European Journal of Neurology 2012, 19: 1159–1179 doi:10.1111/j.1468-1331.2012.03784.x

EFNS-ENS GUIDELINES/CME ARTICLE

EFNS-ENS Guidelines on the diagnosis and management of disorders associated with dementia

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Keywords:
dementia, diagnosis, guideline, management, recommendation, review, treatment

Received 24 April 2012
Accepted 9 May 2012

Background and objectives: The last version of the EFNS dementia guidelines is from 2007. In 2010, the revised guidelines for Alzheimer's disease (AD) were published. The current guidelines involve the revision of the dementia syndromes outside of AD, notably vascular cognitive impairment, frontotemporal lobar degeneration, dementia with Lewy bodies, corticobasal syndrome, progressive supranuclear palsy, Parkinson's disease dementia, Huntington's disease, prion diseases, normal-pressure hydrocephalus, limbic encephalitis and other toxic and metabolic disorders. The aim is 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 dementing disorders. It represents a statement of minimum desirable standards for practice guidance.

Methods: The task force working group reviewed evidence from original research articles, meta-analyses and systematic reviews, published by June 2011. The evidence was classified (I, II, III, IV) 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 and conclusions: New recommendations and good practice points are made for clinical diagnosis, blood tests, neuropsychology, neuroimaging, electroencephalography, cerebrospinal fluid (CSF) analysis, genetic testing, disclosure of diagnosis, treatment of behavioural and psychological symptoms in dementia, legal issues, counselling and support for caregivers. All recommendations were revised compared with the previous EFNS guidelines. The specialist neurologist together with primary care physicians play an important role in the assessment, interpretation and treatment of symptoms, disability and needs of dementia patients.

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This is a Continuing Medical Education article, and can be found with corresponding questions on the Internet at http://www.efns.org/EFNS Continuing-Medical-Education-online.301.0.html. Certificates for correctly answering the questions will be issued by the EFNS.

EUROPEAN JOURNAL OF NEUROLOGY
THE OFFICIAL JOURNAL OF THE EUROPEAN FEDERATION OF NEUROLOGICAL SOCIETIES

Background

The change in global age demographics and the predicted rise in the incidence of age-related diseases, including dementia, are of major public health concern. Dementia affects 5.4% of people over 65 years, and its prevalence further increases with age [1]. The number of people affected will double every 20 years to 115 million by 2040, according to the Alzheimer Disease International (ADI) World Alzheimer Report 2010. In the EU, more than 160 million people are aged over 60 years, the crude estimate prevalence of dementia is 6.2% and almost 9.95 million have a form of dementia. Almost 14 million Europeans are expected to have dementia in 2030.

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 [1]. Primary care physicians play a major role in the identification, diagnosis and management of patients with dementia, but advanced diagnostic techniques necessitate the involvement of specialists, especially neurologists, preferably in multidisciplinary teams established to facilitate the management of the complex needs of patients and caregivers during the course of the dementia disease.

Objective

The present revised guidelines consider dementias other than Alzheimer's disease (AD), which was covered in a recent guideline [2]. The other types of dementia reviewed include mixed dementia, dementia with Lewy bodies (DLB), vascular dementia (VaD), frontotemporal lobar degeneration (FTLD), corticobasal syndrome (CBS), progressive supranuclear palsy (PSP), Parkinson's disease dementia (PDD), Huntington's disease (HD), prion diseases, normal-pressure hydrocephalus (NPH) and limbic encephalitis (LE).

The main goal of the task force was to determine whether further evidence had become available relating to biomarkers such as magnetic resonance imaging (MRI), positron emission tomography (PET) and cerebrospinal fluid (CSF) and to determine the evidence for use in practice. Special attention was given to the results of recent clinical trials, both for cognitive and behavioural aspects of the disease.

These guidelines represent desirable standards, 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. 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 still varies considerably in Europe.

Search strategy

The evidence for these guidelines was collected from Cochrane Library reviews, other published meta-analyses and systematic reviews, evidence-based management guidelines in dementia and original scientific papers published in peer-reviewed journals before June 2011. The search strategy sought only studies published in English. The principal search term was dementia. Other terms entered into the search included diagnosis, guideline, management, recommendation, review, treatment. For each topic, the evidence was sought in MEDLINE according to predefined search protocols*. The scientific evidence for diagnostic investigations and treatments was 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 [3]. In addressing the 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. Final inclusion of articles in this practice parameter was based on consensus of the committee.

Reaching 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 2010 and 2011 and through five revisions via the web.

Dementia, dementia types and clinical criteria

Dementia

The term dementia refers to an acquired deficit of cognitive function(s), which may include *complex*

*Searching terms used in the search strategy: vascular cognitive impairment, frontotemporal lobar degeneration, dementia with Lewy bodies, corticobasal syndrome, progressive supranuclear palsy, Parkinson's disease dementia, Huntington disease, prion diseases, normal pressure hydrocephalus, limbic encephalitis, dementia, CSF, MR, SPECT, FDG-PET, amyloid-PET, genetics, biopsy, DNA, EEG, dementia and ethics.

attention, *executive ability*, *learning and memory*, *language*, *visuospatial-perceptual ability praxis* and *social cognition*. The cognitive deficits may or may not be accompanied by behavioural disorders and must be sufficient to interfere with functional independence.

The clinical diagnosis of the dementia syndrome should rely on the DSM-IV or ICD-10 criteria [4,5]. In the development of DSM-5, scheduled for 2013, the term 'dementia' is replaced by major or minor neurocognitive disorder [6]. Clinical criteria for the different types of dementia have been published (Table 1).

Frontotemporal lobar degeneration

'Frontotemporal lobar degeneration' (FTLD) is a macro-anatomical descriptive term for a clinically and pathologically heterogeneous group of disorders characterized collectively by relatively selective progressive atrophy of the frontal and/or temporal lobes. Our understanding of these diseases has been transformed by recent genetic and histopathological advances [7–12] summarized in Table 2. FTLD is over-represented as a cause of young onset dementia. Onset is typically in the sixth decade of life but may be as early as the third or as late as the ninth decade. Estimates of population prevalence range from 4 to 15/100 000 below age 65 in European and US epidemiological studies [8]. The prevalence of FTLD in older age groups has almost certainly been underestimated, although few data are available. FTLD has a substantial genetic component with an autosomal-dominant inheritance pattern and/or identifiable disease-causing mutations in around 10–20% of cases in large series [13] and some family history in a higher proportion. Most familial cases are attributed to mutations in the microtubule-associated protein tau or progranulin genes or the recently identified hexanucleotide repeat expansion in the C9ORF72 gene [14,15]. Most patients with FTLD present with features conforming predominantly to one of the three canonical clinical syndromes (see Table 2): 'behavioural variant frontotemporal dementia' (bvFTD), semantic dementia (SD) or progressive non-fluent aphasia (PNFA). The clinical spectrum of FTLD overlaps partly with corticobasal syndrome, progressive supranuclear palsy and motor neurone disease. Alzheimer variant syndromes also overlap with FTLD, especially PNFA [16–19]; thus, the 'logopenic' subtype of progressive aphasia appears to be chiefly associated with Alzheimer pathology [12,18]. FTLD continues to present many unresolved nosological and diagnostic difficulties. Recently re-formulated consensus diagnostic criteria for behavioural [11,19] and aphasic [12] subtypes of FTLD are based on class IV evidence.

Table 1 Criteria for clinical diagnosis

Condition	Criteria	References
Dementia	ICD 10	[5,173]
	DSM IV	[4,173]
	Dubois criteria	[174]
Alzheimer disease	NIA and Alzheimer Association Working Group	[175]
Frontotemporal lobe degeneration (FTLD)		
bvFTD	International bvFTD Criteria Consortium	[19]
PNFA	International PPA Consortium	[12]
SD	International PPA Consortium	[12]
Parkinson's disease dementia (PDD)	Clinical Diagnostic Criteria for dementia associated with PD	[27,28]
PSP	NINDS/SPSP Criteria	[32,33]
	NINDS/SPSP Criteria	
Lewy bodies dementia (LBD)	Consensus criteria	[25,176]
	Diagnostic criteria	
Corticobasal syndrome (CBS)	MDS (non-validated formally)	[177]
Huntington disease (HD)	(Genetic criteria)	[178]
Prion diseases		
Sporadic CJD (s-CJD)	Updated WHO Criteria for s-CJD	[42]
	Updated MRI-CJD Consortium Criteria for s-CJD	[41]
Variant CJD (v-CJD)	Diagnostic criteria	[42]
Normal-pressure hydrocephalus (NPH)	NPH diagnostic criteria	[49,179]
Limbic encephalitis (LE)	Diagnostic criteria	[180]
Vascular dementia	Diagnostic criteria	[45]
Subcortical ischaemic vascular disease and dementia (SIVD)	Research criteria	[46]

Behavioural variant frontotemporal dementia (bvFTD)

Behavioural variant frontotemporal dementia accounts for around half of all cases of FTLD and is characterized by a progressive decline in inter-personal and/or executive skills, with loss of emotional responsivity, impaired autonomy and emergence of a variety of abnormal behaviours including disinhibition, adynamia, obsessions, rituals, stereotypies and alterations in feeding and other appetitive functions. More florid psychiatric manifestations including delusions and hallucinations are not uncommon, particularly in association with non-tau pathologies [20]. Within the broad bvFTD phenotype, clinical phenomenology in individual patients is variable, and the bvFTD syndrome is also the most anatomically and pathologically heterogeneous and the most heritable of the FTLD syndromes (see Table 2). Recent work has shown that

Table 2 Summary of clinical, neuroimaging and molecular features of the FTLD spectrum

