10% and may even be lower [55,56] (II). Farina *et al.* performed CT in 513 patients referred to a memory clinic of whom 362 were found demented [57] (II). In 26 of them (7.2%) a potential reversible cause of dementia was detected. However, in none of the cases did CT reveal findings that had not been discovered clinically. Foster *et al.* carried out a systematic review on the use of CT scanning in dementia [58]. Comparing costs and outcome they concluded that scanning each patient under 65 years and treating only subdural haematomas would be the most cost-effective approach. Recently, Condefer [59] showed that in a memory clinic setting, routine CT impacted on diagnosis in 12% of cases and on management in 11% (II), mainly because of the identification of vascular changes. Because Gifford *et al.* [60] showed that there is considerable uncertainty in the evidence underlying clinical prediction rules to identify which patients with dementia should undergo neuroimaging and application of these rules may miss patients with potentially reversible causes of dementia, it is generally felt that a structural imaging investigation in the evaluation of a patient suspected of dementia should be performed routinely.

#### *Magnetic resonance imaging*

Magnetic resonance imaging (MRI) may be used for the same reason as CT but has the ability to increase specificity to an already quite high sensitivity of the clinical diagnosis.

*Hippocampal atrophy in AD.* Hippocampal atrophy is an early and specific marker of the AD process [61–65]

(II–IV). This structure has been measured using a variety of tracing techniques and anatomical boundaries. Some studies have employed linear or visual measurements [66–71]. Because of their supposedly (but debatable) greater accuracy and reliability, other studies have used volumetric measures of medial temporal lobe structures. Comparative studies have found good correlations between these assessment techniques [72,73]. Several studies used a qualitative method that involves a visual rating scale, usually a four or five point scale ranging from absent to severe atrophy [74]. Frisoni *et al.* used a compound score of linear measurements that included the temporal horn [75]. Pucci *et al.* found the best discriminating parameter to be just the height of the left hippocampus [76]. In a novel approach, Frisoni and co-workers used the radial width of the temporal horn of the lateral ventricle on axial MR scans as measured with a calliper on paper printouts [66]. Visual assessment is considerably less time consuming than volumetry and easily applicable in clinical practice [77]. The down-side may be a larger inter-rater variability [68]. The overall sensitivity and specificity figures for detection of mild to moderate AD versus controls were 85% and 88% in a meta-analysis [78], and the accuracy of hippocampal atrophy in mild AD ranged from 67% to 100% in a systematic review [79] (I–II).

*Fronto-temporal lobar degeneration.* Asymmetric, predominantly left-sided peri-sylvian atrophy characterizes progressive non-fluent aphasia and asymmetric anterior temporal lobe atrophy is diagnostic of SD. In both conditions, with time, atrophy becomes more widespread but usually remains asymmetric. The pattern of atrophy may be more useful than atrophy of single regions in the differential diagnosis of FTD versus AD (II) [80–83].

*Vascular dementia.* In the most often used NINDS–AIREN international work group criteria for VaD brain imaging is thought to be essential for the diagnosis, and without it VaD will be ‘possible’ at best [15]. In addition, the criteria specify which vascular territories are ‘relevant’ for VaD. These include large vessel strokes, such as bilateral infarcts in the anterior or posterior cerebral artery areas, in the association areas, or in the watershed regions. Using operational guidelines on how to classify radiological features as fitting into the NINDS–AIREN criteria, inter-observer reliability of the diagnosis went up significantly from 40% to 60% [84] (II).

*Identifying vascular disease in dementia.* Like AD, the prevalence of cerebrovascular disease (CVD), both symptomatic and asymptomatic, increases dramatically with age, and pathological studies often find concomitant

cerebral infarction in patients with definite AD [85]. Even small, concurrent infarctions significantly increase the likelihood of expressed dementia, suggesting a synergistic effect. Given that concurrent CVD may be amenable to targeted interventions potentially ameliorating disease progression, brain imaging may prove important to the clinical care of the demented patient with coexisting CVD. Preliminary evidence from anti-hypertensive treatment trials of older individuals supports this notion, although further prospective clinical trials involving brain imaging are necessary.

*Miscellaneous.* In addition to the above specific imaging signs may include bilateral caudate atrophy in Huntington's disease, hyperintense signal in the putamen in sporadic Creutzfeldt Jakob Disease (CJD) and hyperintense signal change in the pulvinar in new variant CJD [86] (II). Diffusion-weighted MRI shows (the earliest) focal changes in CJD not yet apparent on FLAIR images, and may widely involve the cortex [87] (II). Corticobasal degeneration shows a typical MRI pattern, with striking, asymmetric parietal (peri-Rolandic) and frontal atrophy, sparing medial temporal regions [88] (II). Normal pressure hydrocephalus (NPH) is a questionable disease entity, and it may be difficult to decide whether such a patient would benefit from a shunting procedure. Strict adherence to clinical and MRI criteria is important, with additional information from a positive – but not a negative – cerebrospinal fluid (CSF) tap and the occurrence of B-waves [89] (II). These MRI criteria include widened ventricles with normal sulci and without white matter pathology. In DLB, MRI has been reported to show medial temporal lobe atrophy in a lower frequency than in AD, and therefore the *absence* of medial temporal lobe atrophy may be suggestive of a diagnosis of DLB [90] (II).

#### *Single photon emission computed tomography and positron emission tomography*

Single photon emission computed tomography (SPECT) and positron emission tomography (PET) are often used as a part of the work-up especially in memory clinics and as a complement to structural imaging in difficult differential diagnostic questions. Here again, the quest should be to increase specificity to augment clinical diagnostic criteria and structural imaging. The most often applied functional imaging studies include regional blood flow measurements performed with SPECT ( $^{99m}\text{Tc}$ -HMPAO or  $^{133}\text{Xe}$ ) and measurement of glucose metabolism performed with  $^{18}\text{F}$ -FDG-PET. A reduction in blood flow or glucose metabolism in parieto-temporal areas is the most commonly described diagnostic criterion for AD. In a recent meta-analysis, functional imaging studies with SPECT in which AD was contrasted

