

# Clinical features and multidisciplinary approaches to dementia care

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**Abstract:** Dementia is a clinical syndrome of widespread progressive deterioration of cognitive abilities and normal daily functioning. These cognitive and behavioral impairments pose considerable challenges to individuals with dementia, along with their family members and caregivers. Four primary dementia classifications have been defined according to clinical and research criteria: 1) Alzheimer's disease; 2) vascular dementias; 3) frontotemporal dementias; and 4) dementia with Lewy bodies/Parkinson's disease dementia. The cumulative efforts of multidisciplinary healthcare teams have advanced our understanding of dementia beyond basic descriptions, towards a more complete elucidation of risk factors, clinical symptoms, and neuropathological correlates. The characterization of disease subtypes has facilitated targeted management strategies, advanced treatments, and symptomatic care for individuals affected by dementia. This review briefly summarizes the current state of knowledge and directions of dementia research and clinical practice. We provide a description of the risk factors, clinical presentation, and differential diagnosis of dementia. A summary of multidisciplinary team approaches to dementia care is outlined, including management strategies for the treatment of cognitive impairments, functional deficits, and behavioral and psychological symptoms of dementia. The needs of individuals with dementia are extensive, often requiring care beyond traditional bounds of medical practice, including pharmacologic and non-pharmacologic management interventions. Finally, advanced research on the early prodromal phase of dementia is reviewed, with a focus on change-point models, trajectories of cognitive change, and threshold models of pathological burden. Future research goals are outlined, with a call to action for social policy initiatives that promote preventive lifestyle behaviors, and healthcare programs that will support the growing number of individuals affected by dementia.

**Keywords:** dementia, Alzheimer's disease, clinical features, multidisciplinary care, BPSD, prodromal dementia

## Introduction

The clinical syndrome of dementia as a progressive deterioration of cognitive abilities and functional impairments has been recognized for over a century; however it has only been understood within the context of its current characterization in the past few decades. In the early 20th century, a shift in the conceptualization of mental illness away from causation towards disease etiology occurred, with dementia being conceived as a direct effect of age-related processes. Alzheimer's disease (AD) as a progressive neurodegenerative disorder did not emerge as a distinct entity until the mid-20th century, which led to the recognition of multiple disease states with unique etiologies. Contemporary dementia research has progressed rapidly on multiple fronts, including epidemiology, pathology, diagnosis, and treatment. As a result, four

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primary dementia groupings have been defined according to clinical and research criteria: 1) Alzheimer's disease (AD; including mixed-AD); 2) vascular dementias (VaD; including large and small vessel disease); 3) frontotemporal dementias (FTD; including Pick's disease, progressive nonfluent aphasia, and semantic dementia); and 4) dementia with Lewy bodies (DLB; including Parkinson's disease dementia [PDD]). The cumulative efforts of multidisciplinary research teams across the world have advanced our understanding of dementia beyond basic descriptions of clinical symptoms and neuropathological correlates, towards a more complete elucidation of risk factors and underlying pathobiological disease mechanisms and, importantly, have led to targeted treatments, management, and care.

The needs of individuals affected by dementia are extensive, and the management of the clinical syndrome is complex, extending beyond traditional bounds of medical practice. Whereas medicine has historically focused on the effects of disease on the patient, dementia care requires a broader focus extending to family members, caregivers, and support networks. This broad-based approach to the care and management of dementia involves consideration of the quality of life for affected individuals to a greater extent than many other disease states. Dementia is characterized by significant impairments in multiple cognitive domains, functioning, and behavior, and places a tremendous burden not only on individuals, but also on society. Early detection and management may prevent overuse of costly healthcare resources and allow affected individuals and caregivers time to prepare for future medical, financial, and emotional challenges. Many of the most effective management approaches are nonpharmacologic, and provided by healthcare professionals from multiple disciplines. We are now entering an era of dementia care that will be based upon the identification of early disease markers and potentially modifiable risk factors, along with the application of novel diagnostic tools, treatment modalities, and care practices.

In this review, we briefly summarize the current state of knowledge and directions of research for dementia epidemiology, its clinical presentation, multidisciplinary approaches to care, treatment options, management challenges, and future research goals.

## Population aging and dementia epidemiology

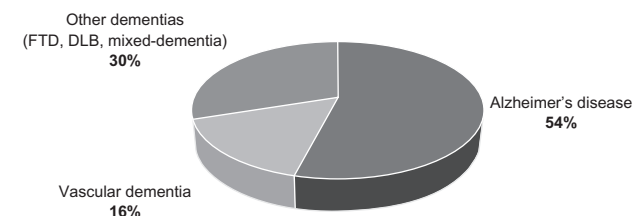
Population aging and increased life expectancy has become a worldwide epidemiological phenomenon. Global projections for the number of older individuals ( $\geq 65$  years) are expected

to increase from 420 million in 2000, to nearly 1 billion by 2030, with a corresponding increase in the proportion of older individuals rising from 7% to 12%.<sup>1,2</sup> Developing countries will see the greatest rise in absolute numbers of older individuals, and will contribute to worldwide population aging with an increase from 59% to 71%.<sup>3</sup> Dementia is strongly associated with increasing age, and consequently neurodegenerative disorders are anticipated to pose significant challenges to public healthcare systems worldwide in the coming decades.

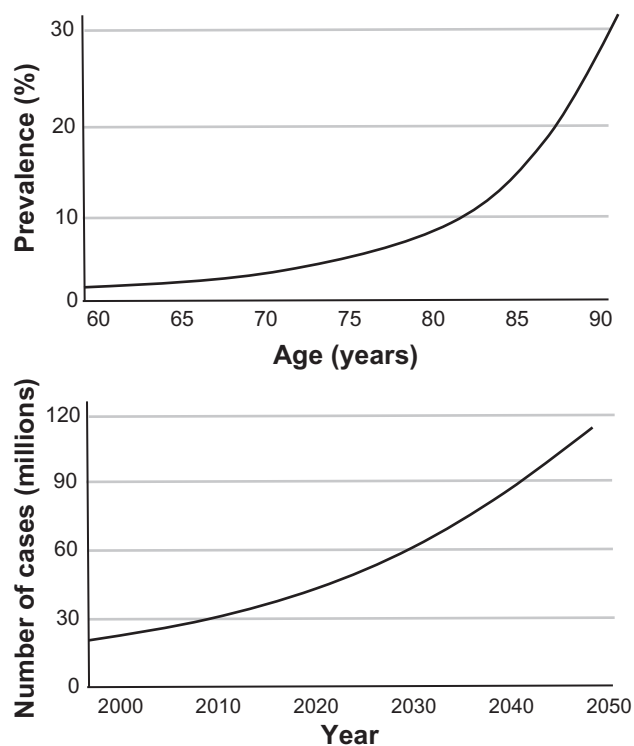
The prevalence of dementia is also rising, particularly AD, which is the most common form of dementia accounting for approximately 60% of all cases.<sup>4,5</sup> Worldwide, the global prevalence of dementia is estimated to be 3.9% in individuals over the age of 60 years, with regional prevalence rates of 1.6% in Africa, 4.0% in China and Western Pacific Regions, 4.6% in Latin America, 5.4% in Western Europe, and 6.4% in North America.<sup>3</sup> Greater than 25 million people in the world are currently affected by dementia syndromes, with most individuals suffering from AD and vascular dementia (VaD) (Figure 1).<sup>4-6</sup> Approximately 5 million new cases are estimated to occur each year, and the number of individuals with dementia is expected to double every 20 years (Figure 2).<sup>2,3,6</sup>

## Risk factors, clinical presentation, and diagnosis of dementia

The clinical syndrome of dementia generally follows three primary expressions.<sup>7-10</sup> First, a neuropsychological component consisting of a range of cognitive impairments, often including: memory impairments (declarative and procedural memory problems), aphasias (either receptive or expressive language difficulties), apraxias (inability to carry out directed coordination of movements despite intact sensory and motor nervous systems), agnosias (inability to recognize specific elements of an individual's environment or self), attentional difficulties (including sustained and divided attention), and executive functioning impairments (including difficulties



**Figure 1** Worldwide subtypes of late onset dementia ( $\geq 65$  years). Copyright © 2007, Elsevier Inc. Adapted with permission from Brookmeyer et al.<sup>6</sup> **Abbreviations:** DLB, dementia with Lewy bodies; FTD, frontotemporal dementias.