Clinical syndrome	Cognitive associations			Neurological associations			AAO (yrs)	Dur (yrs)	MRI atrophy	Molecular associations[a]
	Ofa	PL	mem	park	MND	other				
bvFTD		+		+			50–60	5–15	asymm F L, R TL	Tau: 3r-Pick's
		+		+			50–70	5–10	asymm FL-PL	Tau: 4r-CBS
				+		gaze palsy	55–75		rel symm FL, midbrain	Tau: 4r-PSP
			+	+			40–60	10–15	rel symm aTL, FL	Tau: 4r/3r[b]
		+	+	+	rare		40–80	5–10	asymm R >>L FL, PL, TL	TDP43: type A[c]
					+		50–70[d]	3–10	rel symm FL–TL	TDP43: type B/A[e]
					+	IBM[f]	40–60	10–>20	FL, TL*	TDP43: type D[g]
				h	h		20–70	5–10	FL, caudate	FUS[i]
		+	+	+	+		45–65	3–20	Generalized*	Ubiquitin+TDP/FUS-[j]
PNFA	+	+		+			50–60	5–15	L > R peri-Sylvian	Tau: 3r-Pick's
	+			+			50–70	5–10	asymm FL-PL	Tau: 4r-CBS
	+					gaze palsy	55-75		asymm FL, midbrain	Tau: 4r-PSP
	+		+	+			40–60	10–15	rel symm aTL, FL	Tau: 4r/3r[b]
	+				+		50–70	3–10	L > R peri-Sylvian	TDP43: type B/A[e]
		+	+	+			40–80	5–10	asymm L>>R FL, PL, TL	TDP43: type A[c,k]
SD					?		55–70	10–15	asymm aTL, usu L > R	TDP43: type C[L]
					+		rare			TDP43: type B
		+		?			50–60			Tau: 3r-Pick's
				+			40–60		rel symm aTL, FL	Tau: 4r/3r[b]

AAO, age at onset (typical values shown, where sufficient data available); asymm, asymmetric; aTL, anterior temporal lobe; bvFTD, behavioural variant frontotemporal dementia; CBS, corticobasal syndrome; Dur, clinical disease duration; FL, frontal lobe; FUS, fused-in-sarcoma protein; IBM, inclusion body myopathy; L, left; mem, episodic memory impairment; MND, motor neurone disease; ofa, orofacial apraxia; park, parkinsonism; PL, parietal lobe; PNFA, progressive non-fluent aphasia; PSP, progressive supranuclear palsy; r, repeat number (tau isoform); R, right; rel, relatively; SD, semantic dementia; symm, symmetrical; TDP, transactive response DNA-binding protein; usu, usually; *limited information.

[a]predominant histopathological inclusion type;

[b]particularly mutations in tau (MAPT) gene;

[c]TDP43 subtyping here follows Mackenzie 2011 [181] harmonized classification scheme, type A includes mutations in progranulin (GRN) gene;

[d]earlier onset in some genetic cases;

[e]includes C9ORF72 mutations [14,15]; rarely mutations in TDP43 gene;

[f]also associated with Paget's disease (variable clinical and cognitive features);

[g]mutations in valosin-containing (VCP) protein;

[h]in familial FTD-MND cases with FUS mutations and sporadic cases with neuronal intermediate filament inclusion disease (NIFID);

[i]cases include atypical FTLD with ubiquitin inclusions (aFTLD-U) and NIFID, rare mutations in FUS gene;

[j]rare mutations in charged multivesicular body protein 2b (CHMP2b);

[k]phenotype of progranulin-associated aphasia continues to be defined; [L]>75% of cases of SD.

structural and functional changes in a medial paralimbic network (including anterior cingulate, orbital frontal and frontoinsular cortices) occur early in bvFTD [8], but this insight is of limited diagnostic usefulness in the individual patient. Phenocopies of bvFTD with normal structural and functional brain imaging and lack of clear progression on serial neuropsychological assessment are increasingly recognized [21]: the nature of the underlying disease in these cases (and whether it is neurodegenerative in nature) remains unclear.

Semantic dementia (SD)

This is a fairly uniform syndrome led by progressive breakdown of semantic memory, typically initially affecting knowledge of words [22]. Patients commonly present with fluent but empty speech with loss of vocabulary and surface dyslexia and dysgraphia. A more pervasive semantic impairment affecting visual information (prosopagnosia, visual agnosia) and other non-verbal domains generally supervenes later in the course. SD is associated with selective, asymmetric antero-inferior temporal lobe atrophy [23], which is predominantly left-sided in the majority of cases but may be predominantly right-sided in cases led by non-verbal semantic deficits. This anatomical profile of SD is the best defined amongst the FTLD syndromes, and SD also shows the closest histopathological association (>75% of cases have TDP43-positive

inclusions [7,22] and the least heritability of the FTLD syndromes [13]). A small proportion of cases with SD have other pathologies, including tauopathies and Alzheimer's disease.

Progressive non-fluent aphasia (PNFA)

Progressive non-fluent aphasia is led by a progressive breakdown in language output, initially affecting speech but subsequently also literacy skills in most cases; patients commonly present with effortful, non-fluent speech containing articulatory errors (speech apraxia), agrammatism and variable involvement of more posterior cortical functions. The broad category of non-fluent language breakdown encompasses several more or less distinct clinical syndromes [18]. Brain atrophy in PNFA frequently involves anterior peri-Sylvian cortices, more prominently in the left hemisphere [23], but varies widely in extent and severity between patients. Non-fluent speech breakdown and the development of parkinsonism are more frequently associated with tau than non-tau pathologies; however, there are important exceptions to these broad generalizations. In particular, non-fluent aphasia syndromes caused by TDP43 pathologies are associated with motor neurone disease and with GRN mutations [7,8]. 'Progranulin-associated aphasia' may constitute a distinct language-led syndrome within the FTLD spectrum [18]: this syndrome is often associated with early prominent parietal signs but lacks the prominent speech apraxia that is a hallmark of most PNFA cases.

Dementia with Lewy bodies (DLB)

Dementia with Lewy bodies is the second most common type of degenerative dementia accounting for 10–15% of cases [24], and it represents one part of a spectrum of neurodegenerative disorders that share dysregulation and aggregation of alpha-synuclein. The clinical manifestations of Lewy body disease include DLB, Parkinson's disease and autonomic failure. Clinically, DLB is characterized by progressive cognitive decline accompanied by core features: recurrent visual hallucinations, fluctuating attention and cognition, and motor features of parkinsonism [25]. Suggestive features include neuroleptic sensitivity, changes in dopamine transporter SPECT imaging and REM sleep behaviour disturbance [25].

Most previous studies observed a more severe impairment in visual-spatial abilities, attention and executive functions in persons with DLB compared with persons with AD [24] (class IV evidence). The complex visual hallucinations with emotional responses to these experiences, which vary from intense fear to indifference or even amusement, are very typical observations in these patients. The presence of visual hallucinations and delusional misidentification as early symptoms showed sensitivities and specificities of >50% but <75% (class IV evidence) [24–26]. Cognitive impairment is usually the presenting feature with extreme fluctuation within a single day over minutes or hours and is associated with shifting levels of attention and alertness. The BrainNet European Consortium recently published a protocol for post-mortem assessment [26].

Dementia in Parkinson's disease

The suggested clinical diagnostic criteria for PDD [27,28] involve four domains that are anchored in core features, associated clinical features, features that make the diagnosis uncertain, and features that are not compatible with the diagnosis of PDD. When all four criteria are satisfactorily met, probable PDD is designated; when the first and last criteria are met, but clinical characteristics are atypical or uncertainty factors exist, possible PDD is designated (class IV evidence) [27,28].

The point prevalence of dementia in PD is close to 30%, and the incidence rate is increased 4–6 times compared to age-matched controls. The cumulative prevalence is at least 75% of PD patients who survive for more than 10 years [29]. PDD and DLB are both synucleinopathies that differ clinically in the temporal evolution of parkinsonism and dementia with a time-period of 12 months being the arbitrary cut-off for the development of dementia (class IV evidence). But even in PDD alone, the time from onset of PD to dementia varies considerably and is related to the type and extent of brain pathology [30,31] (class IV evidence). The major neurotransmitter deficit is cholinergic, related to the loss of cholinergic neurons in the nucleus basalis of Meynert (NBM) and projecting cortical pathways (class IV evidence) [30].

Progressive supranuclear palsy (PSP)

Progressive supranuclear palsy is a tauopathy leading to a clinical syndrome featuring parkinsonian signs, impairment of vertical gaze, postural instability and dementia [32]. The National Institute of Neurological Disorders and Stroke (NINDS) have published PSP clinical diagnostic criteria [33]. Most patients become dependent within 3–4 years of diagnosis. Recently, two clinical phenotypes have been described in autopsy-proven cases: Richardson's syndrome (RS) and PSP-parkinsonism (PSP-P) [34]. Cases of RS were characterized by the early onset of postural instability

and falls, supranuclear vertical gaze palsy and cognitive dysfunction, and cases of PSP-P were characterized by asymmetric onset, tremor and a moderate initial therapeutic response to levodopa and were frequently confused with Parkinson's disease. Patients with RS showed shorter time from disease onset to diagnosis and more neuropsychological and neurobehavioural deficits than patients with PSP-P. Cognitive impairment in PSP sufficient to be labelled 'dementia' varies with rates up to 70% reported [35]. The degree of cognitive slowing in PSP appears independent of motor slowing. Frontal executive impairments are early and pervasive. Non-verbal reasoning and tasks of verbal fluency are greatly reduced with poorer performance on letter than semantic fluency. Memory complaints in PSP are usually mild and consist of impaired free recall with preserved recognition memory. Personality and behaviour change can be quite florid; limb apraxia in PSP is typically ideomotor, symmetrical and a common finding (40%) when studied systematically (class IV evidence) [34,35]. As in CBD, language and speech disorders, logopenia or dynamic aphasia and apraxia of speech are a feature of PSP; in particular, progressive non-fluent aphasia because of PSP pathology is well recognized [35] (class IV evidence).