against control subjects yielded pooled weighted sensitivities ranging from 65% to 71%, with specificity of 79% [91]. A very few SPECT studies have adequately addressed the comparison between AD and other dementias. The few that did provided a pooled weighted sensitivity and specificity for AD versus FTD of 71% and 78%, respectively, and for AD versus VaD of 71% and 75%, respectively [91]. In a recent meta-analysis, the summary sensitivity of PET in diagnosing AD versus control subjects was 86%, and the summary specificity was 86% [92]. The majority of SPECT and PET studies were class II, although many did not have blinded evaluation of imaging results (IV). The fact that all positive likelihood ratios were  $< 5$ , indicates that cerebral blood flow assessed with SPECT or glucose metabolism assessed with PET moderately improves the diagnostic certainty either when AD is contrasted against controls or against other dementias [93]. Interestingly, there is no difference in diagnostic value between regional cerebral blood flow assessed with SPECT and glucose metabolism assessed with PET. Furthermore, a very few studies addressed the additional value of functional imaging over structural imaging. On the other hand, an international consortium of investigators argued that, although FDG-PET had moderate specificity (73–78%) for the diagnosis of AD both for clinical and pathological diagnosis, due to its high sensitivity, a negative (i.e. normal) PET strongly favours a normal outcome at follow up [94].

There have been studies suggesting that SPECT using the pre-synaptic dopamine transporter ligand  $^{123}\text{I}$ -FP-CIT (DAT-SPECT) can distinguish DLB from AD and normal ageing. Low striatal dopamine transporter activity is seen in idiopathic Parkinson's disease (PD), DLB, and PSP, but not in AD (II–III) [95–97]. The positive outcome has led the consensus committee on the diagnosis of DLB to include it in the most recent version of its guidelines [98].

#### **Recommendations: neuroimaging**

Structural imaging should be used in the evaluation of every patient suspected of dementia: Non-contrast CT can be used to identify surgically treatable lesions and vascular disease (*Level A*). To increase specificity, MRI (with a protocol including T1, T2 and FLAIR sequences) should be used (*Level A*). SPECT and PET may be useful in those cases where diagnostic uncertainty remains after clinical and structural imaging work up, and should not be used as the only imaging measure (*Level B*).

#### **Electroencephalography**

Electroencephalography (EEG) is widely available, non-invasive and suitable for repeated recording.

Generalized slowing of background rhythm is a feature of AD and DLB. The EEG may be entirely normal in advanced frontal lobe degeneration although abnormalities are relatively common in the overall group of FTD [99]. There is an overall relationship between the severity of dementia and abnormalities on the EEG in AD and DLB. There have been many studies demonstrating the ability of the EEG to distinguish clinically diagnosed AD from controls with a sensitivity that is comparable with other techniques such as neuroimaging [100–103]. However, there is a paucity of studies that explore the differential diagnosis of the dementia and which have neuropathological confirmation. Robinson *et al.* reported a series of neuropathologically confirmed AD (86 patients) and mixed and VaD (17 patients) with blinded assessment of the EEG (II) [104]. Abnormalities on the EEG were frequent in uncomplicated AD with a sensitivity of 87%. Importantly, a normal EEG had a negative predictive value of 82% with respect to a diagnosis of AD. There have been few studies exploring the added value of the EEG over and above a full clinical and neuroimaging assessment. Claus *et al.* investigated the added value of the EEG in a study of 49 control subjects with and without minimal cognitive impairment and 86 probable AD patients (II) [103]. The maximum diagnostic gain of 38% for an abnormal EEG was found when the prior probability was low at 30–40%. If there was a high pre-test probability of 80–90% then the diagnostic gain of an abnormal EEG was much lower, between 7% and 14%.

In some specific dementia conditions, the EEG has a higher diagnostic contribution. Periodic sharp wave complexes are part of the clinical criteria for the diagnosis of CJD, particularly the sporadic variety. Zerr *et al.* reported on 805 patients with neuropathologically confirmed CJD disease in whom the EEG was available (I) [105]. The presence of periodic sharp wave complexes provided 66% sensitivity and 74% specificity, comparable with the smaller series of Steinhoff *et al.* (I) [106]. The appearance of periodic sharp wave complexes is, however, variable and can disappear during the course of the disease making repeated EEG measurements valuable.

Transient epileptic amnesia due to focal temporal lobe seizure activity can masquerade as AD [107,108]. The EEG may be diagnostic in this situation.

#### **Recommendation: EEG**

The EEG may be a useful adjunct, and should be included in the diagnostic work up of patients suspected of having Creutzfeldt-Jakob disease or transient epileptic amnesia (*Level B*).

#### **CSF analysis**

Examination of CSF (with routine cell count, protein, glucose and protein electrophoresis) is mandatory when inflammatory disease, vasculitis or demyelination is suspected, and in cases of dementia with early onset, rapid decline, marked fluctuations, or extensive white matter changes on MRI or CT. A vast body of literature has emerged investigating the added value of 'specific' biomarkers in CSF such as amyloid  $\beta$  (1–42) ( $A\beta_{42}$ ), total tau (tau), phospho-tau and the 14-3-3 protein.  $A\beta_{42}$  is decreased in the CSF of AD patients possibly as a result of the deposition of fibrillar  $A\beta_{42}$  in senile plaques. Tau is increased in CSF of AD patients, as a reflection of the release of tau in CSF with neuronal loss. Phospho-tau derives from tangle deposition. The presence of the 14-3-3 protein in CSF is a measure for (acute) neuronal loss and brain damage and is associated with CJD.

#### *Alzheimer's disease versus controls*

$A\beta_{42}$  is decreased and tau increased in CSF of AD patients compared to non-demented controls, patients with depression, and patients with memory complaints on the basis of alcohol abuse [109–111]. The pooled sensitivity and specificity for  $A\beta_{42}$  in AD versus controls from 13 studies was 86% and 90%. For tau the sensitivity was 81% and the specificity 90%, pooled from 36 studies (II–III) [110]. A recent meta-analysis showed considerable differences in absolute concentrations of  $A\beta_{42}$  and tau between laboratories, even when the same test kit was used [112]. Using the combination of both markers for AD versus controls, a high sensitivity (85–94%) and specificity (83–100%) can be reached (II) [113]. In patients with early onset AD compared with controls, a sensitivity of 81% with specificity of 100% was found (III) [114]. As the reference test, the clinical diagnosis is usually used, sometimes also with a follow-up period in which the diagnosis did not change [114,115]. Only two studies had neuropathological validation of the diagnosis [116,117]. In these studies, the same high sensitivity and specificity for the distinction of AD from controls was found (I). One study investigated and found an association between number of senile plaques and concentration of  $A\beta_{42}$  in CSF [118].