**Figure 2** Global prevalence of Alzheimer's disease as a function of age and total number of worldwide cases per year. Copyright © 2006, Lancet Publishing Group. Adapted with permission from Ferri et al.<sup>3</sup>

with abstraction, cognitive flexibility, inhibition, planning, organizing, and adaptation to novel stimuli). The second primary expression of this syndrome is a neuropsychiatric element with associated symptoms and behavioral disturbances. These psychiatric features are present in a substantial proportion of affected individuals, and are commonly referred to as behavioral and psychological symptoms of dementia (BPSD). Common BPSD disturbances include depression, paranoid ideation, delusions, hallucinations, aggression, and wandering.<sup>11</sup> The third primary clinical expression includes deficits in activities of daily living (ADL).<sup>8</sup> In the early stages of dementia, impaired instrumental activities of daily living (IADL) may be manifest including self-neglect of diet, personal hygiene, and common household tasks. Towards the later stages of dementia, basic activities of daily living (BADL) are often impaired, presenting with obvious problems in dressing, eating, and bathing.<sup>12,13</sup>

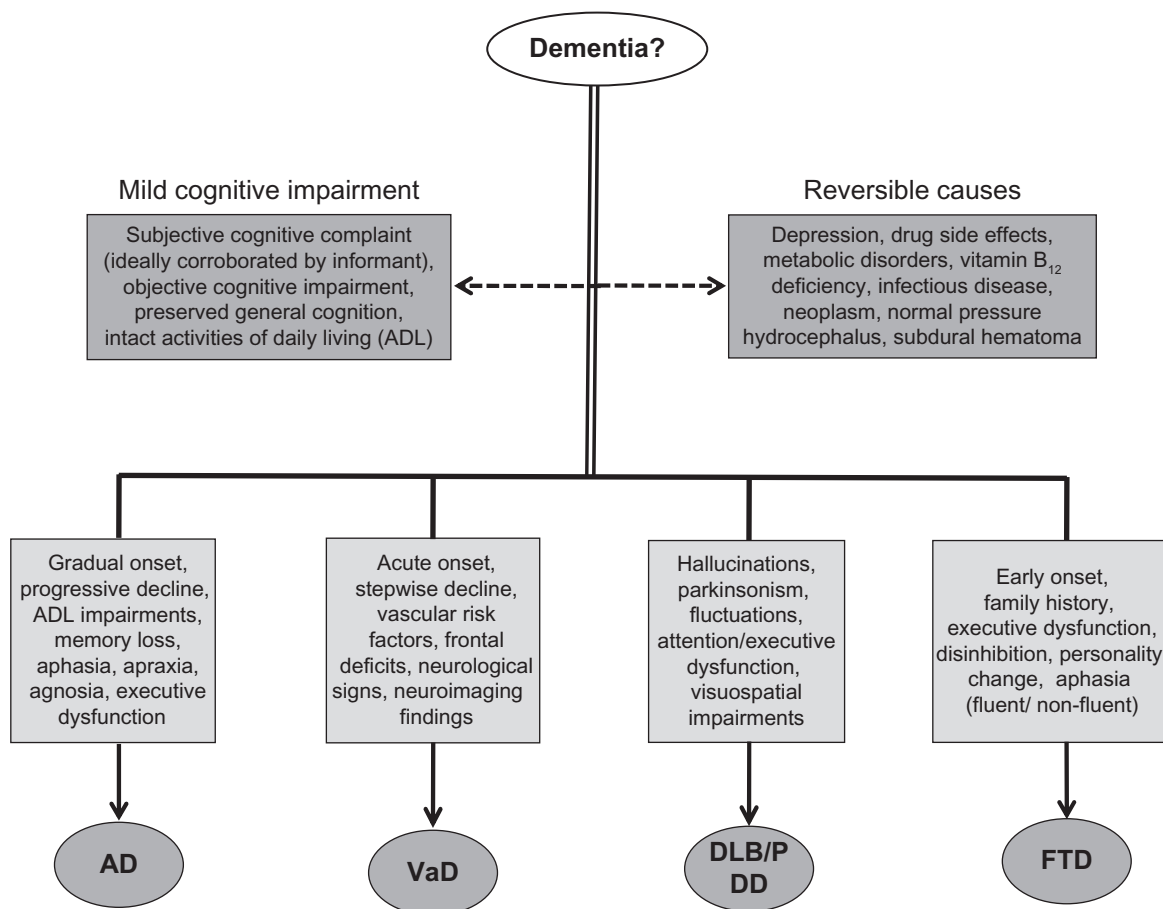
This triad of features is common to most dementias, with the differentiation of subtypes based on clinical presentation, the presence of comorbid symptoms, and other aspects of the individual's history and examination.<sup>7,8,14</sup> Individuals with dementia tend to present to specialist healthcare services (eg, neurologist, neuropsychologist, memory disorders clinic) only when symptoms begin to interfere with everyday activities and

functioning. Depending upon the stage of disease progression, the patient is often unable to provide an accurate history and may deny any presence of impairments. Therefore, a detailed history from a reliable primary informant (eg, family, caregiver) is essential to provide collateral information of previous baseline functioning, symptom onset, and supportive evidence of changes in cognitive and behavioral functioning.<sup>15</sup> Depending on the dementia subtype, there is wide variability in rates of decline from person to person and in the rapidity with which the disease process develops. Nevertheless, all dementias are degenerative and progressive. Early detection and the differential diagnosis of dementia subtype, disease complexity, and sequelae requires skilled clinical judgment and is based on multiple sources of information (see Figure 3).<sup>16</sup>

### Mild cognitive impairment

Clinical AD is often preceded by a prodromal phase commonly referred to as mild cognitive impairment (MCI).<sup>17</sup> Despite several operational definitions, a diagnosis of MCI is generally applied to individuals with a primary complaint and objective demonstration of cognitive impairments in one or more domains (usually memory difficulties), but with relatively preserved ADL.<sup>9,17</sup> Debate continues regarding the most useful way to operationalize the clinical and research criteria for a diagnosis of MCI.<sup>18-24</sup> Most MCI classifications require a subjective memory complaint, informant corroboration of memory difficulties, relatively intact ADL, and normal or mild problems in nonmemory cognitive functioning.<sup>9</sup> More stringent classifications specify unique cutoff points for the severity of memory impairment on standardized neuropsychological tests (eg, performance < 1.5 SD below the mean).<sup>25</sup> The clinical utility of MCI as a diagnostic classification is evidenced by estimates of increased risk for conversion to AD.<sup>24,26,27</sup> While there are considerable individual differences in trajectories of change, in general, individuals with MCI progress to AD at a rate of 10% to 25% per year, compared with healthy elderly controls who progress at a rate of approximately 1% to 2% per year.<sup>9,18,24,28</sup>

Individuals with MCI tend to demonstrate impaired performance on neuropsychological tests of memory.<sup>9</sup> This is in part a reflection of diagnostic criteria such that individuals with mild impairment in other cognitive domains may be missed. The pattern of memory decline observed in MCI appears to reflect a degradation of information in memory storage and retrieval, rather than an impairment of information encoding.<sup>25</sup> The storage deficit is demonstrated in the loss of information over time, with minimal or no improvement in performance when assessed using tests



**Figure 3** Differential diagnostic considerations for dementia.

**Abbreviations:** AD, Alzheimer's disease; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; MCI, mild cognitive impairment; PDD, Parkinson's disease dementia; VaD, vascular dementia.

of recognition. This pattern of decline is generally consistent with that observed for individuals with AD, and is thought to be evidence that MCI is a preclinical stage of AD.

Recent research has revealed early changes associated with MCI including difficulties with executive functioning and increased apathy.<sup>9,29-31</sup> Individuals with MCI have also been found to have difficulties dealing with financial matters, including problems related to cash management and bill payment.<sup>32</sup> Given the overall high level of functioning, individuals with these difficulties tend to remain undetected, thereby making them more vulnerable for potential future decline.<sup>29,31</sup> Therefore, sensitive measures of memory, executive functioning, and personality shifts may help to improve prediction of conversion from MCI to more severe forms of dementia.<sup>9,29,31</sup>

## Alzheimer's disease

### Risk factors

AD is the most common form of dementia, accounting for an estimated two-thirds of dementia cases in individuals

aged 65 years or older.<sup>4,5</sup> Age is the most consistent risk factor for AD, presumably due to lifelong exposure to various forms of neural damage, including minor vascular events, white matter disease, and inflammation.<sup>5,7,10,18</sup> Other potential risk factors include: level of education (higher education potentially conferring increased brain and cognitive reserve), gender (increased risk for female sex), family history of dementia (particularly for first degree relatives), genetic factors (familial forms of AD are associated with mutations in three autosomal dominant genes: presenilin 1 (*PS-1*), presenilin 2 (*PS-2*), and amyloid precursor protein (*APP*), which are thought to work through increased production of A $\beta$  peptides; and polymorphisms of apolipoprotein E, particularly Apo $\epsilon$ 4 which is associated with 2 to 3 times (heterozygotes) and 6 to 8 times (homozygotes) increased risk of developing AD), vascular risk factors (including hypertension, hypercholesterolemia, diabetes mellitus), mood disorders (particularly depression), and psychosocial lifestyle factors