Corticobasal syndrome (CBS)

Corticobasal syndrome is a rare syndrome with a progressive course, in most cases unresponsive to levodopa or other medication (class IV evidence) [36]. At onset, CBS typically presents with asymmetrical rigidity, bradykinesia and apraxia of the affected limbs, usually of the limb-kinetic type. During the evolution of the disease, postural and action tremor, limb dystonia, focal reflex myoclonus, postural instability and falls, alien hand-like phenomenon, corticospinal signs, oculomotor and eyelid motor deficits and dysarthria develop in more than half of cases. CBD, the commonest cause of CBS, is a 4-repeat tauopathy defined by unique neuropathological features including cortical atrophy, nigral degeneration, achromasia (swollen neurons with eccentric nuclei and loss of cytoplasmic staining) in the cortex and underlying white matter and tau immunoreactive astrocytic plaques. Dementia is not an early feature in classical CBS, occurring in approximately one quarter of cases at a later stage. However, dementia is more common in patients with CBD who do not present with classical CBS (class IV evidence) [36]. CBD is currently considered to involve a spectrum of different clinical phenotypes, such as CBS, PSP, dementia, bvFTD, progressive non-fluent aphasia, speech apraxia. Conversely, CBS can be associated with different pathological types: CBD (55%), PSP (20%), Pick's disease (7%) and non-tau pathologies for the remainder [36]. The clinical onset of CBD occurs usually during the sixth to eighth decades of life, and the mean survival is about 7 years [37].

Limbic encephalitis (LE)

The clinical features of LE are diverse, and early diagnosis of the disorder is frequently difficult [38,39]. The cardinal sign of LE is a severe impairment of short-term memory or of episodic, anterograde memory (class IV evidence) [38,39]. Anterograde amnesia is often associated with behavioural and psychological symptoms of dementia (BPSD) such as anxiety, depression, irritability, personality change, acute confusional state, hallucinations and complex partial and secondary generalized seizures. The symptoms typically develop over a few weeks or months, but they may evolve over a few days. Examination of the CSF may show lymphocytic meningitis. The main differential diagnoses include infectious encephalitis, corticosteroid-responsive autoimmune encephalopathy, glioma or lymphomatous infiltration, and Wernicke–Korsakoff encephalopathy. It often has a paraneoplastic origin mostly associated with lung or testicular cancer and in women with ovarian teratomas (class III evidence) [39]. It is often associated with antibodies against intracellular neuronal antigens or with antibodies to voltage-gated potassium channels (VGKC). Neuropathological studies show dominant parenchymal infiltrates of T cells supporting the hypothesis that the disorder is mediated by a T cell driven immune response, presumably against the same antigens recognized by the antibodies.

Huntington's disease (HD)

Huntington's disease is an autosomal-dominant neurodegenerative disease caused by the expansion of a cytosine–adenine–guanosine trinucleotide $(CAG)_n$ repeat within the *HD* gene, encoding an abnormally long polyglutamine moiety within the huntingtin protein (class I evidence) [40] that leads to marked atrophy of basal ganglia structures, the caudate and putamen, as well as less marked atrophy of other brain nuclei. It is probably the most common inherited adult neurodegenerative disease, affecting 1 in 15 000. The average age of onset is 30–50 years of age; in some cases, symptoms start before the age of 20 years with behaviour disturbances and learning difficulties at school (Juvenile Huntington's disease; JHD) and onset in older adults also occurs. The hallmark of the illness is chorea, but some patients have little or no chorea and instead appear with parkinsonian features [40].

Cognitive decline often accompanied by psychiatric symptoms is the other main sign of HD and can be present long before the first motor symptoms appear, but can also remain mild in far-advanced stages of the disease. Changes are mostly in executive functions including changes in goal-directed and planned abilities as well as the capacity to distinguish what is relevant and what can be ignored (class III evidence) [40]. The patients become rapidly unable to organize their life with frequent misjudgements. Usually language is relatively spared. Episodic memory becomes impaired, although semantic memory is relatively spared. The illness leads to death, with an average duration of symptoms of about 20 years. How the mutation leads to the onset of a disorder of motor, emotional and cognitive control in people who have matured normally until middle age is still unknown. The discovery of mutations in the HD gene has made genetic diagnosis common, both in neurologically normal patients (pre-symptomatic testing) and in neurologically or psychiatrically impaired patients (diagnostic testing) (class III evidence) [40].

Prion diseases

Creutzfeldt–Jakob disease (CJD)

Sporadic CJD, the most common prion disease (85% of cases), has a prevalence estimated to be 0.5–1.5 cases per million; the mean age at onset is 65 years (range, 14–92 years), and the median and mean duration of illness are 4.5 and 8 months, respectively; only 4% of patients survive longer than 2 years. Diagnostic criteria for sporadic CJD have been published based on clinical signs, EEG, 14-3-3 protein in CSF and MRI findings (class IV evidence) [41,42]. The classical diagnostic triad is a rapidly progressive dementia, myoclonus and a characteristic EEG pattern. Myoclonus is an important manifestation, but seen often only in late stages of the disease. Ataxia and visual abnormalities are frequent, with visual field defects, perceptual abnormalities and occasionally hallucinations [43].

Genetic prion diseases

Genetic prion diseases occurring in 10–15% of cases are caused by prion protein gene (*PRNP*) mutations, showing the patterns of autosomal-dominant inheritance with incomplete penetrance. The disorders manifest as familial Creutzfeldt–Jakob disease (fCJD), Gerstmann–Sträussler–Scheinker disease (GSS) or fatal familial insomnia (FFI).

Accidentally transmitted (iatrogenic)

CJD has been related to corneal graft transplantation, contaminated human pituitary-derived growth hormone or gonadotropin and dura mater grafts. Increased awareness has raised concern about the risk that human prion diseases (especially vCJD) are transmissible by blood transfusion. The very rare *new variant CJD* (*vCJD*) is related to BSE (bovine spongiform encephalopathy). More than 200 vCJD cases have been reported since 1996, the majority in the UK. vCJD is characterized by a younger age of onset (mid-teens to early 40s) and by longer illness duration (range, 4–25 months). Clinical features are often limited to psychiatric disturbance or sensory symptoms, until ataxia, cognitive impairment and involuntary movements develop later in the course [42].

Vascular cognitive impairment and vascular dementia

Recently, the term vascular cognitive impairment (VCI), which reflects an awareness of the importance of the vascular burden on cognition, has been proposed [44]. The previous concept of VaD caused by small or large brain infarcts (strokes) was recently extended from only multi-infarct (multi-stroke) dementia (MID) to a whole spectrum of vascular causes of cognitive impairment and dementia, subsumed within the term vascular cognitive impairment [44].

The main subtypes of VaD included in current classifications are large vessel (LV) VCI, also referred to as cortical VCI, multi-infarct VCI or post-stroke VCI, small vessel (SV) VCI, subcortical ischaemic vascular disease and dementia (SIVD), strategic infarct dementia and hypoperfusion VCI resulting from global cerebrovascular insufficiency. Further subtypes include haemorrhagic dementia, hereditary vascular causes (e.g. cerebral autosomal dominant arteriopathy with subcortical infarct and leucoencephalopathy (CADASIL) and AD with cerebrovascular disease (CVD). The most widely used clinical diagnostic criteria for VaD are the NINDS-AIREN criteria [45]. In addition, research criteria for SIVD have also been proposed [46].

The NINDS-AIREN criteria handle VaD as a syndrome with different aetiologies and different clinical manifestations rather than a single entity and list possible subtypes to be used in research studies. These criteria incorporate different levels of certainty of the clinical diagnosis (probable, possible, definite). However, in randomized clinical trials using the NINDS-AIREN criteria, all potential subtypes have been lumped together as 'general VaD'. The SIVD criteria of Erkinjuntti *et al.* [46] represent an attempt to define a more homogeneous subtype.

In a neuropathological series, the sensitivity of the NINDS-AIREN criteria for probable and possible VaD was 58% and specificity was 80% [47]. The

inter-rater reliability of the NINDS-AIREN criteria is moderate to substantial (kappa 0.46–0.72) [44].

The research criteria for SIVD represent a more recent development. In SIVD, the biological markers of small vessel disease are confluent white matter lesions along with lacunes. Furthermore, changes in the normal appearing white matter, frontal cortical atrophy, as well as microinfarcts may be important surrogates. A similar approach to the small vessel dysexecutive phenotype criteria of SIVD is that of the recent criteria for the amnestic phenotype of AD.

VCI cases that do not meet the criteria for dementia can also be labelled as VCI with no dementia or vascular cognitive impairment, no dementia (CIND). These patients have also been labelled as vascular mild cognitive impairment (vMCI) in a similar way to amnestic mild cognitive impairment (aMCI) for AD.

Normal-pressure hydrocephalus (NPH)

Data about the prevalence of normal-pressure hydrocephalus (NPH) syndrome vary between 0.12% and 2.9% with an estimated incidence of 5.5/100 000/year [48]. Clinical diagnosis of NPH is difficult as the critical features of NPH represented by insidious onset of gait disturbance, incontinence and dementia are very common in the elderly. Furthermore, a cognitive profile may overlap with AD or subcortical VaD and gait disturbances may overlap with PD. The presence of typical clinical features accompanied by supplemental investigations enable the classification of NPH as possible, probable or unlikely. International guidelines suggest that probable clinical diagnosis has to be based on all three core features (class III of evidence) [49].

Diagnostic evaluation

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 activity of daily living (ADL) and any associated non-cognitive symptoms. Past medical history, co-morbidities and family and educational history are important. Information from the history can guide and target subsequent examinations. The neurological examination is particularly important in distinguishing primary degenerative and secondary dementias and co-morbidities [2,4–6] (class III evidence). It is largely normal in early AD with the exception of mental status evaluation. Additional abnormalities 'dementia plus' syndromes can suggest specific diagnoses (class IV evidence) [50]. Alterations may be suggestive of other forms of dementia. For example, increased muscle tone and bradykinesia in the absence of tremor may be suggestive of DLB; asymmetric reflexes, visual field deficit, pyramidal or other lateralizing signs may be indicative of VaD; myoclonus is suggestive for CJD; peripheral neuropathy may suggest toxic and metabolic encephalopathies. It is of particular importance to evaluate hearing and vision because impairment can influence mental status and neurological examination. Neurological examination should be accompanied by general medical examination to disclose systemic contribution to the cognitive impairment.