#### *Alzheimer's disease versus other dementias*

A decreased CSF- $A\beta_{42}$  is being found in FTD [114,119], DLB [120], VaD [121,122], and CJD [123] when compared with controls (for AD versus FTD: specificity 59–81% (I) [114–115,119]; for AD versus VaD: specificity 71% (II) [124]). Tau is increased in

many other dementias such as FTD (II) [114,119,125,126] and CJD (I) [127]. In VaD conflicting results have been reported; specificity varied between 14% and 83% (II–III) [124,128,129] compared with AD. In FTD specificity varied from 26% to 75% (II–III) [114,115,119]. In DLB tau is usually normal (II) [120]. The combination of A $\beta$ 42 and total tau increases specificity and the negative predictive value (II): AD versus total group other dementias: 58–85% [113]; AD versus FTD: 85% [119]; AD versus DLB and VaD specificity 67% and 48%, respectively, with a negative predictive value of 95% (I) [130].

Alzheimer's disease compared with an age matched FTD group yielded good sensitivity (72%), and high specificity (89%) and a very low negative likelihood ratio ( $-LR = 0.03$ ) [114]. In general, for studies in which phospho tau was added, specificity was even higher (II–III) [110].

#### *Creutzfeldt Jakob Disease*

In CJD, very high tau levels have been reported, higher than in AD, yielding a high sensitivity and specificity, 93% and 90–100% (I) [127,131]. Assessment of the 14-3-3 protein in the sporadic form of CJD has a sensitivity of 90–100% and a specificity of 84–96% (I–II) [105,127,132–134]. False positive results are found in cerebral infarcts, encephalitis, tumours and rapidly progressive AD (I–II) [132,133,135]. When the clinical suspicion of CJD is high, the combination of EEG [135] MRI, and 14-3-3 assessment has the maximum accuracy (I–II) [136].

#### **Recommendations: CSF**

CSF analysis with routine cell count, protein, glucose and protein electrophoresis is recommended in patients with a clinical suspicion of certain diseases and in patients with atypical clinical presentations (*Good Practice Point*). CSF total tau, phospho-tau, and Ab42 can be used as an adjunct in cases of diagnostic doubt (*Level B*). For the identification of CJD in cases with rapidly progressive dementia, assessment of the 14-3-3 protein is recommended (*Level B*).

#### **Genetic testing**

Many degenerative dementias can occur as autosomal dominant disorders with similar phenotypes to sporadic disease apart from an earlier age at onset. The prevalence of autosomal dominant disease varies from <1% in AD to nearly 50% in some series of FTD. Three causative genes have been identified in familial AD, the amyloid precursor protein (APP) gene and the presenilin 1 and 2 genes. Tau mutations are found

in some cases of familial FTD and mutations in the prion protein gene in familial CJD. There is an increasing range of rarer genes, especially in the dementia plus syndromes. The yield of mutation screening in unselected populations is low, for example, no tau mutations were found in a large series of clinically diagnosed non Alzheimer dementias [137]. However, with an appropriate phenotype an autosomal dominant family history gene testing for known mutations can provide a specific diagnosis. This should only be undertaken in specialist centres with appropriate consent and counselling. The identification of a known pathogenic mutation in an affected family member can permit pre-symptomatic testing, and the Huntington's disease protocol for predictive testing and counselling should be followed [138]. Autopsy diagnosis in familial dementias can be valuable for establishing the significance of gene sequence variation in a family for subsequent diagnosis and counselling.

A variety of risk genes have been identified and the most carefully studied has been the Apolipoprotein (Apo) E4 polymorphism. The addition of Apo E testing increased the positive predictive value of a diagnosis of AD from 90% to only 94% in a neuropathologically confirmed series [139]. In those patients with a clinical diagnosis of non-Alzheimer dementia the absence of an Apo E4  $\epsilon$ 4 allele increased the negative predictive value from 64% to 72%.

#### **Recommendations: genetic testing**

Screening for known pathogenic mutations can be undertaken in patients with appropriate phenotype or a family history of an autosomal dominant dementia. This should only be undertaken in specialist centres with appropriate counselling of the patient and family caregivers, and with consent (*Good Practice Point*).

Pre-symptomatic testing may be performed in adults where there is a clear family history, and when there is a known mutation in an affected individual to ensure that a negative result is clinically significant. It is recommended that the Huntington's disease protocol is followed (*Good Practice Point*).

Routine Apo E genotyping is not recommended (*Level B*).

#### **Other investigations**

Additional investigations may provide critical information in the differential diagnosis of dementia, e.g. metabolic studies from fibroblast cultures, white cell enzyme assays, urinary aminoacids, etc. Moreover,

extensive imaging may provide diagnostic information in paraneoplastic syndromes. Biopsies of specific tissues can also be invaluable, for example, liver biopsy in Wilson's disease and skin and muscle biopsies in conditions such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) (100% specificity and 45% sensitivity) [140], Lafora body disease and mitochondrial cytopathies. Tonsillar biopsy can demonstrate the presence of prion protein in variant CJD.

Cerebral biopsy can provide a specific histological diagnosis but should only be undertaken where a treatable disorder is considered, such as cerebral vasculitis. In general, a non-dominant frontal or temporal pole full thickness biopsy to include leptomeninges and white matter should be performed. In many cases, prion disease cannot be excluded from the differential diagnosis and either disposable craniotomy instruments should be used or the instruments should be quarantined until a specific diagnosis has been made.

#### **Recommendation: tissue biopsy**

Tissue biopsy can provide a specific diagnosis some rare dementias. This should only be undertaken in specialist centres in carefully selected cases (*Good Practice Point*).