(including reduced intellectual, physical, recreational, and social engagement).<sup>7,33</sup>

### Clinical features

AD presents with an insidious onset and progresses gradually and inexorably.<sup>34</sup> Therefore, identifying specific time points corresponding to initial symptom onset is often difficult.<sup>28</sup> The diverse clinical features of cognitive impairment in AD reflect dysfunction of multiple regions of the cerebral cortex. Memory decline is commonly the presenting complaint in AD, and represents a cardinal feature of the disease. The memory changes associated with AD are characterized as storage deficits, with rapid forgetting and poor delayed memory recall. In mild-AD, core episodic memory impairments are observed, reflecting early medial temporal lobe and limbic involvement.<sup>8,35</sup> For example, AD individuals may have difficulty recalling details of recent events, personal conversations, or specific elements of a task they may be performing (eg, preparing a meal). Often, they will ask the same question multiple times and may deny their repeated line of questioning.<sup>8</sup> Individuals with AD also tend to confabulate and generate inaccurate responses to questions.<sup>36</sup> On neuropsychological tests of word recall, AD patients produce more intrusions of incorrect word responses and inaccurately recognize words as being part of the original list (false positive responses) compared with individuals with other subtypes of dementia.<sup>9</sup> In general, deficits in declarative memory (episodic memory) are prominent at the disease outset, with more severe memory impairments (semantic memory) emerging later in the disease course.<sup>35,37</sup>

Orientation to time and place are also disrupted early in the disease, probably because these abilities require effective learning and encoding of information from recent memory. As the disease progresses, orientation worsens to include problems identifying familiar places, family members, or other people well known to the individual.<sup>9</sup>

Procedural memory may also decline as the disease worsens, resulting in reduced ADL. Problems may include dressing or using common utensils and can be characterized as an ideomotor apraxia. On testing, these maladaptive behaviors are commonly seen when AD individuals use their finger as a toothbrush rather than pantomiming holding the toothbrush as requested.<sup>14</sup>

Language impairment, although generally preserved early in the disease, is also a prominent clinical feature. Initial signs of language dysfunction often include reduced expressive language (conversational output), word-finding difficulties, and limited vocabulary. Category fluency (eg, naming animals or

furniture) tends to be more impaired than semantic fluency (eg, naming words that begin with a particular letter), perhaps because category fluency is dependent on access to temporal-lobe semantic stores.<sup>38,39</sup> As the disease progresses, language difficulties become more pervasive and nonfluent. Spoken language may become less meaningful with an increase in comprehension difficulties, eventually resulting in global aphasia late in the course of illness.<sup>14</sup>

Although memory decline and language impairment are prominent findings in AD, involvement of other cognitive domains is also common. Visuospatial dysfunction may manifest as impaired driving ability, getting lost, and difficulty producing drawings of figures. Problems with mathematical calculations may impair the individual's ability to use money and balance their finances. Executive dysfunction results in deficits in problem solving, abstraction, reasoning, decision making, and judgment, particularly for novel situations. For example, AD individuals often display difficulty executing complex tasks, such as planning a vacation or negotiating a business deal.<sup>8</sup>

In addition to cognitive impairments, behavioral and psychiatric symptoms are common in AD. Depression rates vary by severity and disease stage, and can occur in up to 50% of AD individuals.<sup>40</sup> Early in the disease course, depression may be attributed to awareness of the individual's cognitive changes. In the later stages, features related to apathy may present, but are often confused with depression, particularly by caregivers. Apathy is associated with significant caregiver distress and greater use of healthcare services in AD.<sup>41</sup> Psychosis generally occurs later in the disease course. Delusions are predominantly paranoid in nature, with fears of personal harm or mistreatment, theft of personal property (usually related to financial matters), and marital infidelity. Hallucinations are less common than delusions, and tend to be visual. Other behavioral symptoms include agitation, wandering, and sleep disturbances. The primary treatable behavioral and psychiatric symptoms in AD include psychosis, agitation, depression, anxiety, and insomnia.<sup>42</sup>

### Diagnosis

The diagnosis of AD is based on identification and evaluation of features of the individual's history and clinical exam that are suggestive of the disease, while excluding other causes of dementia through the use of laboratory tests and neuroimaging. The two most commonly used diagnostic criteria for AD are those of the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition Revised (DSM-IV-TR),<sup>43</sup> and those created by the National

Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) joint task force (Table 1).<sup>44</sup> The DSM-IV-TR criteria require an insidious onset with progressive decline of cognitive function that results in impairment of social and occupational functioning, along with memory impairment and at least one other cognitive deficit that cannot be attributed to other psychiatric, neurological, or systemic disease. The NINCDS-ADRDA criteria classify AD according to three levels of diagnostic certainty: *definite*, *probable*, and *possible*. A definite diagnosis of AD is restricted to individuals who meet the clinical criteria for probable AD and have corroborating neuropathological evidence of the disease (by biopsy or autopsy). Probable AD is the most definitive level of diagnostic certainty, without pathological confirmation. Probable AD requires a progressive decline of memory, along with at least one other cognitive domain that is confirmed through clinical examination and neuropsychological testing. The individual must have a preserved level of consciousness, with exclusion of other conditions that may account for the symptoms. Additional features supportive of a probable AD diagnosis include: progressive decline of language functions, praxis, visual recognition, and impaired ADL, with normal results on laboratory tests (eg, cerebrospinal fluid examination), electroencephalogram, and neuroimaging. A diagnosis of possible AD is appropriate when the clinical course of cognitive decline is atypical, when focal neurological findings are present, or when comorbid disorders exist that may account for the dementia-like symptoms. The NINCDS-ADRDA criteria are widely used for research and clinical diagnosis, and have been shown to have a predictive accuracy of up to 90%.<sup>35,45,46</sup>

## Vascular dementia

### Risk factors

VaD is a clinical syndrome of acquired cognitive and functional impairments resulting from the effects of cerebrovascular disease. Due to the multiple etiologies of cerebrovascular disease, VaD can be characterized across a range of neurological and neuropsychological features that vary in presentation by onset (insidious or abrupt) or course (progressive, remitting, or static) of the dementia syndrome.<sup>47</sup> Alternate definitions of VaD and a lack of universally accepted diagnostic criteria make it difficult to accurately estimate global prevalence rates. Nevertheless, general trends have been observed with prevalence estimates of 1% to 4% in individuals over 65 years, and worldwide prevalence rates of 15% to 22%.<sup>5,48</sup> The association of stroke with cognitive impairment and vascular dementia has been demonstrated in a number of epidemiological, clinical, and neuropathologic studies.<sup>49-51</sup> Comorbid disorders leading to hypoxemia (seizures, cardiac arrhythmia) have been shown to be potential risk factors for dementia in stroke patients.<sup>51</sup> Other clinical factors associated with a higher risk of VaD include increasing age, lower education, cortical atrophy, previous vascular events, and atherosclerosis.<sup>50,51</sup> The association between hypertension and cognitive impairment remains a widely investigated area of research. Most longitudinal studies have found a significant association between elevated blood pressure and the occurrence of dementia 10 to 15 years later. In this association, diastolic pressure appears to be of greater importance than systolic pressure.<sup>52</sup> A history of coronary artery disease, myocardial infarction, diabetes mellitus, smoking, and hyperlipidemia are additional risk factors for VaD.<sup>51-53</sup> The underlying mechanism by which cerebrovascular risk factors lead to cognitive impairment

**Table 1** Summary of DSM-IV and National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for the diagnosis of Alzheimer's disease (AD)