There exists no evidence-based data to support the usefulness of specific routine blood tests for the evaluation of those with dementia but these tests are useful in excluding co-morbidities, revealing potential risk factors, origin of confusional states and, rarely, in identifying the primary cause of dementia. The value of laboratory tests was assessed by the American Academy of Neurology practice parameter publication [51]. Most expert opinion advises screening for vitamin B12, folate, thyroid-stimulating hormone, calcium, glucose, complete blood cell count, renal and liver function abnormalities. Abnormal vitamin B12 levels and thyroid function are commonly encountered co-morbidities. They can influence cognitive function, and it is useful to assess them even if the treatment of these disorders may not completely reverse dementia (class IV evidence) [51]. Serological tests for syphilis, Borrelia and HIV should be considered in individual cases at high risk or where there are suggestive clinical features (class IV evidence) [51].

Recommendations: clinical diagnosis: medical history, laboratory, neurological and physical examination

- Clinical history should be supplemented by an informant (Good Practice Point) [2,4–6]. A neurological and general physical examination should be performed in all patients with dementia (Good Practice Point) [2,4–6,50]. Routine blood tests are useful in excluding co-morbidities (Good Practice Point) [51].

Assessment of cognitive functions, screening tests and assessment of specific cognitive domains

Specific patterns of cognitive and behavioural dysfunctions are detectable in early rather than in advanced stages and reflect the disruption of specific brain structures [51]. Thus, episodic memory impairment is often the first symptom in AD with early involvement of entorhinal cortex and hippocampus

[52] (class II evidence). Disinhibition, apathy and emotional disorders characterize the first stages of bvFTD, with predominant atrophy in the antero-mesial and orbito-frontal cortices (class II evidence) [19,20]. SD with atrophy of the left anterior temporal region is characterized by word finding and semantic disorders, whereas a left anterior peri-Sylvian atrophy is usually associated with a PNFA (class II evidence) [22]. CBS features visual-spatial impairment, limb apraxia and an alien hand syndrome reflecting parietal and frontal lobe atrophy (class II evidence) [36,37]. Parietal occipital atrophy is associated with the visual hallucinations and the visual-spatial disorders of DLB. On the other hand, the subcortical forms of dementia (PDD, NPH and VaD with multiple subcortical infarcts), in which the subcortical-frontal loops are usually disrupted, are characterized by psychomotor slowing and executive dysfunctions subsumed by the frontal lobes.

The most widely used cognitive screening test is the Mini-Mental State Examination (MMSE) [53] which does not investigate frontal functions. Other screening tests are available of good accuracy in the general diagnosis of dementia or have been proposed specifically for the differential diagnosis between the different forms of dementia. These two groups of screening tests are given in Table 3, together with some neuropsychological batteries oriented to the differential diagnosis of dementia.

The patterns of impairment observed on the screening tests reported in Table 3 can guide the differential diagnosis. Thus, in addition to the characteristic episodic memory impairment of AD:

- **(a)** visual-constructive disorders on copying the pentagons of the MMSE are associated with DLB with a sensitivity of 88% and a specificity of 59% [54] (class II, Level B). Also associated with DLB are reduced attention and working memory scores of the MMSE [55] and of the Addenbrooke's Cognitive Examination Revised (ACE-R) [56] (class II, Level B);
- **(b)** reduced scores on the 'letter fluency' subtest of the ACE-R are associated with FTD, CBS and PSP [56] (class II, Level B);
- **(c)** stimulus-bound responses of the clock-drawing test are associated with PDD and subcortical forms of vascular dementia (class II, Level B) [57].

Similar results are obtained on the more complex screening and neuropsychological batteries reported in Section 2 of Table 3. Thus, according to Slachevsky *et al.* [58], but not to Lipton *et al.* [59], the results obtained on the FAB correctly identify about 80% of patients affected by bvFTD. Furthermore, the results obtained on the Philadelphia Brief Assessment of Cognition (PBAC) and the Cambridge Cognitive Examination (CAMCOG) show that patients with DLB [60] and with CBS [61] are particularly impaired on visual-spatial tasks; patients with bvFTD and with CBS show pathological scores on letter fluency tasks [60] and on measures of social-behavioural disturbances, whereas those with SD are selectively impaired on tests of visual naming and category fluency [61].

Memory functions

Episodic memory: A comparison between scores obtained on free recall and on cued recall is very useful in the differential diagnosis between AD and non-AD dementia (class II evidence), because the provision of a cue (helping encoding and retrieval processes) significantly improves the memory scores of patients with lesions affecting the frontal lobes and subcortical structures. The provision of a cue is, on the contrary, of no help in AD patients, where delayed recall is severely impaired as a consequence of mesial temporal lobe atrophy, which disables consolidation. Investigations conducted with the Buschke's Free and Cued Selective Reminding Test (FCSRT) and the California Verbal Learning Test (CVLT) have shown that cues provided more benefit to patients with VaD [62] and with FTD [63] than to AD patients.

Semantic memory: Selective impairment is typical of SD. Several authors [64] have shown that patients with SD perform worse in categorical fluency and visual naming tests, compared with bvFTD and AD.

Executive functions

A predominance of executive dysfunction over episodic memory impairment is typical for bvFTD [58,65], CBS [65], VaD [66] and DLB [67]. Decreased fluency on verbal fluency tests [68], perseverations on the Wisconsin Card Sorting Test (WCST) [69], reduced speed of processing on the Trail-Making Test (TMT) [70], and defects in inhibiting the automatic responses on the Stroop test [71] may be caused by subcortical or frontal lesions [65,66,68,69,71]. However, it must be noted that Reed *et al.* [72] have recently reported that executive impairment is not a useful diagnostic marker for VD, when assessed in a series of autopsy confirmed AD and cerebrovascular cases.

Visuospatial and visual recognition abilities

Results of individual studies [60,61] and of systematic reviews (e.g. [67]) have shown that patients with DLB [60,67] and with CBS [61] are particularly impaired on visual-spatial tasks. On the other hand, several authors have shown that in patients with right temporal variant of FTD, a defect of familiar people recognition, affecting both faces and voices, is frequently observed (see [73] for a systematic review).

Table 3 Assessment of cognitive functions in dementia

(1) Screening tests of good accuracy in the general diagnosis of dementia

	Diagnostic accuracy for dementia		Coverage of cognitive (and social-emotional) domains					
Test	Sensitivity	Specificity	Verbal memory recall	Attention working memory	Language	Visual-spatial functions	Verbal fluency	Emotional behavioural disorders
MMSE [53]	71–92	56–96	+	+	+	+		
ACE-R [182]	94	89		+	+	+	+	
MDRS [183]	98	97 (in AD)	+	+	+	+		
CDT [184]	67	97			+		+	

(2) Screening tests and neuropsychological batteries proposed for the differential diagnosis amongst different forms of dementia

Test	Sensitivity	Specificity	Verbal memory recall	Attention working memory	Language	Visual-spatial functions	Verbal fluency	Emotional behavioural disorders
PBAC [61]				+	+	+	+	+
FAB [58]	78.9[a]							
CAMCOG [185]	93	87		+	+	+	+	

(3) Assessment of specific cognitive domains

		References
Episodic memory (benefit obtained by a cue provision)	FCSRT	[62]
	CVLT	[186]
Semantic memory	Category fluency	[187]
	Boston naming test	[187]
Executive functions	Verbal fluency tests	[64]
	WCST	[68]
	TMT	[70]
	Stroop test	[71]
Visual-spatial functions	Judgment of Line Orientation	[185]
	Clock-drawing test	[184]

MMSE, Mini-Mental State Examination; ACE-R, Addenbrooke's Cognitive Examination Revised; MDRS, Mattis Dementia Rating Scale; CDT, clock-drawing task; PBAC, Philadelphia Brief Assessment of Cognition; FAB, Frontal Assessment Battery; CAMCOG, Cambridge Cognitive Examination; FCSRT, Free and Cued Selective Reminding Test; CVLT, California Verbal Learning Test; WCST, Wisconsin Card Sorting Test; TMT, Trail-Making Test.

[a]Accuracy in distinguishing FTD from AD patients.

Recommendations: assessment of cognitive functions, screening tests and assessment of specific cognitive domains

- Cognitive assessment is central to diagnosis and management of dementias and should be performed in all patients (Level A) [51]. Screening tests are available of good accuracy in the general diagnosis of dementia or have been proposed specifically for the differential diagnosis between the different forms of dementia (Good Practice Point) [51]. Neuropsychological assessment should be performed in all patients in the early stages of the disease (Level B) when the cognitive impairment reflects the disruption of specific brain structures [2,4–6,52]. The neuropsychological assessment 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) [51].

Assessment of behavioural and psychological symptoms

The term behavioural and psychological symptoms of dementia (BPSD) is used to describe the spectrum of non-cognitive symptoms of dementia (apathy, psychosis, affective and hyperactive behaviours) [74]. Identification of neuropsychiatric symptoms is essential for both the diagnosis and treatment, as some BPSD constitute the core or supportive diagnostic features of some non-AD dementias such as DLB, PDD or FTLD [12,19,24,27] (class IV evidence). BPSD are associated with declining cognitive and functional ability, decreased quality of life and increased institutionalization (class III evidence) [74,75]. Somatic comorbidity and environmental triggers should always be ruled out as a possible cause.

Several global informant-based scales are used to assess BPSD (class IV) [76] (see Table 4); however, most of them have been specifically developed for AD, displaying low sensitivity for some characteristic forms of BPSD occurring in non-AD dementias [77]. The neuropsychiatric inventory (NPI) is a comprehensive instrument used in most non-AD drug studies although the change in the scale representing a clinically meaningful improvement has not yet been established [78]. Different versions have been available including both an abbreviated version for routine clinical practice and a more expanded version comprising, for example, euphoria, disinhibition, compulsive and repetitive behaviours [77]. The Middelheim frontality score (MFS) is a validated scale that measures frontal features and reliably discriminates FTLD from AD patients with a sensitivity and specificity of almost 90% [77] (class II evidence).