#### **Disclosure of diagnosis**

Of particular interest to specialist physicians are laws pertaining to the disclosure of diagnosis to the person him/herself rather than his/her family. Most European countries have not established the right to a diagnosis into an absolute right without any possible exceptions and most legislations allow doctors to refrain from disclosing a diagnosis, if this is considered to be in the 'best interests' of the person or if such disclosure could cause 'serious harm' to the physical or mental health of the patient [141]. Nevertheless, a growing consensus [142] has emerged in favour of disclosing a diagnosis to the person at a time when the person is capable of understanding this. It has been shown that such disclosure relieves the anxiety of uncertainty and maximises individual autonomy and choice by providing information necessary for decision making and advance planning (IV) [143], including the decision to give informed consent to research projects and autopsy.

#### **Recommendation: disclosure of diagnosis**

Disclosure of diagnosis should be done tactfully and should be accompanied by information about the consequences and the progression of the disease, as well as

useful contacts such as the local or national Alzheimer's association. In countries where this is possible physicians may also wish to encourage patients to draw up advance directives containing future treatment and care preferences (*Good Practice Point*).

### **Management of Alzheimer's disease and other disorders associated with dementia**

To address the complex needs of the patient with dementia and the caregiver during the course of a dementia disorder the specialist physicians should collaborate with other health care professionals with special training in dementia. The specialist physician should schedule regular follow-up visits, the purposes of which include: (1) to assess cognitive, emotional, and behavioural symptoms together with the functional status; (2) to evaluate treatment indications and to monitor pharmacological and non-pharmacological treatment effects; (3) to ensure identification and appropriate treatment of concomitant conditions and of complications of the primary dementia disorder; (4) to assess caregiver burden and needs; (5) to assess sources of care and support; (6) to provide continuous advice and guidance to patient and caregiver on health and psychological issues, safety measures, driving, and legal and financial matters; and (7) to administer appropriate patient and caregiver interventions. The primary caregiver, when available, should accompany the patient with dementia at follow-up visits and investigations.

In this guideline, the main emphasis is on recommendations for pharmacological treatment, and many important aspects of the care for patients with dementia, e.g. living arrangements, cognitive rehabilitation, nursing care and end-of-life issues are not covered. For pharmacological treatment, this review is confined dementia (not MCI) and to drugs which have been clinically tested in dementia and which are available on the market, although they may not be registered for dementia worldwide. Negative results were also included, if published, whereas experimental substances were not covered. It must be emphasized that the class of evidence does not necessarily reflect the effect size and the potential clinical relevance thereof, which were taken in consideration in making recommendations.

#### **Treatment of Alzheimer's disease**

##### *Cholinesterase inhibitors*

Cholinesterase inhibitors (ChEIs) represent the first class of drugs approved for the specific symptomatic treatment of AD. Following the introduction of tacrine, the first ChEI to be approved, donepezil, rivastigmine

and galantamine became available. There are multiple randomized, placebo-controlled, large scale clinical trials with these substances establishing efficacy on cognitive functions, overall evaluation, and ADL in patients with mild to moderate AD, with modest effect sizes [144–149] (I). The ChEIs are generally well tolerated, although gastrointestinal adverse effects such as nausea, diarrhoea, and vomiting are the most common adverse effects, and may lead to discontinuation of treatment in some patients. The use of ChEIs in mild to moderate AD has also been subject to systematic reviews and meta-analyses, and their efficacy was confirmed [150–152]. Likewise, practice parameters such as those provided by AAN, recommend that ChEIs should be considered in patients with mild to moderate AD [8]. Although their appraisal report is currently being revised, the National Institute for Clinical Excellence (NICE) in the UK in their health technology appraisal from 2001 recommended that ChEIs should be considered in mild to moderate AD [153].

With regard to duration of efficacy the longest lasting placebo-controlled studies with continuous treatment were with donepezil, performed over 1 year. These studies revealed that efficacy, in terms of difference from placebo treated patients, was maintained for at least 1 year and there was a 38% reduction in the risk of functional decline compared with placebo [154,155] (I). A recent placebo-controlled study over 3 years, in which multiple withdrawal phases were involved, revealed that cognitive scores and functionality were significantly better with donepezil over 2 years, but the differences were small and did not translate into benefits in primary outcome measures defined as institutionalization or progression of disability over 3 years [156] (II). There have been extensions of placebo-controlled studies with follow-up up to 5 years, where historical data or model-based predictions for non-treatment were used as a control. These studies suggest a slower progression of symptoms in treated patients. Lack of control in these studies and bias due to drop-outs, however, limit their conclusions [157–159] (III).

The initial assessments of efficacy of ChEI were focused on cognitive functions, scales of global change and ADL. Subsequently, small beneficial effects of ChEI on behavioural symptoms of AD were also shown [148,160,161] (I). With regard to disease stage, placebo-controlled randomized trials with donepezil confirmed efficacy in patients with early, mild AD as well as those with moderate to moderately severe AD [160,162] (I). There has been only one large randomized controlled double-blind study with direct comparison of the efficacy of cholinesterase inhibitors: a comparison of rivastigmine with donepezil in a large, randomized

controlled trial over 2 years revealed that the efficacy was comparable in the primary outcome measure, some of the secondary efficacy measures favoured rivastigmine, and tolerability was better with donepezil [163] (II). There is some evidence from open-label studies that patients who do not tolerate or do not seem to benefit from one AChE-I may tolerate or draw benefit from the other (III) [164,165]. Several attempts were made to quantify the clinical usefulness of ChEIs, which are not considered to be disease modifying [161,166,167]. A meta-analysis on the cost-effectiveness of ChEIs concluded that on the basis of the current evidence the implications of the use of donepezil, rivastigmine or galantamine to treat patients with AD are unclear [167]. A meta-analysis of 29 controlled studies with ChEIs revealed a modest beneficial impact on neuropsychiatric and functional outcomes, but there seemed to be no difference between the different drugs in this regard [161] (I).

#### *Memantine*

Memantine, an non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, represents the second class of drugs approved for the specific symptomatic treatment of AD. The compound blocks the chronic hyper-activation of NMDA receptors that is thought to contribute to the symptomatology and pathogenesis of AD. A number of large-scale, randomized placebo-controlled trials with memantine were reported in patients with dementia.

Two studies were performed in patients with moderate-to-severe AD (I) [168,169], one of them in patients on stable treatment with donepezil [169]. Another randomized placebo-controlled study was performed in a mixed population of severe AD and severe VaD patients [170] (I). To date, no studies in mild AD have been published in peer-reviewed journals.