DSM-IV criteria	NINCDS-ADRDA criteria
<ul style="list-style-type: none"> <li>• <b>Insidious onset</b> with <b>progressive decline</b> of cognitive function resulting in impairment of social or occupational functioning from a previously higher level</li> <li>• Impairment of <b>recent memory</b> and <b>at least one</b> of the following cognitive domains: <ul style="list-style-type: none"> <li>– Aphasia</li> <li>– Apraxia</li> <li>– Agnosia</li> <li>– Executive functioning (planning, organizing, sequencing, abstraction)</li> </ul> </li> <li>• Cognitive deficits are not due to other neurological, psychiatric, toxic, metabolic, or systemic diseases</li> <li>• Cognitive deficits do not occur in the setting of a delirium</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Probable AD</b> <ul style="list-style-type: none"> <li>– Deficits in two or more domains of cognition</li> <li>– Progressive decline of memory and other cognitive functions</li> <li>– Preserved consciousness</li> <li>– Onset between ages 40 and 90 years</li> <li>– Absence of systemic or other brain disease that could account for symptoms</li> </ul> </li> <li>• <b>Possible AD</b> <ul style="list-style-type: none"> <li>– Atypical onset, presentation, or clinical course of dementia</li> <li>– Presence of another illness capable of producing dementia</li> </ul> </li> <li>• <b>Definite AD</b> <ul style="list-style-type: none"> <li>– Clinical criteria for probable AD</li> <li>– Tissue diagnosis by autopsy or biopsy</li> </ul> </li> </ul>

and dementia remains to be fully elucidated. Most studies suggest that cerebrovascular risk factors are associated with an increased prevalence of cerebral white matter abnormalities, whole brain atrophy, and silent stroke.<sup>54</sup> Associations have also been found between the extent of brain atrophy or white matter hyperintensity volumes and decreased cognitive abilities. Therefore, growing evidence suggests that cerebrovascular disease, even in the absence of clinical symptoms, may lead to subsequent cognitive impairment.<sup>55–57</sup>

### Clinical features

Vascular dementia is a diagnostic classification used to describe a constellation of clinical features, including cognitive and functional impairments.<sup>58</sup> Three vascular syndromes are commonly cited in the literature: multi-infarct dementia, strategic single infarct dementia, and small vessel disease with dementia.

Multi-infarct dementia (also known as post-stroke dementia) is the most common form of vascular dementia.<sup>59</sup> It is attributable to multiple infarcts with occlusion, usually in large vessels, that cause cortical and subcortical infarcts. Occlusion of these arteries occurs as a result of atherosclerotic thrombosis or cardiac embolization, and typically has an abrupt onset with stepwise progression. Multi-infarct dementia is characterized by variable impairment across several cognitive domains.<sup>60</sup> Individuals may present with severe deficits in certain domains, while other cognitive abilities may be spared and remain relatively intact. With recurrent stroke episodes, greater areas of cognitive functioning become impaired and the dementia syndrome emerges. VaD individuals often present with lateralized sensorimotor changes, including hemiparesis, hemisensory loss, visual field disturbances, and pathological reflex asymmetries. Agnosia and apraxia may also be part of the clinical features in multi-infarct dementia.<sup>60</sup>

In strategic single infarct dementia, ischemic damage is focal and involves functionally important cortical and subcortical regions including the thalamus, basal ganglia, angular gyrus, and frontal white matter.<sup>54</sup> For example, an infarct in the angular gyrus may result in clinical features such as fluent aphasia, alexia with agraphia, and spatial disorientation. Single lesions in the carotid, anterior, middle, and posterior cerebral arteries are known to give rise to clinical dementia symptoms with a number of neurological and neurobehavioral features.<sup>51</sup> Clinical evidence of stroke may or may not be present, but the onset of dementia is generally abrupt with a stepwise decline in cognitive functioning.

Small vessel disease with dementia refers to a syndrome in which occlusion of small vessels causes lesions of subcortical structures, including the thalamus, basal ganglia, internal capsule, and sub-hemispheric white matter. Disruption of these structures results in a form of subcortical dementia. This state is characterized by insidious onset of symptoms including psychomotor slowing, memory impairments, changes in speed, and neuropsychiatric features such as depression and apathy. Neurological features include parkinsonism, ataxia, and urinary incontinence.<sup>61</sup> Individuals with small vessel disease with dementia often present with slow, progressive, dementia-like features, often without clinical symptoms of stroke. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is thought to be the hallmark disease associated with this clinical syndrome.<sup>62</sup>

### Diagnosis

Several clinical criteria currently exist for the diagnosis of VaD dementia. The Hachinski Ischemic Scale (HIS) is a commonly used set of criteria for VaD that is easily applied in clinical practice.<sup>63</sup> The HIS is based on 13 features used to obtain a total ischemic score. The current modified HIS emphasizes a subset of clinical symptoms as a means of distinguishing VaD from AD.<sup>64</sup> The general features of the scale include: abrupt onset, prior history of stroke, focal neurological signs, focal neurological symptoms, stepwise deterioration, somatic complaints, emotional ability, and history of hypertension. Despite a sensitivity and specificity of 70% to 80% in separating VaD from AD, the HIS is limited in its clinical use by not integrating neuroimaging information into the diagnostic process. The DSM-IV-TR approach utilizes clinical evidence of stroke-based signs from the neurological examination or neuroimaging evidence for infarcts as the primary basis for a diagnosis of VaD.<sup>43</sup> These criteria do not require that the dementia be temporally associated with the occurrence of stroke, which in effect decreases its specificity and clinical utility. Another definition of VaD is based on the World Health Organization's International Statistical Classification of Diseases, 10th Revision (ICD-10), which requires a temporal link between a stroke event and dementia, along with signs of stroke on neurological examination or imaging evidence of an infarct.<sup>65</sup> A final diagnostic classification for VaD is based on the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Neurosciences (NINDS-AIREN). These criteria are the most widely used for VaD in clinical trials research and

emphasize the heterogeneity of vascular syndromes and white matter lesions. The NINDS-AIREN criteria require neuroimaging evidence of lesions in key areas involved in VaD (frontal, temporal, or parietal cortex, thalamus, basal ganglia), along with critical abnormal white matter signals (>25% of total white matter volume).<sup>47</sup>

## Frontotemporal dementia

The clinical and pathological understanding of frontotemporal dementia (FTD) has undergone considerable changes in the past decade. Frontotemporal lobar degeneration (FTLD) is a descriptive term that encompasses a variety of clinical syndromes associated with nonAlzheimer pathology and arises from degeneration of the anterior hemispheres.<sup>66</sup> This heterogeneous group of clinical syndromes includes frontotemporal dementia (FTD), FTD with motor neuron disease (FTD/MND), progressive nonfluent aphasia (PNFA), semantic dementia (SD), and progressive apraxia.<sup>66</sup> The most commonly occurring syndrome is frontotemporal dementia (FTD) which is characterized by profound alterations in personality and behavior, and is associated with bilateral atrophy of the frontal and anterior temporal lobes.<sup>67</sup> Panels of expert international working groups have developed a number of clinical diagnostic criteria for FTD.<sup>67-69</sup> The characteristic feature of FTD is a slowly progressive dementia that presents with either predominant behavioral or language disturbances (Table 2).<sup>70</sup> FTD tends to have a younger age of onset than other dementias, typically between

45 to 65 years, and approximately 20% to 30% of cases are familial and may be associated with mutations in the progranulin or *MAPT* gene.<sup>71</sup> Prevalence studies of FTD are variable, with estimates ranging between 3.6 to 15.0 per 100,000 individuals.<sup>72</sup>

Of the two FTD clinical presentations, the more common form is that of a behavioral disturbance, which is associated with profound changes in personality. Typical behavioral changes include apathy, lack of initiation, disinhibition (verbal, physical, and sexual disinhibition), perseveration, tactlessness, lack of social graces, emotional blunting, and loss of insight. FTD individuals tend to be unaware of or unconcerned about the social, occupational, and financial consequences of their behavioral changes.<sup>73</sup> Cognitive deficits tend to occur in the domains of attention, abstraction, shifting, planning and problem solving, reflecting an executive dysfunction.<sup>9</sup>

The less common presentation of FTD is that of a progressive and relatively isolated language disturbance. This language presentation can either be that of a difficulty with expression and naming, suggestive of a primary progressive aphasia (usually a nonfluent aphasia), or that of difficulty with word meaning, consistent with a semantic dementia.<sup>68</sup> Progressive nonfluent aphasia presents with a gradual disturbance of expressive language with effortful speech production, phonological and grammatical errors, and word retrieval difficulties, ultimately followed by later mutism. Reading and writing can also be impaired. Other cognitive functions are usually spared and these individuals have relatively preserved social skills early in the disease.<sup>9</sup> Semantic dementia presents with progressive impairment of comprehension of words and naming in the context of fluent, effortless and grammatically correct speech output. Memory functions are relatively preserved, along with word repetition, reading skills, and mathematical abilities.<sup>9</sup>

The different clinical presentations of FTD are thought to be associated with the initial focal pattern of cortical atrophy of the frontal lobes. However, as the disease progresses a more global pattern of cognitive impairment emerges.<sup>68</sup> On examination, early signs include the presence of a grasp, snout, or palmomental reflex. Further, disinhibition and perseverative behaviors are often observed. The presence of additional neurologic abnormalities may suggest early motor neuron disease (MND) or parkinsonism. There are no widely accepted bedside cognitive or behavioral tests for FTD, and measures of global cognition like the Mini-Mental State Examination (MMSE) are insensitive to change in behavior,

**Table 2** Common clinical presentations of frontotemporal dementia

Presentation	Clinical features
<b>Behavioral</b>	<ul style="list-style-type: none"> <li>• Impulsive behaviors and disinhibition (eg, inappropriate sexual behaviors)</li> <li>• Change in personality (eg, indifference, apathy, mental inflexibility)</li> <li>• Poor judgment and poor insight into consequences of behaviors (eg, financial risk taking)</li> <li>• Repetitive, compulsive, stereotypic behaviors (eg, hyperorality)</li> <li>• Loss of personal hygiene (eg, wearing same clothes for multiple consecutive days)</li> <li>• Loss of social graces/insight (eg, making jokes during a funeral)</li> </ul>
<b>Language</b>	<ul style="list-style-type: none"> <li>• Non-fluent aphasia → with anomia, agrammatism, phonemic paraphrasias, impaired word repetition, alexia, agraphia</li> <li>• Fluent-aphasia → with early loss of word meaning (ie, empty speech), poor comprehension, semantic paraphrasias, prosopagnosia, associative agnosia</li> </ul>

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aphasia detection, and evaluation of executive function. If FTD is suspected, a more extensive neuropsychological battery should be administered and the individual should be monitored closely.