A behavioural scale of frontal lobe dysfunction providing a behavioural cut-off to diagnose early FTD and distinguish it from AD and VaD is available with a specificity of 95% and sensitivity of 91% [79] (class II evidence).

Table 4 Specific scales used to assess BPSD in dementing disorders

Scale/questionnaire	Purpose of use	Behavioural domains assessed	Other characteristics	Reference
Middelheim frontality score (MFS)	To discriminate FTLD and AD	Frontal features	Validated scale; sensitivity and specificity close to 90%	[77]
Manchester Behavioural Questionnaire	To differentiate FTLD from AD/CVD	Frontal features	Semi-structured questionnaire; overall accuracy of classification 95%	[188]
Frontotemporal behavioural scale	To diagnose early FTLD and distinguish it from AD and VaD	Frontal features	Validated scale; specificity of 95% and sensitivity of 91%	[79]
Cambridge behavioural questionnaire	To differentiate FTLD from AD; discriminate frontal variant FTLD and semantic dementia	Frontal features	Questionnaire; overall accuracy of classification 71.4%	[189]
Geriatric depression scale (GDS)	To assess depressive symptoms, diagnosis of depression	Affective symptoms	15-item validated scale	[76]
Cornell scale for depression in dementia	To assess depressive symptoms, diagnosis of depression	Depression	Validated scale; developed specifically for use in dementia	[76]
Dementia mood assessment scale (DMAS)	To assess depressive symptoms, diagnosis of depression	Depression	Validated scale; developed specifically for use in dementia	[76]
REM sleep behaviour disorder screening questionnaire	To screen for REM sleep behaviour disorder in PDD/DLB	REM sleep behaviour disorder (RBD)	Validated questionnaire	[81]
Questionnaire for impulsive-compulsive disorders in PD	To screen for impulsive-compulsive disorders in PD	Impulsive-compulsive disorders	Validated questionnaire	[82]

Other useful scales discriminating FTLD from AD in particular are listed in Table 4. More focused scales evaluating specific symptoms as well as possible treatment complications [80] of some non-AD dementias have been available, including the assessment of depression (particularly the 15-item geriatric depression scale, Cornell scale for depression in dementia) [76], REM sleep behaviour disorder [81] or impulsive-compulsive disorders [82] (class II evidence).

Recommendations: assessment of behavioural and psychological symptoms

- Assessment of BPSD is essential for both diagnosis and management and should be performed in each patient (Good Practice Point) [74]. Information is gathered from an informant using an appropriate rating scale (Good Practice Point) [76]. Although specific BPSD form the core or supportive features of some non-AD dementias, co-morbidity should always be considered as a possible cause (Good Practice Point) [12,19,24,27].

Assessment of activities of daily living

Impairment of everyday function is a key feature of dementia. Assessment of function in daily life is part of the diagnostic work-up. Different scales are used to measure these abilities objectively. These are based mainly on the interview with the patient and his/her caregiver. Most scales include measurement of two fields: basic (self-maintenance skills, such as eating, dressing, bathing) and instrumental activities (complex higher order skills such as the use of devices, managing finances, shopping). Frequently used scales include the AD Cooperative Study (ADCS) ADL Scale [83], Functional Activities Questionnaire (FAQ) [84], the Progressive Deterioration Scale (PDS) [85], Instrumental Activity of Daily Living (IADL) [86] and the Disability Assessment for Dementia (DAD) [87]. These scales are validated for different populations and translated into most European languages; however, they are not validated in low-income countries [88]. There are differences in functional impairment across subtypes of dementia [89], and these scales may be used to monitor rate of change of functional abilities in dementia [83–89] (class IV).

Recommendations: assessment of activities of daily living

- ADL and IADL impairment because of cognitive decline is an essential part of the diagnostic criteria for dementia and should be assessed in the diagnostic evaluation (Good Practice Point) [83–89]. A semi-structured interview from the caregiver is the most practical way to obtain relevant information, and various validated scales translated into different languages are available (Good Practice Point) [83–89].

Assessment of co-morbidity

Studies of the prevalence of co-morbidity and the effect of treatment of co-morbidities in non-AD dementia are limited. A large autopsy study in various dementia cases identified a high number of co-morbidities, which would have affected the clinical management of the patient had they been known ante-mortem. Amongst these, the most frequent were atherosclerotic cardiovascular disease, myocardial infarct, bronchopneumonia, emphysema and pulmonary thromboembolism (class IV evidence) [90]. However, in a large cohort followed for 2 years in nursing homes, patients with dementia had significantly lower overall rates of infection and similar rates of fever, pressure ulcers, and fractures compared to non-demented residents (class IV evidence) [91]. Depression is frequent in the elderly population in general and depressive symptoms are common in dementia, particularly in vascular dementia [92], FTD [93] and PDD [94] and neurologists should be trained to recognize depressive disorders [95]. In PDD, falls, fractures, symptomatic postural hypotension, urinary incontinence and hallucinations are frequent events [96]. Co-morbidity is a significant predictor of the quality of clinical outcome for patients with idiopathic normal-pressure hydrocephalus undergoing shunt therapy (class III evidence) [97].

Recommendations: assessment of co-morbidity

- Assessment of co-morbidity is important in demented patients, both at the time of diagnosis and throughout the course of the illness (Good Practice Point) [90] and should always be considered as a possible cause of BPSD (Good Practice Point) [97]. 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, Borrelia and HIV might also be needed in cases with atypical presentation or clinical features suggestive of these disorders (Good Practice Point) [51].

Neuroimaging

Structural imaging in non-Alzheimer dementias

In clinical practice, CT and standard MRI are used to exclude secondary causes for dementia such as tumour

and inflammatory disease, including abscess or normal-pressure hydrocephalus (class I evidence) [98]. Yet, only 2.2% of demented patients have a condition requiring imaging for diagnosis [98]. Nonetheless, imaging is used to refine ante-mortem diagnosis, and based on current diagnostic criteria it is MRI that is becoming a prerequisite in the diagnostic work-up of dementia.

Vascular dementia

Diagnostic criteria for VaD require the demonstration of cerebrovascular disease and a link between that and the onset of dementia [45]. The NINDS/AIREN (National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences) criteria propose detailed imaging criteria for the diagnosis of VaD [45]. These criteria separate large vessel and small vessel disease and consider both topography and severity. Low inter-rater reliability led to operationalization of these guidelines which resulted in good agreement amongst experienced readers (class III evidence) [99]. Despite these attempts to produce agreement on the types, topography and severity of vascular lesions relating to the diagnosis of vascular dementia, much uncertainty remains. Although imaging criteria appear to be specific for a diagnosis of VaD, sensitivity can be lower than 50% (class III evidence) [100]. At the current state of knowledge, demonstration of cerebrovascular disease on imaging is used to support the diagnosis; subcortical vascular dementia is the most common entity amongst VaD and MRI, and criteria for this entity have been proposed and already used in several clinical studies [46]; a formal neuropathological validation is still pending.

Dementia with Lewy bodies (DLB) and Parkinson disease with dementia (PDD)

Relative preservation of the hippocampus and medial temporal lobe compared with AD has been described in DLB and PDD in around half of the patients, and distinct patterns of grey matter loss have been found in DLB and PDD. These involve frontal areas extending to temporal, occipital and subcortical areas, with occipital atrophy in DLB and PDD being the only difference from the pattern seen in AD [101] (class III evidence). There remains considerable overlap between AD, DLB and PDD, and the utility of MRI for differential diagnosis is unclear.

Frontotemporal lobar degeneration (FTLD)

Frontal and temporal atrophy are supportive diagnostic features for FTLD, but their absence does not exclude the diagnosis. Asymmetric atrophy is often seen in primary progressive aphasia and in semantic dementia with more pronounced atrophic changes occurring in the anterior than in the posterior portions of the temporal lobe (class III evidence) [21]. Greater left temporal atrophy than in AD was described in semantic dementia, and areas such as the temporal pole, parahippocampal gyrus and lateral temporal lobe are also more affected in FTLD (class III evidence) [102]. In semantic dementia, 'knife-edge'-type atrophy is almost always present in the anterior temporal lobes [103] (class IV evidence).

Huntington's disease (HD)

Atrophic changes are seen in the striatum, cortex, substantia nigra, ventrolateral thalamus, subthalamic nucleus, cerebellum and brainstem. The pronounced atrophy of the caudate nucleus and putamen is characteristic, and the so-called bicaudate ratio doubles [104] (class II evidence). The putamen can be hyperintense.

Progressive supranuclear palsy (PSP)

MRI is used to distinguish PSP from Parkinson disease and Parkinson-variant of MSA. Pathological findings and MR imaging evidence indicate that the midbrain and the superior cerebellar peduncles are atrophic in PSP, whereas the middle cerebellar peduncles and the pons are mainly involved in MSA (class IV evidence) [105]. An MR parkinsonism index was introduced for the combined assessment at routine MR imaging of the four brain structures differently involved in atypical parkinsonian syndromes [105] (class IV evidence). Validation is still pending.

Corticobasal syndrome (CBS)

MRI demonstrates characteristically asymmetric frontal and/or parietal atrophy with less frequent involvement of the temporal lobe. Visual assessment of the asymmetry has been reported to differentiate corticobasal syndrome from PSP with high specificity [106] (class III evidence).

Multiple system atrophy (MSA)

Besides atrophic changes, T2-weighted MRI may show a posterolateral putaminal hypointensity because of iron deposition, with a hyperintense rim because of gliosis. Using T2* gradient echo sequences to detect this hypointensity and FLAIR to detect the hyperintense has a sensitivity of 69%, and specificity of 97% was achieved in differentiating MSA from PD [107] (class III evidence).