Recently, the available data were reviewed in a Cochrane meta-analysis, and the authors concluded from the published data that memantine at 6 months caused a clinically noticeable reduction in deterioration in patients with moderate to severe AD (I) [171]. This was supported by less functional and cognitive deterioration (I). Memantine was well tolerated when given alone, and also in the study where it was combined with donepezil (I) [169], and patients taking memantine appeared to be less likely to develop agitation. Whether memantine has any effect in mild to moderate AD is unknown [171].

With the exception of Winblad and Poritis [170], where no performance-based cognitive assessment was performed, all of these studies showed statistically significant superiority in the cognitive performance of memantine treatment of the patients over placebo using

the Severe Impairment Battery (SIB) (I). In the study of Winblad and Poritis, statistically significant effects were demonstrated in functional and global assessments (I). One of the trials in moderate-to-severe AD included a pharmaco-economic questionnaire and demonstrated a reduction in caregiver time and in total societal costs [172]. In the study by Tariot *et al.* [169], memantine showed positive effects on the behavioural disturbances, as assessed by the NPI (I).

#### *Other drugs and interventions*

There are several other treatment measures, which have been suggested for the treatment of AD, including ginkgo biloba, non-steroidal anti-inflammatory drugs (NSAIDs), oestrogens and statins. Three randomized, controlled trials with the ginkgo biloba extract Egb 761 were reported in AD. All of these studies involved mixed patient populations including those with AD, multi-infarct dementia, and in one study also patients with MCI, and the duration of treatment was up to 1 year. In two studies some parameters measuring cognition and behaviour significantly improved [173,174], although assessment methods in one and analysis of results in the other were not standard (II); in the third study there were no significant differences between ginkgo biloba and placebo (II) [175]. A meta-analysis of all published data in patients with dementia concluded that although overall there is promising evidence of improvement in cognition and function, the three more modern trials showed inconsistent results, and there is a need for a large trial using modern methodology [176] (I).

Anti-oxidants such as vitamin E have been studied to see if they can delay progression in patients with AD. In a large randomized, placebo-controlled study [177] in patients with moderate AD, vitamin E (given at the dose of 1000 IU, twice a day over 2 years) was found to significantly delay the time to a composite outcome of primary measures, indicative of clinical worsening, and fewer patients receiving vitamin E were institutionalized when compared with those receiving placebo (I). An attempted meta-analysis of randomized, controlled studies with vitamin E, which could find only the above-mentioned study, concluded that there is insufficient evidence for the efficacy of vitamin E in the treatment of AD, but there is sufficient evidence of possible benefit to justify further studies (I) [178]. Furthermore, a large meta-analysis of studies with vitamin E has shown that high-dosage ( $\leq 400$  IU/day) vitamin E supplements may increase all cause mortality (I) [179].

Chronic exposure to non-steroidal anti-inflammatory drugs was suggested to be protective against AD in a retrospective analysis of epidemiological data [180]. In prospective studies, however, only indomethacin was

suggested to stabilize cognition in a 6-month trial with a high drop out rate (I) [181–185]. Similarly, in a recent large, randomized, double-blind, placebo-controlled trial the cyclo-oxygenase-2 inhibitor rofecoxib, administered for 1 year, was not found to be effective in slowing the progression of AD [186] (I).

Statins used for the treatment of hypercholesterolaemia were found to decrease the prevalence of AD in two studies with retrospective or cross-sectional analysis [187,188]. This effect was found to be independent of indication bias (healthier cohort effect), but confined to those below the age of 80 years [189], and appeared to be modified by the presence of certain chronic medical conditions, in that the reduced risk of AD was observed amongst those with diseases such as hypertension and ischaemic heart disease [190]. Pravastatin showed no significant effect on cognitive function or disability [191]; atorvastatin showed significant effect on cognitive function at 6 months, but not at 12 months (III) [192]. A meta-analysis of available data concluded that there is no good evidence to recommend statins for reducing the risk of AD [193] (II).

In retrospective or cross-sectional analyses, postmenopausal use of oestrogens has been suggested to provide symptomatic benefits or reduce the risk of AD. Prospective, randomized, placebo-controlled studies, however, failed to demonstrate symptomatic beneficial effects of oestrogens, given up to 1 year, in women with mild to moderate AD, with or without hysterectomy (III) [194–196]. Although treatment with oestrogen elevated blood oestradiol and oestrone levels, there was no association between hormone levels and cognitive functioning after 1 year treatment [197]. A meta-analysis concluded that oestrogen replacement therapy is not indicated for cognitive improvement or maintenance for women with AD (I) [198]. Likewise, the results of the large, prospective, placebo-controlled ‘Women’s Health Initiative Memory Study’ revealed that the use of oestrogen plus progestin in postmenopausal women, after a mean follow-up time of 4 years, was associated with a significantly increased risk of dementia [199] (I).

Meta-analyses for several other drugs including selegiline [200], nicergoline [201], nimodipine [202], and piracetam [203] concluded that there was not sufficient evidence to recommend their use in AD (II).

#### **Recommendations: treatment of Alzheimer’s disease**

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*). 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 can be considered, alone or in combination with a ChEI, taking into account expected therapeutic benefits and potential safety issues (*Level A*). Realistic expectations for treatment effects and potential side effects should be discussed with the patient and caregivers (*Good Practice Point*).

Currently, there is insufficient evidence to consider the use of ginkgo biloba, anti-inflammatory drugs, nootropics, selegiline, oestrogens, vitamin E or statins in the treatment or prevention of AD (*Level A–C*).