## Dementia with Lewy bodies

Dementia with Lewy bodies (DLB) usually presents in older adulthood between the ages of 60 and 90 years. The epidemiology of DLB remains to be fully elucidated along with potential risk factors for the disease, but to date no significant gender or ethnic differences in prevalence have been identified.<sup>74</sup> DLB is a neurodegenerative disorder, thus progressive and functionally disabling cognitive impairment is a central feature. Individuals with DLB exhibit a combination of cortical and subcortical impairments with significant attentional deficits and executive and visuospatial dysfunction.<sup>9</sup> Compared to AD, there may be relative sparing of memory functions especially in the early stages of DLB.<sup>75</sup> A recent international consortium has resulted in revised criteria for the clinical diagnosis of DLB, incorporating new information about the core clinical features of the disease. These core features include fluctuating cognition, recurrent visual hallucinations, and spontaneous parkinsonism.<sup>76</sup>

Fluctuations in cognitive function with pronounced variations in attention and alertness can be difficult to evaluate and operationalize, but corroborative reports from primary caregivers can help to clarify these essential clinical features (eg, daytime drowsiness, prolonged staring spells, periods of marked confusion, disorganized speech).<sup>76</sup> Cognitive fluctuations are reported across varying time periods, but generally take place for a minimum of 30 minutes and can last as long as several days.<sup>9</sup>

Visual hallucinations in DLB tend to be recurrent, vivid, and well-formed. The hallucinations tend to emerge early in the disease course, and are therefore a useful diagnostic feature. The content of the hallucinations usually consist of humans or animals, but can be more abstract in nature. Visual illusions and delusions, which typically have a paranoid quality, are also commonly observed. Auditory, tactile, or olfactory hallucinations are rare. Functional neuroimaging studies have demonstrated altered patterns of activation in the visual cortex, along with increased number of Lewy bodies in the anterior and medial temporal lobe of individuals with DLB who report hallucinations.<sup>77</sup> Other common neuropsychiatric features include depression, apathy, and anxiety. Agitation and aggressive behavior tend to occur late in the course of the disease.

Extrapyramidal signs, including bradykinesia, facial masking, and rigidity, are the most frequent signs of parkinsonism in DLB. Resting tremor is distinctly uncommon, and parkinsonism is usually bilateral and occurs with the onset of dementia. There is often more axial rigidity and facial masking in DLB than is typically seen in idiopathic Parkinson's disease.<sup>76</sup>

An important suggestive clinical feature of DLB includes rapid eye movement (REM) sleep behavioral disturbances. Affected individuals often act out their dreams by screaming and kicking, which can cause injuries to themselves and those around them. The dreams tend to have a chasing or attacking theme, and their content usually matches the exhibited behavior. REM sleep behavior disturbances often begin years before the onset of other cognitive or motor symptoms.<sup>78</sup>

Other suggestive features of DLB include severe neuroleptic sensitivity, and low dopamine transporter uptake in the basal ganglia on functional neuroimaging. Additional supportive features that commonly occur in DLB include repeated falls and syncope, transient, unexplained loss of consciousness, severe autonomic dysfunction, hallucinations in other modalities, systematized delusions, relative preservation of medial temporal lobe structures on structural neuroimaging, reduced occipital activity on functional neuroimaging, prominent slow wave activity on electroencephalogram, and low uptake myocardial scintigraphy.<sup>76</sup>

## Multidisciplinary team approach to dementia care

An integrated multidisciplinary approach to diagnosing and managing dementia is highly recommended in clinical practice because no single healthcare specialty has the expertise to deal with the complex range of cognitive, physical, social, and emotional problems associated with dementia. Managing dementia presents unique challenges to the practicing clinician, and effective care hinges on a collaborative team approach. This approach relies less on standard pharmacologically based medical practice, and more on the integration of therapies from a wide range of healthcare providers and community professionals. To implement this approach effectively, the clinician must understand the disease processes involved and the clinical presentation of dementia, and also appreciate the caregiving experience and how it affects patient care. The clinician must be informed about the resources available to meet the medical, social, and emotional needs of the patient in the context of their family and community. Using a multidisciplinary team approach can be complex,

but it benefits both the patient and the clinician. It allows clinicians to focus on the issues most relevant to their area of expertise, and it facilitates management of patient problems that are likely to require valuable healthcare resources.<sup>15</sup>

## Multidisciplinary team structure

The best approach to the care of individuals affected by dementia includes support from multiple sources. These may be integrated, parallel, or a combination of both. It is ideal for patients and caregivers to seek a blend of multidisciplinary services that come from various healthcare providers, social service agencies, and professionals from outside the field of healthcare. Multidisciplinary teams vary in their composition and may be structured either formally or informally. Team construction is usually dictated by resources, including time, availability, finances, and geographic location. Regardless of structure, successful teams are characterized by a shared commitment to quality care and an appreciation for the contributions of each team member.<sup>79,80</sup>

Multidisciplinary teams involved in dementia care tend to be based primarily on the availability of service resources, in addition to the social and cultural context of the community. Team members often include neurologists, geriatricians, neuropsychologists, nurse practitioners, physical/occupational therapists, nutritionists, and social workers.<sup>15</sup>

The neurologist or geriatrician's primary responsibility is the diagnosis of dementia using validated criteria and practice guidelines. Following diagnosis, a prognosis is determined and a treatment plan is formulated to address the disease and underlying symptoms.<sup>15</sup> When diagnostic uncertainty exists, referral to a subspecialist may be useful to refine the diagnosis and help develop a plan of care. Dementia subspecialists may include behavioral neurologists, geriatric psychiatrists, or neuropsychologists. The role of a neuropsychologist is to interpret quantitative cognitive performance data based on the results of psychometric testing. Many neuropsychologists also provide ongoing therapy and support to the dementia patient, and their family members.<sup>9</sup>

The nurse's primary role is to assess and manage the dementia patient and their caregivers' responses to the disease process. This includes monitoring symptom presentation, responding to medication issues, providing education and relevant information to family members, and assisting them in preparing for disease progression. Dementia frequently results in immobility, decreased physical conditioning, loss of muscle strength and tone, and poor coordination. Impaired ambulation is common and increases the risk of falls and injury. Physical therapists can assist dementia patients

to optimize their physical conditioning and maintain safe mobility, helping to prolong independent living and the need for institutionalization.<sup>81</sup>

Another important factor in maintaining the dementia patient's home independence is their ability to manage ADL. Occupational therapists help the patient and their caregivers to adapt to the patient's diminished ability to deal with challenges faced in daily living. Use of devices to assist with toileting, eating, dressing, and home management can be recommended and demonstrated by an occupational therapist. As patient independence is enhanced, caregiver burden decreases.<sup>82</sup> Cognitive impairment related to dementia also places the patient at increased risk for malnutrition and dehydration. In later, more severe stages of dementia, the patient often experiences sensory-motor impairments with ensuing loss of ability to swallow or eat independently. Weight loss then becomes a significant concern as the disease progresses. Comorbid conditions common to older individuals such as diabetes and coronary heart disease also make dietary management more challenging. Dietary intake also extends beyond medical concerns, and becomes an important quality of life consideration.<sup>83</sup>

Social workers base their practice on the philosophy that the individual is part of a larger system, and they are prepared to assist the patient and their family in identifying and acquiring the resources needed to manage the burden of chronic illness.<sup>84</sup> In nearly all cases, patients with dementia and their caregivers will require access to social services including community programming, respite care, financial services, counseling support groups, and crisis management. Therefore, it is often recommended that a referral to a social worker be initiated at the time of formal diagnosis of dementia.<sup>15</sup> As the disease progresses, increasing levels of support will be required. The social worker is able to help anticipate future needs, facilitate the acquisition of services, and navigate the patient and their caregivers through the extended healthcare system. For individuals with dementia, the home environment has been found to promote a sense of personhood, normalcy and continuity in the face of disconnection that is often experienced as a result of multiple losses in functional, cognitive, and social domains of their lives.<sup>85</sup> Consequently, 'aging in place' is considered to be the preferred choice for many older adults to help maintain independence.<sup>86,87</sup> However, individuals with dementia often require care within a structured, institutionalized environment. Caregivers' reasons for placement into institutionalized care are diverse and often include: 1) the need for more skilled care and more assistance, 2) the caregivers' health,

3) the presence of behavioral and psychological symptoms of dementia, 4) caregiver burden, and 5) use of community-based services.<sup>88</sup> Given the practical and emotional challenges involved in transitioning from a home environment to an institutionalized care facility, the social worker can help guide the dementia patient and their family members through this difficult process.