Prion disease

Hyperintensity of the cortical gyri (cortical ribboning), striatum (caudate and putamen) and/or thalamus on FLAIR and DWI scans has high sensitivity and specificity (up to 90% sensitivity and 90% specificity for DWI) in sporadic CJD [108] (class II evidence). MRI imaging is of increasing importance in sCJD diagnosis and has recently been added to updated WHO criteria as a diagnostic marker of probable sCJD, besides 14-3-3 and EEG (class II evidence) [41]. The so-called 'pulvinar sign', that is, symmetrical hyperintensity of the posterior thalamus, has high diagnostic utility for variant CJD (seen in over 90% of patients with subsequently pathologically confirmed vCJD) [109] (class III evidence).

Other rapidly progressing dementias

Other rapidly progressive dementias can have MRI findings similar to CJD. Bartonella hensalae encephalopathy, Wilson's disease and Wernicke's encephalopathy can show DWI hyperintensity in the deep grey nuclei, whilst antibody-mediated encephalopathies and neurofilament inclusion body dementia can have FLAIR hyperintensity in the cortex and deep nuclei. In these conditions, unlike prion disease, the underlying white matter is also often involved [109–113] (class IV evidence).

Normal-pressure hydrocephalus (NPH)

According to Relkin criteria [49], MRI or CT must show an Evan's index (maximal ventricular width divided by the largest biparietal distance between the inner tables of the skull) of at least 0.3, as well as temporal horn enlargement, periventricular signal changes or an aqueductal/fourth ventricular flow void (class III evidence) [49]. A callosal angle of greater than 40° was included in these guidelines [49]. Also, a narrow CSF space at the high-convexity/midline areas relative to Sylvian fissure size was recently shown to correlate with a diagnosis of probable or definite NPH [114] (class III evidence). Volumetric MRI, including ventricular, brain and peri-cerebral CSF volume ratios, has not shown value in predicting which patients will respond to ventricular shunting (class IV evidence) [115]. There is no correlation between outcome of a high-volume lumbar puncture or ventricular shunting and CSF stroke volume as measured by cine phase-contrast MRI, even at a median duration of symptoms of 1 year [116]. At this time, there is insufficient evidence to determine the value of this imaging technique in predicting response to shunting in NPH, but an elevated CSF stroke volume is considered a supportive criterion for diagnosis (class IV evidence) [116].

Limbic encephalitis (LE)

The MR imaging findings of limbic encephalitis have been well described in a number of case reports and during the acute phase of the illness. They include hyperintense signal abnormality on T2-weighted images within medial temporal lobe structures such as the hippocampi and amygdalae and, on occasion, the hypothalamus [117] (class IV evidence).

Functional imaging modalities include diffusion-tensor imaging (DTI) MRI, SPECT and PET

Diffusion-tensor imaging MRI is performed as part of an MRI protocol that usually includes FLAIR, T1, T2 and the DTI uptakes are evaluated in this context. Importantly, DTI sequences add unique information on the integrity of white and of grey matter structure. This information is obtained from data on the mobility (diffusibility) of water molecules in the tissue, and several parameters can be extracted. MD (mean diffusivity), FA (fractional anisotropy), DR (radial diffusivity, perpendicular to axonal tracts) have consistently been shown to be useful, experimental and clinical data, showing close relationships between clinical parameters, tissue and imaging changes (Level A evidence, see below).

Recently, it has been shown that DTI MRI (in combination with morphometric analysis) distinguishes network degeneration in patterns consistent with cognitive impairment in AD and FTLD patients, when diagnosis was confirmed using CSF biomarkers and autopsy [118] (class II evidence). Also, a small case–control study suggests that white and grey matter DTI uptakes may distinguish between FTLD variants [119] (class IV evidence).

Similarly, comparing AD and DLB, diffusivity patterns complement morphometric data in the diagnostic process and correlate with symptoms, DLB patients having a more pronounced increased diffusivity, for example in the amygdalae [120] (class IV evidence). Compared with PDD and corresponding to the cognitive profiles of the patients, DLB patients have higher diffusivity in the posterior temporal, posterior cingulate and visual association fibres [121] (class IV evidence). As for other parkinsonian disorders, data from a small DTI MRI case–control study showed distinct patterns of diffusivity changes, with increases in the anterior thalamus in PSP, in contrast to asymmetric thalamic motor increases in CBS [122] (class IV evidence). Diffusion-weighted imaging is also of value in the early diagnosis of CJD [123] (class IV evidence).

The brain distribution of the SPECT perfusion ligand ^{99m}Tc HM-PAO and PET metabolic ligand [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG) reflect regio-

nal metabolic activity and blood flow, often revealing highly relevant hypoperfusion and hypometabolism in cerebrovascular and neurodegenerative disease. Voxel-based methods for analysis increase sensitivity and specificity. Combined morphometric MRI and SPECT imaging have been reported to reach specificity/sensitivity levels of 89%/84% for the differentiation of DLB from AD, taking into account both occipital hypoperfusion and striatal volume ratios [124] (class IV evidence). In a follow-up study, pre-synaptic dopamine transporter imaging scans at baseline (using ^{123}I-FP-CIT SPECT) were reported to have sensitivity/specificity values of 63%/100% for distinguishing DLB from non-DLB dementia [125] (class II evidence).

SPECT and PET perfusion and metabolic techniques are also useful in FTLD diagnosis, showing typical regional alterations with sensitivity reaching 90% for an FTLD diagnosis [126] (class III evidence), complementing the high specificity of the clinical criteria. These techniques may also distinguish between FTLD language variants [127,128] (class IV evidence).

Recommendations: neuroimaging

Structural imaging

- Structural imaging should be used in the evaluation of every patient affected by dementia (Level A recommendation) [98]. CT and standard MRI are used to exclude secondary causes for dementia such as tumour and inflammatory disease, including abscess or normal-pressure hydrocephalus (Level A recommendation) [98]. It is particularly difficult to attribute clinical significance to the evidence of cerebrovascular disease in patients with cognitive impairment. At the current state of knowledge, demonstration of cerebrovascular disease on imaging is used to support the diagnosis (Good Practice Point) [99,100]. Atrophy distribution is useful in the differential diagnosis of FTLD compared with AD and of the subtypes of FTLD (Level C) [21,102,103]. No established structural MRI pattern is characteristic for DLB and PDD (Good Practice Point) [101]. MRI is used to distinguish PSP from DLB, being midbrain and the superior cerebellar peduncles atrophic in PSP (Good Practice Point) [101]. The pronounced atrophy of the caudate nucleus and putamen is characteristic, and the so-called bicaudate ratio doubles in HD (Level B) [104,105]. MRI showing DWI cortical rims, striatal and/or thalamic hyperintensities is useful for the diagnosis of sporadic CJD (Level A) [41,108]. The MRI pulvinar sign, that is, symmetrical FLAIR hyperintensity of the posterior thalamus, has high diagnostic utility for variant CJD (Level B) [109]. DTI MRI distinguishes FTLD from AD and controls (and AD from controls) (Level B) [118,119]. Measuring flow void on MRI can increase confidence in NPI diagnosis and in the decision about shunt placement (Good Practice Point) [115]. Hyperintense signal abnormality on T2-weighted images within medial temporal lobe structures such as the hippocampi and amygdalae and, on occasion, the hypothalamus are commonly seen in limbic encephalitis (Level C).

Functional imaging modalities

- DTI MRI distinguishes FTD from AD and controls (and AD from controls) (Level B) [118,119]. DTI MRI shows the distinct patterns of diffusivity changes in parkinsonism disorders (PSDD, DLP, PSP, CBS) (Level C) [119]. SPECT perfusion and MRI morphometric imaging are useful to distinguish DLB, CBS, CJD from AD (Good Practice Point) [120,122,123]. SPECT pre-synaptic dopamine transporter imaging is useful to distinguish DLB from non-DLB dementias (Level B) [124,125]. SPECT and PET perfusion and metabolic techniques are highly useful in FTLD diagnosis [126–128] (Level C).

Electroencephalography (EEG)

Electroencephalography can provide early evidence for CJD or suggest the possibility of a toxic-metabolic disorder, transient epileptic amnesia or other previously unrecognized seizure disorder [129] (class III evidence). EEG can also be supportive for the differential diagnosis of the degenerative dementias: EEG with only diffuse abnormalities suggests AD, and EEG with both diffuse and focal changes suggests DLB, VaD or AD [130] (class III evidence). DLB is characterized by slow-wave temporal lobe transients, frontal intermittent delta activity and by a more pronounced EEG slowing during the early phase of the disease compared with AD. FTLD is associated with normal resting-state functional connectivity and preserved dominant posterior alpha activity, more EEG abnormality being present in temporal than in frontal variant. The typical EEG in CJD shows generalized symmetrical periodic 1-Hz triphasic or biphasic sharp-wave complexes [131]. The presence of periodic sharp-wave complexes has a sensitivity of 67% and a specificity of 86% for sCJD (class III evidence) [131]. EEG recordings in vCJD usually show only non-specific slow-wave abnormalities.

Recommendations: electroencephalography

- EEG is recommended in rapid dementia and differential diagnosis when CJD or transient epileptic

amnesia is suspected (Level B) [129–131]. There is not enough evidence to consider resting EEG for the initial assessment of all dementia patients.

CSF analysis

Routine analysis of CSF yields no specific information, but may be performed if there is a suspicion of inflammatory causes of dementia, as well as neurosyphilis, HIV/AIDS, neuroborreliosis and paraneoplastic causes (class III evidence) [132]. Abeta 1–42 is specific for AD, but other isoforms of amyloid-beta, such as amyloid-beta n-40, n-38, n-17, show promise in improving the differential diagnosis [133] (class III evidence) especially for FTLD [134] (class III evidence). Increased concentrations of tau and p-tau signify neuronal death and hyperphosphorylation, respectively. They support the diagnosis of AD, but they do not preclude a diagnosis of DLB, VaD or FTLD.

In CJD, extremely high CSF concentrations of tau (with relatively less-elevated concentrations of p-tau) are observed, yielding very high sensitivity and specificity [135]; the same applies to the 14-3-3 level in CSF [136] (class II evidence). In subtypes of CJD, notably variant CJD, tau levels may be lower than in sporadic CJD, but are still diagnostic [136] (class III evidence). In all other forms of dementia, tau and p-tau values overlap with normal values in controls as well as the increased values seen in AD. This limits their clinical utility and illustrates that other biomarkers are needed to improve the differential diagnosis of dementia [135].