### Treatment of vascular dementia

#### *Cholinesterase inhibitors*

After it became apparent that VaD is also associated with cholinergic deficits, ChEIs were investigated in patients with VaD. Along with patients with dementia due to pure or predominant CVD, vascular pathology can also co-exist with AD pathology, constituting mixed dementia. There have been two large, randomized, placebo-controlled studies with donepezil in patients with possible or probable VaD and one large, randomized, placebo-controlled study with galantamine in patients with VaD or AD combined with CVD. In the two donepezil studies, there was a significant improvement in the two main outcome parameters (cognitive functions and overall scales), ADL was significantly improved in one and showed a trend for improvement in the second study at the end of treatment period [204,205] (I). Results with galantamine were similar: patients on active drug had significant improvement on both primary end-points as well as in ADL and behavioural scales, when compared with placebo (I) [206]. Although the study was not powered to detect changes in the two diagnostic sub-groups (i.e. probable VaD and AD with CVD) the cognitive and overall scales showed significant improvement in AD with CVD group, whereas the differences when compared with placebo were not significant in the probable VaD sub-group [206]. An open label 6-month extension of this study suggested that the benefits may be maintained up to 1 year (III) [207]. A Cochrane meta-analysis concluded that there are some weak indications that galantamine is useful in dementia secondary to vascular damage, but it was associated with higher rates of adverse events and withdrawal (I) [208]. From existing trial data (III–IV), most of which are from open studies or *post-hoc* analyses, there is some evidence of benefit of rivastigmine in vascular cognitive impairment, but larger placebo-controlled double blind RCTs are needed

[209]. A meta-analysis of the two studies with donepezil concluded that the evidence indicates that donepezil is well tolerated and can improve cognitive symptoms and functional ability in patients with vascular cognitive impairment [210] (I).

#### *Memantine*

Two randomized placebo-controlled 6 month studies are available in patients suffering from mild-to-moderate VaD [211,212], using 20 mg/day memantine. These studies included close to 900 patients and were designed according to modern standards, using the ADAS-Cog and a clinical global rating of change as primary efficacy endpoints. They were summarized by the recent Cochrane meta-analysis [171]: in the two studies memantine improved cognition and behaviour, but this was not supported by clinical global measures (I). Memantine was well tolerated (I). In a subgroup analysis of these studies [213], the cognitive benefit seemed to be more pronounced in the subgroup of patients with small vessel disease, which is more closely linked to AD (III). In addition, a number of short-term studies in less well-defined dementia populations have been published and were also reviewed in the Cochrane database, including studies in patients with VaD, and with dementia of un-specified type. In summary, there were beneficial effects on cognition [214], ADL [214], behaviour and global scales [214,215], and in global impression of change [214,215] (III–IV). The meta-analysis concluded that patients with mild to moderate VaD receiving memantine had less cognitive deterioration at 28 weeks, but the effects were not clinically discernible. The drug was well tolerated in general and the incidence of adverse effects was low [171].

#### *Anti-aggregants and other drugs*

There has been one small study with aspirin in patients with VaD. In this study, where the control group was no-treatment, patients treated with aspirin had a better outcome on a cognitive scale by the third year and also a significant improvement in cerebral perfusion in the first 2 years [216] (III). A meta-analysis of available data revealed that, despite its widespread use, there is still no evidence that aspirin is effective in treating patients with a diagnosis of VaD [217]. In a systematic review of clinical studies with pentoxifylline in VaD, four studies were identified fulfilling the criteria (being randomized, double-blind, and placebo-controlled), which revealed a trend toward improved cognitive function, but no statistically significant differences versus placebo [218] (I). When the calcium channel blocker nimodipine was tested in patients with ‘multi-infarct dementia’ in a large, randomized placebo-controlled

study, there were no significant benefits from nimodipine treatment over placebo in cognitive, functional and global assessments [219] (I). Furthermore, in a recent randomized placebo-controlled trial in patients with subcortical VaD there was no significant effect of nimodipine on the primary outcome measure, a global clinical assessment scale [220]. Studies with ginkgo biloba are mentioned above.

#### **Recommendations: treatment of vascular dementia**

ChEIs (currently evidence exists for donepezil) may be considered in patients fulfilling diagnostic criteria for VaD of mild to moderate severity (*Level B*). Realistic expectations for treatment effects and potential side effects should be discussed with the patient and caregivers (*Good Practice Point*). In the presence of severe focal neurological deficits, the accuracy of diagnosis and expected therapeutic benefits should be carefully considered based on the presumed contribution of sensory-motor impairment versus cognitive deficits to the overall disability of the patient (*Good Practice Point*).

There is insufficient evidence to consider the use of memantine in patients with vascular dementia (*Level B*).

There is insufficient evidence to support the use of aspirin, ginkgo biloba, calcium antagonists or pentoxifylline in the treatment of VaD (*Level A–C*).

Optimum management of vascular risk factors, including anti-platelet drugs, should be ensured, not only in vascular dementia, but also in patients with other dementias or co-morbid vascular disease (*Good Practice Point*).

#### **Treatment of Parkinson disease dementia and dementia with Lewy bodies**

There are substantial cholinergic deficits both in Parkinson disease dementia (PD-D) and DLB, and ChEIs have been tested in both of these indications. In total, there have been 14 studies with four compounds (tacrine, donepezil, rivastigmine and galantamine) describing the use of ChEIs in patients with PD-D. All of these studies were small (all including <30 patients), three of them were placebo-controlled, eight were open studies and two case series. Improvement in cognition and neuropsychiatric symptoms, notably hallucinations, were described in the majority of these studies, worsening of parkinsonism was infrequent, and was mostly related to tremor [221,222]. A recent, large, placebo-controlled study with rivastigmine revealed that there was a statistically significant improvement in favour of rivastigmine in both

primary endpoints with modest effect sizes [ADAS-cog for cognitive functions and ADCS Clinical Global Impression of Change (CGIC) for overall evaluation] as well as on all secondary measures. Adverse event profile was comparable with that seen in patients with AD, nausea and vomiting being the most frequent adverse events. In the rivastigmine group, 10% of patients reported subjective worsening of tremor, and 1.7% discontinued treatment for this reason. There were, however, no significant differences between rivastigmine and placebo in objectively measured motor scores [223] (I).

There have been eight studies reporting the use of ChEIs in DLB, involving tacrine, donepezil and rivastigmine. One of these studies was placebo-controlled, three were controlled, but not-randomized and others were case series. All studies but one reported improvement in cognitive functions, and half of them reported improvement in neuropsychiatric symptoms, commonly apathy and hallucinations; worsening of parkinsonism was rare [221]. In the large, prospective, randomized, placebo-controlled study, rivastigmine was found to be significantly better than placebo for one of the two main outcome parameters, cognitive speed score. There was also more improvement in the rivastigmine group for the other parameter, neuropsychiatric symptom score, in the last observation carried forward (LOCF) and observed case analyses, but not in the intention to treat (ITT) population. A responder analysis showed significantly greater reductions in NPI score in all three groups. Rivastigmine did not cause worsening of motor symptoms [224] (I).