## Managing and treating dementia

Current clinical practice encourages open discussion of the diagnosis of dementia with patients and their caregivers to facilitate early implementation of treatment strategies, and to allow families to plan for the future. An integrated approach involving both pharmacological and psychosocial strategies is essential for effective care and management. This approach often includes community support services, professional groups and associations, specialized dementia clinics, and geriatric outreach services.

## Pharmacologic treatment of dementia

Two classes of drugs are currently approved for the symptomatic treatment of dementia: acetylcholinesterase inhibitors (AChEI) and *N*-methyl-D-aspartic acid (NMDA) receptor antagonists (Table 3). These pharmacologic treatments do not target the underlying pathogenesis of dementia, but rather help to improve or maintain function following neuronal damage.<sup>89</sup>

The development of AChEIs emerged from a pathophysiologic model of AD known as the *amyloid cascade hypothesis*. In this model, it is proposed that accumulation of A $\beta$  in the brain is the primary force driving AD pathogenesis, with the rest of the disease process resulting from an imbalance between A $\beta$  production and clearance. Within the cascade, a dysregulation in amyloid precursor

protein (APP) processing by  $\beta$ - and  $\gamma$ -secretases initiates the pathogenic events leading to aggregation of A $\beta$ , specifically A $\beta$ 42, an insoluble fragment that deposits in plaques. The formation of these amyloid plaques further instigates pathological events, including the formation of neurofibrillary tangles (NFTs) from hyperphosphorylation of the tau protein, disruption of synaptic connections, reduction in neurotransmitters, death of tangle-bearing neurons, harmful oxidative processes, damaging inflammatory responses, and the eventual emergence of the clinical symptoms of dementia.<sup>90</sup> Although the amyloid cascade hypothesis has gained wide acceptance in the field of dementia research, it remains controversial. Emerging evidence shows that many other neuropathological processes may be involved, including the theory that the central mechanism is the hyperphosphorylation of the tau protein. More recent data from multidisciplinary research has suggested the importance of vascular risk factors (eg, smoking, obesity, hypercholesterolemia) and vascular morbidity (eg, hypertension, diabetes, silent brain infarcts, and white matter lesions) in the pathology of dementia.<sup>5,91,92</sup>

## Pharmacotherapy for AD

There are four currently approved AChEIs for the treatment of AD: tacrine, donepezil, rivastigmine, and galantamine. All of these drugs are approved for mild to moderate AD, with the exception of donepezil, which is approved for mild to severe AD.<sup>89</sup> Head-to-head clinic trials comparing the effectiveness of each of the AChEIs are rare, thus making it difficult to determine which is best for the treatment of patients with AD. Tacrine has an inconvenient dosing schedule (four doses daily), and significant side effects (hepatotoxicity), and is rarely used in current clinical practice.<sup>91</sup> The other three AChEIs appear to be relatively equivalent in terms of efficacy and are associated with symptomatic improvement in cognitive function in patients with mild to moderate AD. Improvement generally lasts for 6 to 12 months, followed by a gradual decline in most, but not all, cases.<sup>89</sup>

There is some controversy on the duration of use of AChEIs in the treatment of patients with AD. Some clinicians feel that once a patient has reached the stage of severe AD, AChEI use should be discontinued. Others feel that AChEIs may still be useful for managing symptoms in severe AD, but this remains an active and open area of clinical investigation. Despite this controversy, AChEIs represent the primary form of treatment for AD.

Memantine is currently the only NMDA antagonist approved to treat AD. The rationale behind the use of

**Table 3** Pharmacologic treatments for dementia

Drug name	Mechanism	Daily dosage	Side effects
Donepezil	AChE inhibitor	5–10 mg	Nausea, vomiting, diarrhea, vivid dreams, leg cramps
Rivastigmine	AChE inhibitor	3–12 mg	Nausea, vomiting, diarrhea, weight loss, anorexia
Galantamine	AChE inhibitor	8–12 mg	Nausea, vomiting, diarrhea, weight loss, anorexia
Memantine	NMDA receptor antagonist	10–20 mg	Hallucinations, confusion

**Abbreviations:** AChE, acetylcholinesterase; NMDA, *N*-methyl-D-aspartic acid.

memantine is the glutamatergic excitotoxicity theory, which stipulates that an abnormal and sustained increase in glutamate may lead to neuronal degeneration. Memantine, an NMDA receptor, is a low-to-moderate uncompetitive antagonist that blocks glutamate binding to its receptor, thereby decreasing neuronal excitotoxicity and slowing the progression of AD.<sup>93</sup> Memantine has been approved for the treatment of all stages of AD, but in clinical practice is generally used in moderate-to-severe AD. Administered twice daily, compliance is a common issue with memantine, as it is difficult for patients with AD to maintain their dosage schedule. Memantine is a symptomatic treatment for AD, and has been shown to improve cognitive function and slow the rate of decline in moderate-to-severe cases. The duration and extent of cognitive efficacy is approximately 6 months, and may be greater.<sup>94</sup> Additional studies are needed to determine whether the efficacy of memantine in patients with moderate-to-severe AD extends beyond 6 months.

### Pharmacotherapy for non-AD dementias

Vascular dementia can be treated by the use of donepezil, rivastigmine, and galantamine in patients with probable and possible VaD.<sup>47</sup> Several clinical trials have shown that anti-hypertensive therapy can help to prevent the onset of VaD in certain individuals.<sup>95</sup>

DLB is a form of dementia that is not easily treated through the use of pharmacotherapy. Rivastigmine has shown some improvement in DLB patients, and low-dose clonazepam has been used for sleep disturbances. Psychostimulants, including levodopa and dopamine agonists, have been shown to improve cognition, apathy, and psychomotor slowing. Management of cognitive fluctuations in DLB has been difficult. Atypical neuroleptics have also been reported to be helpful for symptoms of delusions and agitation, and selective serotonin reuptake inhibitors (SSRIs) can be effective for the treatment of depression and anxiety in DLB patients.<sup>96</sup>

Frontotemporal dementia is another challenging form of the disease where management and treatment strategies have been inconsistent and disappointing to date. Few large-scale, clinical trials for the treatment of FTD have been conducted, although several smaller trials have been carried out. In these studies, rivastigmine and SSRIs have been shown to improve behavioral symptoms of FTD, but cognitive improvement has been limited.<sup>97,98</sup>

### Goals of pharmacotherapy for dementia

At the initiation of pharmacologic treatment for dementia, the goals of therapy should be clearly established with the

patient and their caregivers. AChEIs and memantine are not as effective as drug medications for other medical conditions, and it is important to clarify that they do not alter the eventual course of the disease. The treatment options available mainly stabilize the patient, delaying subsequent decline, with some individuals experiencing transient symptomatic improvements. Clinicians must set realistic goals that take into account the modest benefits that can be expected in various cognitive, behavioral, emotional, and functional domains.

## Nonpharmacologic treatment of dementia

Over the past 3 decades, interest has grown in the use of non-pharmacologic treatment approaches, alone or in combination with pharmacotherapy, for the treatment and management of dementia. Several therapies have been suggested including cognitive-based therapies, psychosocial therapies, physical therapies, and sensorial therapies. These strategies may be implemented in a variety of settings (home, institutional care facility) and treatment modalities (individual or group-based therapy). The clinical efficacy of nonpharmacologic treatments remains to be fully evaluated, but it is understood that the primary goal of these approaches is to improve the quality of life for individuals with dementia.