Alpha-synuclein has been studied as a biomarker for DLB, but results have not been convincing [135]. In NPH, lumbar CSF opening pressure should be within the range 5–18 mmHg (60–240 mmH_2O). Gait improvement following the drainage of 40–50 ml is indicative of NPH, but cannot serve as an exclusionary test because of its low sensitivity of 26–61% [137] (class IV evidence).

Recommendations: CSF analysis

- Routine CSF analysis may help to rule out or rule in certain infectious causes (Good Practice Point) [132]. CSF abeta 1-42/tau/p-tau assessment helps to differentiate AD (Level B) [133]. Assessment of CSF total tau and 14-3-3 protein is recommended in rapidly progressive dementia when sCJD is suspected (Good Practice Point) [135,136].

Genetic testing

The genetics of FTLD dementias is a very young field, and it is likely that additional genes will be identified. Therefore, not finding a mutation does not exclude a genetic cause. There are identical risks for male and female offspring of an affected parent in the familial forms, which are estimated at 30–50% of total FTLD, and currently, changes in five genes have been associated with autosomal-dominant FTLD [10]. Mutations in the microtubule-associated protein tau (*MAPT*) and progranulin (*GRN*) genes on chromosome 17 were identified as important causes of FTLD, explaining 10–25% of familial FTLD patients and 5–10% of all FTLD (class III evidence) [10].

Approximately 10–15% of people with prion disease have a genetic form. Genetic CJD is a single-gene disorder because of mutations in the prion gene (*PRNP*) on chromosome 20. Several other changes in the *PRNP* gene (called polymorphisms) do not cause prion diseases directly, but may affect an individual person's risk of developing prion diseases or alter the course of the disease. Male and female are equally likely to inherit the mutation and to be affected (class III evidence) [138–140]. Cerebral autosomal-dominant arteriopathy with subcortical infarct and leucoencephalopathy (CADASIL) is the most common autosomal-dominant inherited cause of stroke and vascular dementia [141] caused by mutations in the *NOTCH3* gene, which encodes a single-pass transmembrane receptor. Other clinical signs are migraine with aura, mood disturbances and apathy. Genetic testing is indicated if the patient has a combination of characteristic clinical and neuroimaging features or a positive family history, particularly if there is no history of hypertension (class IV evidence). Genetic testing is more debatable if a patient without a family history has only migraine with aura and a few hypersignals on T2-weighted imaging [142] (class IV evidence).

The role of genetics in Huntington's disease is well established, and guidelines for the molecular genetics predictive test in Huntington's disease are available [143,144] (class IV evidence).

Recommendations: genetic testing

- No studies have addressed the value of genetic counselling for patients with dementia or their families when autosomal-dominant disease is suspected. Because the genetics of dementing illnesses is a very young field, expertise in genetic counselling for the dementias of the elderly is likely to be found only in specialized dementia research centres (Good Practice Point) [10,138,144]. 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).

Biopsy and other investigations

Retrospective studies performed in tertiary centres between 1989 and 2009 show that the overall sensitivity of brain biopsy procedures for diagnostic purposes ranges between 57% and 74% [145] (class IV evidence) with the tendency to carry out fewer biopsies with increased diagnostic yield in more recent years. Although information obtained at biopsy determined treatment in only 11% of patients [146] (class IV evidence), it may still provide useful diagnostic information in patients with particularly rapid progressive dementia where a treatable disease cannot be excluded by other means.

Biopsies of specific tissues can also be of diagnostic value, such as a liver biopsy in Wilson's disease or skin and muscle biopsies in cerebral autosomal-dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL), Lafora body disease or mitochondrial diseases (class IV evidence) [50]. Tonsillar biopsy can demonstrate the deposition of the pathological form of prion protein in vCJD (class IV evidence) [50].

Recommendations: biopsy and other investigations

- Brain and other specific tissue biopsies can provide a diagnosis in rare or rapidly progressing dementias, but should only be carried out in specialist centres in carefully selected cases (Good Practice Point) [145,146].

Management of the dementias

Primary and secondary prevention

A number of trials were identified that assessed dementia incidence or cognitive decline as a primary or secondary study outcome [147,148]. Stimulating activity (cognitive, physical and social), vascular risk factors and diet may be important in preventative strategies (class IV evidence) [147,148]. Dementia risk may be modified by participation in stimulating activities (class IV evidence) [147,148]. People with vascular risk factors (hypertension, diabetes, dyslipidaemia and obesity) appear to be at higher risk for dementia than those without in observational and clinical trials [147] (class IV evidence). Controlled trials suggest that vascular risk management via some pharmaceutical interventions may benefit cognition, although results are inconsistent (class IV evidence) [147,148]. Finally, people who adhere to a Mediterranean diet or who have high intake of antioxidants and omega-3 fatty acids have reduced likelihood of dementia in observational studies (class IV evidence) [147,148]. However, supplementation in controlled trials has not generally proved successful at improving cognitive outcomes. Results of randomized controlled trials (RCTs) have so far been negative and conflicting with those of observational studies, perhaps due to methodological issues. Therefore, future trials must carefully consider the target population, outcomes and duration of follow-up to be used and should assess the problem of attrition [148].

Recommendations: primary and secondary prevention

- No treatments or lifestyle have demonstrated efficacy for preventing or delaying the development of the different types of dementias until now.

Treatment of cognitive deficits in non-Alzheimer dementias

With few exceptions, there are no established pharmacological treatments approved by the regulatory agencies for non-Alzheimer dementias. However, as the underlying proteinopathies in the individual neurodegenerative entities are being elucidated, the targeting of pathological protein misfolding has become an attractive goal for future mechanism-based treatments.

Frontotemporal lobar degeneration

There is no approved treatment for any of the FTLD subtypes. One study demonstrated that despite the lack of evidence from randomized, placebo-controlled clinical trials off-label use of established cholinesterase inhibitors (ChEIs) and memantine is common in bvFTD (class III evidence) [149]. There are three notable open-label studies with each of the ChEIs [150–152], and two open-label studies with memantine in FTLD [153]: all failed to provide robust evidence for efficacy in FTLD. A recent systematic review stated that antidepressant treatment significantly improves behavioural symptoms in FTLD, but most studies were small and uncontrolled; serotonergic treatments with SSRIs appeared to provide inconsistent improvement in the behavioural but not cognitive symptoms of FTLD [154,155]. In a small RCT with

trazodone, the cognitive measure MMSE remained unchanged, whilst there was a significant improvement in behavioural symptoms [156]. Dopaminergic replacement in FTLD ameliorates only the motor symptoms with no evident effect on cognition [8]. An RCT with bromocriptine in language variant FTLD patients was negative (class III evidence) [157]. There is no relevant Cochrane review.

Corticobasal syndrome and progressive supranuclear palsy

One open-label study [158] and one RCT [159] in PSP showed no conclusive evidence in favour of donepezil. No evidence exists for CBS.

Huntington's disease

The Cochrane Library review included 22 randomized, double-blinded, placebo-controlled clinical trials with a total of 1254 participants conducted on any symptomatic therapy used for HD and concluded that there were no data for the treatment of cognitive impairment [160]. The Cochrane Library has also reviewed eight studies on 1366 patients with agents with possible disease-modifying properties (i.e. vitamin E, idebenone, baclofen, lamotrigine, creatine, coenzyme Q10+ remacemide, ethyl-eicosapentanoic acid) and found no effect on outcome measures [160].

Dementia associated with Lewy bodies and Parkinson's disease dementia

Whilst patients with DLB respond to cholinesterase inhibitors with improvement in cognitive and psychiatric symptoms, they show a propensity to have exaggerated adverse reactions to neuroleptic drugs, with a significantly increased morbidity and mortality (class IV evidence) [161]. The Cochrane Library review on ChEI treatment in PDD included only the EXPRESS study and concluded that there was evidence that rivastigmine had had a moderate effect on cognition. However, concerns about rivastigmine tolerability were stated [161]. The IDEAL study [162] was a large-scale RCT in patients with AD and showed that the new transdermal patch form of rivastigmine is as efficacious as its conventional capsule form, whilst having a comparable tolerability profile to placebo.

There are three RCTs with memantine. In a small RCT, a significantly smaller proportion of memantine-treated participants deteriorated globally compared with those treated with placebo [163]. In another medium-sized RCT, at the end of the study, the patients in the memantine group had significantly better global scores (class II evidence) [164]. The larger RCT randomized 34 DLB and 62 PDD patients to the memantine arm, and 41 DLB and 58 PDD patients received placebo. Significant benefits were observed for memantine on the global measure for DLB and PDD patients. No statistically significant differences were observed for individual cognitive test (class II evidence) [165]. There are no Cochrane Library reviews on memantine in DLB or PDD yet.

Prion diseases

There are no Cochrane Library reviews. A systematic review [166] found 33 published studies describing the use of 14 drugs, 10 of which had been reported in single studies of three or fewer patients. No specific treatment for prion diseases can be recommended at the present time. A recent observational study with the antimalarial drug Quinacrine [167] showed that it was reasonably tolerated but did not significantly affect the clinical course of prion disease. Further studies are ongoing [168].

Normal-pressure hydrocephalus

NPH may represent a treatable form of dementia; however, it is difficult to decide whether a patient would benefit from a shunting procedure (class III evidence) [169]. Surgery seems to be more helpful in the cases that did not start with dementia, have milder cognitive impairment, no aphasia and short duration, or where a drainage test is positive. Cortical atrophy reduces but does not eliminate the chance of improvement with surgery. Surgical treatment carries considerable short- and long-term risks (class III evidence) [137]. However, there are no class I studies comparing operative versus conservative management of NPH, and therefore surgical treatment cannot be considered as a standard approach. The online 2008 assessment as up to date of the 2002 Cochrane intervention review [169] failed to find randomized controlled trials of shunt placement versus no shunt, thus concluding that there is no evidence to indicate whether placement of a shunt is effective in the management of NPH.