The efficacy of memantine has not been formally assessed in DLB. The very limited case report literature available suggests that about two-thirds of DLB patients can tolerate memantine, but the symptomatic effects are variable. A significant minority experience worsening of agitation, paranoid delusions, and visual hallucinations when exposed to memantine [225,226] (*IV*).

#### **Recommendations: treatment of Parkinson disease dementia and dementia with Lewy Bodies**

Treatment with ChEIs (currently evidence exists for rivastigmine) can be considered in patients with PD-D or DLB (*Level A*), taking in account expected therapeutic benefits and potential safety issues. Realistic expectations for treatment effects and potential side effects should be discussed with the patient and caregivers (*Good Practice Point*).

There is insufficient evidence for the use of memantine in PD-D or DLB (*Level C*).

### Monitoring treatment with ChEIs and memantine in patients with dementia disorders

Monitoring treatment with ChEIs and memantine must be guided by the adverse event profiles and the clinical condition of the patient. Monitoring should include regular assessments of compliance, efficacy (cognitive functions, ADL, and behavioural symptoms), and side effects. In patients with known cardiac disease or significant cardiovascular risk factors a baseline ECG may be helpful for future monitoring purposes. There is no evidence from appropriately designed studies, which can guide the clinician in determining when to stop treatment.

### Recommendations: monitoring treatment with ChEIs and memantine

Efficacy and side effects should be regularly monitored during treatment (*Good Practice Point*). In case of rapid worsening or an apparent loss of efficacy discontinuation of treatment may be considered on a trial basis. Such patients should be closely monitored in order to assess withdrawal effects or worsening in which case the treatment should be re-started (*Level C*).

### Treatment of other dementia disorders

There have been no large, randomized, controlled studies in other types of degenerative dementias such as FTD, PSP, or CBD. In a small open and another small randomized, double-blind, placebo-controlled cross-over study, donepezil was not found to be effective in patients with PSP: there were at best modest effects on cognition but deleterious effects on ADL and mobility [227,228] (III). Selective serotonin reuptake inhibitors (SSRIs), particularly paroxetine, were used in two open and one small placebo-controlled cross-over study in patients with FTD. Whilst the open studies suggested some benefits, especially with regard to behaviour, the placebo-controlled study suggested no benefits, rather a deterioration of cognitive functions [229–231] (III).

### Recommendations: treatment of other dementia disorders

There are no drugs available for the specific treatment of other degenerative dementias such as FTD, PSP and CBD (*Level C*). A number of pathological conditions and systemic or central nervous system disorders can be associated with dementia. Their specific treatment must be based on the underlying etiology (*Good Practice Point*).

### Treatment of behavioural and psychological symptoms in dementia

It is the BPSD that contribute most to patient distress and carer burden and which frequently need treatment, sometimes urgently [38]. The sudden onset or worsening of symptoms such as hallucinations, insomnia, anxiety, agitation or aggression may be indicative of a super-added delirium, as may apathy or apparent depression. A physical re-evaluation should therefore always be the first stage of managing BPSD, paying close attention to recent changes in medications, signs of infection or systemic toxicity and evidence for parallel decline in cognitive function [42] (II). Drugs with potential to worsen confusion and psychosis, e.g. anticholinergics, are contra-indicated and should be avoided. Pre-intervention measures of behavioural disturbance or psychiatric symptoms should ideally be established using an appropriate rating scale to help assess treatment effects. Psychosocial interventions may be classified into cognition-orientated, behaviour-orientated, emotion-orientated and stimulation-orientated. There is limited randomized controlled trial evidence about their specific effects upon BPSD, and they tend to be applied in an individualized way or to group settings such as care homes. Education, information and support groups for patients and carers are helpful and should be offered by a skilled multidisciplinary team. Environmental manipulations can be important. A non-confrontational approach to dealing with delusions, wandering, agitation and aggression may be difficult for lone carers to maintain at home and there may be considerable value in providing day and respite care. Locked doors may reduce concerns about wandering although may increase patients attempts to escape from their surroundings. Specific behavioural interventions may help reduce incontinence [8] (I), and good sleep hygiene may reduce insomnia.

The pharmacological management of BPSD is particularly problematic since very few placebo-controlled randomized controlled trials have been conducted [38]. A target symptom approach, e.g. a focus upon the reduction of agitation or psychosis, is preferable to attempting to reduce BPSD generally. Such fine distinctions may not always however be easy to apply in clinical practice.

There has been recent interest in the potential role of ChEIs for managing BPSD, e.g. rivastigmine reduced apathy, anxiety, hallucinations, delusions and irritability in DLB [224] (I) and galantamine reduced the emergence of neuropsychiatric features in mild to moderately impaired AD patients [152] (I). ChEIs are increasingly being used for BPSD in AD and other dementias. Although they may impact on BPSD they

may also need to be used in combination with other agents. The mainstay of pharmacological management of the symptom cluster agitation, delusions, hallucinations and irritability has been with neuroleptic agents such as haloperidol [232] and more recently with atypical antipsychotics, usually prescribed at a third to half the young adult dose. There is little consistent evidence that these drugs significantly modify unwanted behaviours other than aggression [233,234], and there is often a considerable side effect cost with sedation, weight gain, extrapyramidal features and falls. There are recent reports that atypical antipsychotic medication may be associated with an increased risk of cerebrovascular events and mortality in elderly patients with dementia [234–237]. However, a retrospective cohort study suggested that conventional antipsychotic medications are at least as likely as atypical agents to increase the risk of death amongst elderly persons [238], and more information is required to help clinicians make judgements about risk-benefits in individual patients [38]. In DLB severe neuroleptic sensitivity reactions are associated with a two- to threefold increased mortality, and antipsychotics should only be used with great caution [239] (II). Thus, in all elderly patients with dementia, conventional as well as atypical antipsychotics should be used with caution and only after careful estimation of risk-benefits. Patients and caregivers should be informed about the expected therapeutic benefits and risks, and the treatment must be reviewed at close intervals. Carbamazepine [240] and valproic acid [241] have both been used to treat agitation in dementia, but with inconsistent effects (II).