### Cognitive-based interventions

Cognitive interventions for dementia rely on the plasticity hypothesis, which theorizes that the brain is able to achieve neural and functional improvements by reorganizing its constituent elements and internal network connectivity according to environmental constraints.<sup>99</sup>

Cognitive training and cognitive rehabilitation are the two most commonly applied nonpharmacologic strategies to implement in the early stages of dementia. These interventions involve targeted practice and training of specific cognitive domains, with a primary emphasis on memory, attention, and executive functions. Cognitive rehabilitation differs from cognitive training in that it is a more individualized therapeutic approach, and its goals are to enhance functioning in everyday life, rather than improve performance on cognitive tasks. A recent Cochrane review examined the efficacy of cognitive training and rehabilitation in patients with early stage AD and VaD in five domains from nine randomized controlled trials including participant scores on cognitive screening measures, neuropsychological tests, self-reported functioning, informant ratings of functioning, and reactions to memory impairments and behavioral difficulties. While some positive results were found in specific cognitive

domains, overall improvements were limited and there were no significant differences between cognitive training and control groups.<sup>100</sup>

### Psychosocial therapies

Psychosocial therapy is an intervention that is intended to enhance self-esteem, well-being, social and communication skills, and to decrease behavioral disturbances.

Reminiscence therapy is a common psychosocial intervention in dementia care. Initially introduced in the 1980s, this approach is based on evocation and discussion between the dementia patient and trusted individuals to think about and revisit past events, experiences, and activities. It often involves the use of objects and supports (eg, photos, personal belongings, music) to help trigger specific memories. Very few randomized controlled trials have assessed reminiscence strategies in dementia. A recent Cochrane meta-analysis concluded that reminiscence therapy resulted in significant improvements in behavioral functioning, as well as cognitive and depressive symptoms, compared with no-treatment and social-contact control groups, with sustained effects 4 to 6 weeks after cessation of the intervention.<sup>101</sup>

Validation therapy is another form of psychosocial intervention for the treatment of dementia. The goal of validation therapy is to promote and stimulate communication skills in the dementia patient, and to provide the individual with insight into their external reality. A recent Cochrane review found little evidence supporting this form of intervention, but noted that the limited information from randomized controlled trials is insufficient to draw reliable conclusions about the efficacy of validation therapy in dementia.<sup>102</sup>

### Physical activity therapy

Physical activity can be used as a therapeutic approach in a wide range of target populations including healthy aging adults and individuals with dementia. The benefits of physical activity have been demonstrated in terms of mood, quality of life, falls, cardiovascular function, and disability rates.<sup>103–106</sup> Regular exercise can also slow down or help prevent functional decline associated with aging, improve muscle mass, arterial compliance, energy metabolism, cardiovascular fitness, and overall functional capacity.<sup>107</sup>

An individual's overall physical fitness is composed of several components including cardiorespiratory and muscular fitness, flexibility, and balance. Cardiorespiratory fitness, also known as aerobic training, is a condition in which the cardiovascular and respiratory systems function together to ensure that adequate oxygen is supplied to working muscles

to produce energy. A high level of cardiorespiratory fitness permits continuous physical activity without a decline in performance and allows for rapid recovery. It is also believed that cardiovascular fitness can improve cognitive capacities. Animal research has demonstrated beneficial effects of aerobic physical activity on cognition, through physiological processes involved in increased cerebral blood flow, oxygen extraction, and glucose utilization.<sup>108</sup> It has therefore been suggested that physical activity may act as a protective factor for cognitive decline in older adults.<sup>109</sup>

A recent Cochrane review examined the effects of physical activity (aerobic exercise training or physical activity of any length of time) on cognition, function, and behavior in individuals with dementia. The review also evaluated caregiver outcomes and healthcare service use. No significant results were observed but numerous methodological factors limited the potential findings of the meta-analysis.<sup>110</sup> More studies with homogeneous populations, in terms of dementia subtype and severity, are required to fully investigate the role of physical activity in dementia. Moreover, several key questions about physical activity remain to be clarified, including how long the effects of exercise last after cessation of training, and how much exercise is required to exert a beneficial effect.

## Managing and treating BPSD

BPSD occur in individuals with any of the dementia subtypes and include a heterogeneous range of psychological reactions, psychiatric symptoms, and behavioral disturbances. BPSD can cause serious complications often leading to increased emergency department visits, caregiver distress and illness, increased financial costs to society, early institutionalization, and diminished quality of life.<sup>12,13,81,111,112</sup> Therefore, effective management of BPSD in dementia is an important treatment consideration.

BPSD can generally be separated into behavioral excesses, wherein the occurrence of the behavior is problematic (eg, physical and verbal aggression, agitation, anxiety, disinhibition, depression, aberrant motor behavior, irritability, hallucinations, and delusions) and behavior deficits, wherein the nonoccurrence of the behavior causes the complications and challenges (eg, apathy leading to withdrawal from social interactions, cessation of self-care including eating and dressing, and sleep disturbances (Table 4)).<sup>11,113,114</sup> The most frequently occurring BPSD are apathy, depression, and anxiety.<sup>115,116</sup> BPSD can occur at any stage along the dementia continuum, but certain symptoms have been found to be more common in mild dementia (eg, depression, anxiety,

**Table 4** Neuropsychiatric features of behavioral and psychological symptoms of dementia

Presentation	Clinical features
Behavioral and psychological excess	<p><b>Aggression:</b> aggressive resistance, verbal or physical aggression</p> <p><b>Agitation:</b> aimless walking, pacing, trailing, restlessness, repetitive actions, sleep disturbances</p> <p><b>Psychosis:</b> hallucinations, delusions, misidentification</p>
Behavioral and psychological deficits	<p><b>Depression:</b> sad, tearful, hopeless, low self-esteem, anxiety, guilt</p> <p><b>Apathy:</b> withdrawal, lack of motivation, loss of interest</p>

irritability, and apathy), while others occur more frequently in later stages of the disease process (eg, aberrant vocalizations, delusions, hallucinations, and disinhibition).<sup>117–119</sup> Agitation and aggression are among the most challenging BPSD for caregivers, and along with psychosis and depression are the leading predictors of institutionalization.<sup>120</sup> When present, inappropriate sexual behaviors have been rated by caregivers as the most difficult symptom of BPSD to manage.<sup>121,122</sup>

A variety of biological, psychosocial, and environmental factors have been proposed to explain the development of BPSD. Psychosocial models of BPSD include: Need-Driven Dementia Compromised Model, Progressively Lowered Stress Threshold Model, and the Biopsychosocial Model of Dementia.

### Need-Driven Dementia Compromised Model

Within the context of the Need-Driven Dementia Compromised Model, BPSD is considered to be the most integrated and meaningful response possible by an individual with dementia to their environment.<sup>123</sup> According to Algate, BPSD arise due to the pursuit of a goal or as an expression of a need by the individual with dementia. It is also suggested that the presence, severity, and type of BPSD is a reflection of the interaction between salient background factors which are somewhat stable individual characteristics (eg, gender, personality type, general health), and proximal factors which are more fluid or fluctuating aspects of the immediate physical and social environment, as well as the dynamic or changing needs and internal states of the person with dementia (eg, temperature, excessive noise, hunger, fear). Seen this way, the Need-Driven Dementia Compromised Model defines BPSD as meaningful and potentially useful behaviors that can direct and inform appropriate caregiver responses. The primary goal is therefore not to eliminate

the behaviors completely, but rather to understand them and enable caregivers to more readily and accurately meet the needs of the person with dementia.<sup>123</sup>

### Progressively Lowered Stress Threshold Model

The Progressively Lowered Stress Threshold Model posits that persons with dementia are increasingly less able to manage stress as the disease progresses.<sup>124</sup> This reduction in their capacity to tolerate stress results in anxious behaviors as an attempt to alleviate perceived stress. According to Hall and Buckwalter, BPSD (referred to as catastrophic reactions) occur if the stress is unrelieved through either adaptation of the environment or appropriate responses from caregivers or both.<sup>124</sup>

### Biopsychosocial model of dementia

The biopsychosocial model of dementia is a theoretical framework developed to illustrate the role of psychosocial factors within the context of biological processes and to increase understanding of the factors that may lead to improvement or deterioration in dementia.<sup>125</sup> This model suggests that in both biological and psychosocial domains there are fixed factors, which are not amenable to change (eg, age, education, gender, personality traits), and tractable factors, which are more flexible and adaptive (eg, pain, physical and social environment, level of physical and social activity). The trajectory of dementia is presented as a process, beginning with aging, early organic change, initial cognitive impairments, formal diagnosis of dementia, and then moves progressively towards dependency, institutionalization, end of life care, and eventual death. In the biopsychosocial model, the fixed and the tractable factors will simultaneously influence the point at which the symptoms of dementia begin, the nature and speed of the deterioration, and the effectiveness and appropriateness of interventions used by caregivers to assist persons with dementia. The primary aim of this model is to increase caregivers' ability to identify ways to improve the quality of life and reduce excess disability (often by reducing BPSD) for the person with dementia.<sup>125</sup>