Recommendations: treatment of cognitive deficits in non-Alzheimer dementias

- Use of ChEIs, memantine or SSRIs in any of the FTLD subtypes is possibly ineffective for cognitive improvement (Level C) [149,156]. Dopaminergic replacement with bromocriptine in progressive aphasias is probably ineffective (Good Practice Point) [157]. Given the insufficient classes II and III evidence and the evidence being largely based on class IV, the use of ChEIs and memantine in FTLD cannot be recommended. There is little class III evidence in support of rivastigmine and memantine

[149,156]. There is no independent evidence for recommending any therapeutic intervention for CBS [159,168]. Rivastigmine is the approved ChEI for the treatment of PDD with class I evidence. PDD diagnosis warrants the use of rivastigmine (Good Practice Point) [161]. Parallels with PDD in terms of clinical picture and disease mechanisms suggest that rivastigmine is possibly effective in DLB (Good Practice Point). The evidence for the efficacy of galantamine is insufficient for both PDD and DLB. Memantine is probably effective for both PDD and DLB (Level B) as there were consistently significant improvements in global measures but not in cognitive measures in two class II studies [164,165]. There is insufficient evidence for recommending any specific agent in the treatment of human prion diseases. Surgical treatment can be considered in NPH (Level C), and risk to benefit ratio must be individualized for each patient [137,169]. There is insufficient evidence for recommending any of the non-pharmacological treatments.

Treatments of BPSD

Pharmacological treatments in BPSD should be evidence-based and targeted to specific syndromes that are clinically significant because of their frequency, pervasiveness or impact. Antipsychotic medications, conventional and atypical agents, have been increasingly utilized in clinical practice for aggression, psychosis and agitation (class IV evidence) [170], but only a small number of clinical studies have investigated their relative cost–benefit ratio. Moreover, these benefits have to be considered in the context of significant adverse events, including extrapyramidal symptoms, accelerated cognitive decline, stroke and death [170] (class IV evidence).

For depression in dementia, although there is little placebo-controlled evidence to guide practice, clinical experience indicates that selective serotonin re-uptake inhibitors are safe and effective in treating mood disorders in dementia (class IV evidence) [161].

Cholinesterase inhibitors improve the apathetic syndrome in AD and also may decrease or prevent psychotic symptoms, particularly hallucinations, in AD and DLB.

A variety of non-pharmacological treatments, namely interventions relating to quality of life, motor activity, behaviour, speech and language therapy, cognitive stimulation, have been proposed and are unevenly utilized in different settings in Europe [170]. Some specific behaviour interventions have been found to improve certain troubling behavioural symptoms in dementia, but more evidence is required in this area although there are several methodological difficulties in performing such studies.

Recommendations: treatments of BPSD

- Antipsychotic medications, conventional and atypical agents, may be utilized in clinical practice for aggression, psychosis and agitation as well-selective serotonin re-uptake inhibitors for mood and behavioural disorders (Good Practice Point) [170]; however, there is little evidence to guide practice.

Counselling and support for caregivers

In patients with mild to moderate dementia, the assistance of a caregiver 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 (Good Practice Point) [170].

The caring family members of people suffering from dementia are exposed to a great number of physical, mental and social burdens, and restrictions, putting themselves at risk of falling ill (Good Practice Point). Caring family members need adequate forms of relief to be able to care for the family member at home for as long as possible, and with the best possible physical and psychological status (Good Practice Point) [170]. A systematic literature review shows that a number of different intervention programmes have been described in the literature for caregivers of people with dementia, but the nature of intervention has varied widely. Psycho-educational, relieving, supportive, psychotherapeutic and multimodal offers, as well as counselling and case/care management amongst caring family members all have been shown to have positive effects on burden and satisfaction for caregivers of people with dementia (Good Practice Point) [170]. Further investigations are needed.

Recommendations: counselling and support for caregivers

- A dementia diagnosis mandates an inquiry to the community for available public health care support programmes (Good Practice Point) [170]. Counselling and case/care management amongst caring fam-

ily members have positive effects on burden and satisfaction for caregivers of people with dementia (Good Practice Point).

Decision-making and participating in research

People with dementia often lack mental capacity and subsequently need assistance in their decision-making. Research involving persons affected by dementia can be ethically challenging as the lack of capacity may limit their ability to give free and informed consent. The need to adopt special cautions in research involving individuals with compromised capacity has been highlighted by the most relevant declarations on research ethics, like the Nuremberg Code and the Declaration of Helsinki. There is consensus over the fact that adults who lack capacity should be supported by proxy consent when involved in research (Good Practice Point) [171]. Recently, Gainotti *et al.* [171] have reviewed how legal proxy differs between countries and how they are appointed.

The different ways of obtaining surrogate consent for a subject's participation in research in the EU countries may have an impact on a country's 'attractiveness' for dementia research.

Recommendations: decision-making and participating in research

- Research involving persons affected by dementia needs to adopt special precautions, and there is consensus over the fact that adults who lack capacity should be supported by proxy consent when involved in research (Good Practice Point) [171].

Driving

Driving is a complex activity that always becomes impaired at some point in older adults with degenerative dementia [172]. Neuropsychological tests measure several aspects of cognition and are useful to evaluate elderly drivers with cognitive impairment (class IV evidence) [172]. However, there is no consensus on a standard battery of tests that could accurately predict safe driving. Tests highlighting visuospatial attention demands and executive function may be useful to predict the driving competence of demented individuals. However, all drivers with dementia must ultimately retire from driving when dementia becomes moderately severe, and often in earlier stages of the illness. However, there is a considerable variability across Europe with respect to the national driving regulations for patients with dementia, the assessment of driving capabilities and the confidentiality of medical data with regard to third parties, such as national driving licence authorities.

Recommendations: driving

- Assessment of driving ability should be made after diagnosis with particular attention paid to visuospatial, visuo-perceptual and executive abilities (Good Practice Point). Advice either to allow driving but to review after an interval, to cease driving, or to refer for retesting should be given (Good Practice Point) [172].

Disclosure of conflicts of interest

For the conception and writing of this guideline, no honoraria or any other compensations were received by any of the authors.

The authors report the following financial supports: Hort Jakub has received speaker's honoraria from Pfizer, Elan, Novartis and EFNS. Pasquier Florence has received speaker and consultancy honoraria from Bayer, Lilly, Janssen, Servier; Bogdan Ovidiu Popescu has received speaker's honoraria from Novartis, Glaxo Simth Kline, Pfizer, Boehringer-Ingelheim, Lundbeck and UCB. Rektorova Irena has received speaker's honoraria from Novartis, Glenmark and UCB. Rusina Robert has received speaker's honoraria from Pfizer, Lundbeck and Novartis. Rossor Martin is a member of Servier and Johnson & Johnson Data Monitoring Committees for which UCL receive reimbursement. Sorbi Sandro has received a consultancy honorarium from Bayer and Novartis. Stefanova Elka received speaker's honoraria from Lundbeck, Novartis, Glaxo Simth Kline, Pfizer and Boehringer-Ingeleim. All other authors have nothing to declare.

Abbreviations

ADL, activity of daily living; ACE-R, Addenbrooke's Cognitive Examination Revised; AD, Alzheimer's disease; ADCS, AD Cooperative Study; ADI, Alzheimer Disease International; aMCI, amnestic mild cognitive impairment; BPSD, behavioural and psychological symptoms of dementia; BSE, bovine spongiform encephalopathy; bvFTD, behavioural variant frontotemporal dementia; CAG, adenine–guanosine trinucleotide; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarct and leucoencephalopathy; CAMCOG, Cambridge Cognitive Examination; CDT, clock drawing task; CVLT, California Verbal Learning Test; CBS, corticobasal

syndrome; CBD, corticobasal degeneration; CSF, cerebrospinal fluid; CIND, vascular cognitive impairment no dementia; CJD, Creutzfeldt–Jakob disease; CVD, cerebrovascular disease; DAD, Disability Assessment for Dementia; DLB, dementia with Lewy bodies; DMAS, dementia mood assessment scale; DR, radial diffusivity; DTI, diffusion-tensor imaging; EEG, electroencephalography; FA, fractional anisotropy; FAB, Frontal Assessment Battery; FAQ, Functional Activities Questionnaire; FDG, 2-fluoro-2-deoxy-D-glucose; FLAIR, fluid attenuated inversion recovery; fCJD, familial Creutzfeldt–Jakob disease; FCSRT, Free and Cued Selective Reminding test; FFI, fatal familial insomnia; FTLD, frontemporal lobar degeneration; GDS, geriatric depression scale; *GRN*, progranulin; GSS, Gerstmann–Sträussler–Scheinker disease; HD, Huntington's disease; JHD, juvenile Huntington's disease; IADL, Instrumental Activity of Daily Living; LV, large vessel; LE, limbic encephalitis; *MAPT*, protein tau; MD, mean diffusivity; MDRS, Mattis Dementia Rating Scale; MFS, Middelheim frontality score; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; MSA, multi-system atrophy; NBM, nucleus basalis of Meynert; NINDS, National Institute of Neurological Disorders and Stroke; NINDS/AIREN, National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences; NPH, normal-pressure hydrocephalus; PBAC, Philadelphia Brief Assessment of Cognition; PDD, Parkinson's disease dementia; PDS, Progressive Deterioration Scale; PET, positron emission tomography; PNFA, progressive nonfluent aphasia; PRNP, prion protein gene; PSP, progressive supranuclear palsy; PSP-P, PSP-parkinsonism; RS, Richardson's syndrome; SD, semantic dementia; SV, small vessel; SIVD, subcortical ischaemic vascular disease and dementia; TMT, Trail-Making Test; VaD, vascular dementia; VCI, vascular cognitive impairment; vMCI, vascular mild cognitive impairment; vCJD, new variant CJD; WCST, Wisconsin Card Sorting Test.

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