The principles of treatment of depression in dementia are probably similar to that in non-demented people of the same age, although adequately conducted trials are lacking for most agents [242]. Selective serotonin reuptake inhibitors and other newer antidepressants are less likely to induce confusion and the anti-cholinergic effects typically seen with tricyclics. Emotional lability and compulsive behaviours have been reported to improve with SSRIs in FTD, and they may have similar effects in other dementias [38] (II).

#### **Recommendations: treatment of behavioural and psychological symptoms in dementia**

Clinicians treating patients with dementia should be aware of the importance of treating behavioural and psychiatric symptoms and the potential benefits for patient and carer (*Good Practice Point*). Somatic co-morbidity should be considered as the cause of the symptoms (*Level C*). Non-pharmacological and then pharmacological interventions for BPSD may both be

effective and should be applied in a targeted symptom approach. The short, medium and long term benefits and adverse effects of such interventions should be regularly reviewed (*Level C*). Antipsychotics, conventional as well as atypical, may be associated with significant side effects and should be used with caution (*Level A*).

#### **Counselling and support for caregivers**

In patients with mild to moderate dementia, the assistance of a caregivers is necessary for many complex ADL, for instance travelling, financial matters, dressing, planning, and communication with family and friends. With the progression of the disease, increasing amounts of time must be spent on supervision. In patients with moderate to severe dementia caregivers often provide full time assistance with basic ADL, dealing with incontinence, bathing, feeding, and transfer or use of a wheelchair or walker. The majority of AD caregivers provide high levels of care, and at the same time they are burdened by the loss of their spouse or good friend. Caregivers are twice as likely to report physical strain and high levels of emotional stress as a direct result of caregiving responsibilities. They are more likely to report family conflicts, to spend less time with other family members, and to give up vacations, hobbies, and other personal activities. Caring for someone with dementia may also cause a high level of financial strain. Interventions developed to offer support for caregivers to patients living at home include counselling, training and education programmes, homecare/health care teams, respite care, information-technology based support. Many small quantitative or qualitative studies on the effectiveness of formal interventions seeking to support carers and alleviate the burden of caring have been published. Two meta-analyses [243,244] and one systematic review [245] on the effect of caregiver intervention have been published. In general, there is evidence from a few class II randomized trials to support the view that carers to patients with moderate to severe dementia benefit from structured support initiatives, which may reduce depressive symptoms [246,247]. There is a lack of appropriately designed randomized controlled studies, particularly in mild dementia [248]. As a dementia diagnosis is often established early in the course of the disease, intervention programs should also include support, counselling, and education activities for the patient, but there are no appropriately designed quantitative studies which have addressed the outcome of supportive interventions directed towards the patient with mild dementia.

### **Recommendations: counselling and support for caregivers**

A dementia diagnosis mandates an inquiry to the community for available public health care support programs (*Good Practice Point*). Specialist physicians should assess caregiver distress and needs at regular intervals throughout the course of the disease (*Level C*). Caregivers should be offered support and counselling (*Level B*). This includes information about patient organizations (*Good Practice Point*).

### **Legal issues**

Dementia involves a gradual loss of cognitive and physical capacities and thereby affects memory, decision-making and the ability to communicate one's wishes to others. For these reasons, a person with dementia may be unable to consent to treatment, take part in research or be involved in decisions relating to his or her care. In everyday life, problems may arise if the person with dementia wants to continue driving, make a will or carry out financial transactions. In many cases, it may be necessary to appoint a guardian or tutor [141].

In almost all countries specialist physicians play an important role in the assessment of mental capacity or incapacity, as they may be required to make an assessment of capacity prior to medical treatment, provide a medical certificate at a lawyer's request as to a particular capacity unrelated to medical treatment, witness or otherwise certify a legal document signed by someone, or give an opinion as to a particular legal capacity which is relevant to court proceedings [249].

Although assessing a person's capacity does not require a high degree of legal knowledge, the doctor should understand the relevant legal terms in broad terms as the doctor's role is to provide information on which an assessment of the person's capacity can be based [249].

### **Recommendations: legal issues**

Specialist physicians responsible for the care of patients with dementia should be aware of national legislations relating to assessment of capacity, consent to treatment and research, disclosure of diagnosis, and advance directives (*Good Practice Point*).

A diagnosis of dementia is not synonymous with mental incapacity, as a determination of capacity should always involve a 'functional' analysis: does the person possess the skills and abilities to perform a specific act in its specific context? (*Good Practice Point*).

### **Driving**

At the time of diagnosis, a patient's driving skills should also be assessed and discussed, since advice about driving is an essential part of the management of dementia [250] and because patients with AD who continue to drive are at an increased risk for crashes [251] (I). In particular, drivers with mild AD (CDR 1) pose a significant traffic safety problem [252]. There is, however, considerable variability across Europe with respect to the national driving regulations for patients suffering from disorders associated with dementia, the role of specialist physicians in the assessment of driving capabilities, and the confidentiality of medical data with regard to third parties, such as national driving licence authorities [253].

### **Recommendations: driving**

Assessment of driving ability should be done after diagnosis and be guided by current cognitive function, and by a history of accidents or errors whilst driving. Particular attention should be paid to visuo-spatial, visuo-perceptual, praxis and frontal lobe functions together with attention. Advice either to allow driving, but to review after an interval, to cease driving, or to refer for retesting should be given (*Level A*). This decision must accord with the national regulations of which the specialist physician must be aware (*Good Practice Point*).

### **Conclusion**

The assessment, interpretation, and treatment of symptoms, disability, needs, and caregiver stress during the course of AD and other dementia disorders require the contribution of many different professional skills. Ideally, the appropriate care and management of patients with dementia requires a multidisciplinary and multi-agency approach. Neurologists should be involved together with old age psychiatrists and geriatricians in the development and leadership of multidisciplinary teams responsible for clinical practice and research in dementia. This review contributes to the definition of standards of care in dementia by providing evidence for important aspects of the diagnosis and management of dementia.

### **Conflicts of interest**

Potential conflicts of interest: Gunhild Waldemar, Bruno Dubois, Murat Emre, Ian McKeith, Philip Sheltens, Peter Tariska, and Bengt Winblad have received speaker's and/or consultancy honoraria from

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