### Environmental factors

Environmental factors that have been found to contribute to the development of BPSD can be divided into two subgroups: the physical environment (eg, architectural features, interior design features, and sensory attributes such as lighting and noise levels) and the social environment (eg, optimizing the mix of residents, social stimulation, and sensory stimulation). Physical environmental factors that are precursors to BPSD include inadequate lighting, confusing surroundings,

excessive noise/stimulation, and poorly designed care environments.<sup>120,126</sup> Social environmental factors that have been found to contribute to the presence of BPSD include a lack of daily routine, excessive demands from caregivers, distressing behavior of others, loneliness/boredom, and social isolation.<sup>120</sup>

## Person-centered care for BPSD

Many management and treatment interventions for BPSD are underpinned by a person-centered care approach. An important aspect of the person-centered approach is the therapeutic benefit of positive interpersonal interactions. The conditions that influence positive change include having a therapist who provides unconditional positive regard, is empathetic, and is genuine or congruent within the client–therapist relationship.<sup>127</sup> This person-centered approach has been adopted and applied to dementia individuals in long-term care settings.<sup>128</sup> It involves recognizing and identifying the personal preferences and needs of dementia patients as a way to guide caregiving, thus enabling the individualization of care plans and routines. Additionally, a central feature of person-centered care is the recognition that all human life is grounded in relationships, and that individuals with dementia need an enriched social environment that fosters opportunities for personal growth while compensating for their cognitive and functional impairments.<sup>128,129</sup>

The key elements of person-centered care include 1) knowing the person as an individual; 2) providing care that is meaningful to the person in ways that respect their values, preferences, and needs; 3) viewing patients as biopsychosocial beings; 4) enabling the development of consistent and trusting caregiving relationships; 5) emphasizing freedom of choice and individually defined risk taking; 6) promoting emotional and physical comfort; and 7) involving patients' family, friends, and social networks in care decisions.<sup>129</sup>

Findings from empirical studies demonstrate that the application of person-centered care results in reduced neuroleptic medication use and agitation.<sup>130,131</sup> Despite the widespread recognition and application of person-centered care for individuals with dementia, many studies to date are conceptual or anecdotal, highlighting the need for more research on this treatment approach.<sup>132</sup>

## Nonpharmacological treatments for BPSD

Nonpharmacological treatments for BPSD can be grouped into two categories: 1) indirect interventions aimed at decreasing BPSD through indirect work with caregivers or

the environment, and 2) direct interventions targeted directly at individuals to decrease BPSD.

## Indirect interventions

### Caregiver training

The aim of caregiver training is to increase formal and informal caregiver understanding of BPSD, and improve skills in managing and responding to problem behaviors. Education and training programs have been found to be effective in the reduction of BPSD in both nursing home environments, and the community.<sup>133,134</sup> Multidisciplinary team approaches and individualized treatment plans developed according to the unique needs of the individual with dementia, combined with caregiver problem-solving techniques are key features of successful education and training interventions.<sup>135,136</sup>

### Environmental adaptations

When BPSD appear to be triggered by environmental factors, interventions aimed at modifying the individual's environment may be the most effective means to address the behaviors. Key environmental features include: 1) architectural elements, such as room layout and size (eg, smaller social spaces); 2) interior design features, such as furniture type and arrangement (eg, homelike furnishing, familiar objects, and personalized rooms); and 3) sensory attributes (eg, noise, lighting, and visual accessibility). Adaptations of these environmental features have been found to reduce anxiety, increase a sense of emotional well-being, and enhance social interaction for individuals with dementia.<sup>126,132,137–139</sup>

## Direct interventions

### Sensory therapy

Various sensory-based therapies have been developed for use with dementia populations, including music therapy, light therapy, and Snoezelen therapy. Music therapy is defined as the use of music or musical elements (voice, sound, rhythm) by a qualified music therapist. This nonpharmacologic approach is believed to promote nonverbal communication, relationships, learning, expression, and to improve emotional, social, and cognitive functioning through increased quality of life. Music therapy can be applied on an individual or group level, and may be active or receptive. Several randomized controlled trials of music therapy in dementia have recently been conducted, and significant positive effects have been found in the reduction of BPSD. Specific improvements were found on indices of anxiety and depression for up to 8 weeks after discontinuation of music therapy.<sup>140–142</sup> Background music has also been shown to be effective in reducing agitation.<sup>143,144</sup>

The complexity of BPSD in dementia suggests that a multi-factorial and integrated approach is required for appropriate intervention and management. Approaches that do not take into consideration the complex biological, psychosocial, psychological, and environmental factors will likely produce results that are sporadic, inconsistent and short lived. Consequently, a comprehensive and integrated approach, which addresses the needs of the individual with dementia, the caregivers, and the physical and psychosocial environment is highly recommended.

## Empirical research on dementia: toward facilitating early detection of those at risk

Considerable effort has been devoted to better understanding change in cognitive functioning during the prodromal phase of dementia.<sup>145</sup> This research focus is well intentioned given the protracted nature of neuropathological change in dementia, coupled with the fact that *effective* treatment pharmacotherapy remains elusive.<sup>146</sup> Ultimately, the success of potential interventions will be further augmented through the early detection of those at risk. In this spirit, we briefly summarize some recent empirical findings of preclinical cognitive deficits in AD, and discuss some potentially fruitful avenues for future research.

## Characterizing cognitive decline during the prodromal phase of dementia

A recent meta-analysis examined 47 studies comprising more than 1200 AD cases and 9000 controls.<sup>147</sup> Among the primary foci, the meta-analysis examined preclinical AD impairment across multiple cognitive domains, as well as the moderating impact of the length of the prodromal period on the magnitude of the preclinical AD effect. Consistent with expectation, larger prodromal deficits were observed for studies characterized by a time interval of less than 3 years between cognitive assessment and clinical diagnosis, relative to studies with average follow-up periods greater than 3 years. For example, episodic memory differences between cases and controls were characterized by a large effect (1.12 SD units) within 3 years of diagnosis, but a moderate effect (0.76 units) for studies with follow-up intervals greater than 3 years between testing and diagnosis. Another critical finding from the meta-analysis concerned the pattern of deficits as a function of cognitive domain. Consistent with the etiology of AD, large magnitude deficits in episodic memory were observed for AD cases relative to controls.

Large-magnitude cognitive deficits were also observed, however, for measures of executive functioning, processing speed, and global cognition, consistent with the notion that deficits in multiple cognitive domains characterize the prodromal phase of dementia.

On the surface, detecting such large-magnitude deficits would represent seemingly positive news vis-à-vis early detection of those at risk of dementia. However, despite the large magnitude differences in mean performance across multiple cognitive outcomes, considerable overlap (>40%) remained across performance distributions for the preclinical AD vs nondemented groups, with this overlap severely impairing task sensitivity for detecting those at risk of dementing.<sup>147</sup> Further to the point, it is arguably unrealistic to expect nonoverlapping distributions of cognitive performance many years before diagnosis given the large interindividual variability in both preclinical AD cases, and those who will remain without dementia.<sup>148–150</sup> Numerous factors can result in cognitive impairment with increasing age, leading to false-positive detection including psychiatric, metabolic, immunological, and circulatory conditions.<sup>151–154</sup> Moreover, some individuals who will convert to dementia show accelerated decline only in close proximity to diagnosis, leading to false negatives.<sup>149</sup>

## Change-point models of onset and rate of cognitive decline before dementia diagnosis

Given the problem of overlapping distributions for groups of preclinical AD and nondemented controls, an obvious question concerns what can be done to improve classification of those at risk? Based on recent findings from our research group, we argue that facilitating early disease identification and targeting successful intervention requires moving beyond static mean-difference comparisons at one point in time to consideration of the relative onset and rate of cognitive decline across a continuum of cognitive measures.<sup>155</sup> To examine these issues, Thorvaldsson and colleagues employed data from two population-based Swedish longitudinal studies of aging.<sup>155</sup> Participants from the age-heterogeneous Kungsholmen Project (Stockholm, Sweden) were aged 75 years or older and completed up to 5 measurement occasions (417 dementia cases and 249 non-cases). The Gerontological and Geriatric Population Studies (Gothenburg, Sweden) included participants who were all initially 70 years of age and who were followed for up to 13 retest occasions spanning 30 years (113 dementia cases and 272 noncases). A series of linear mixed change-point models (see Hall, Lipton, Sliwinski, and Stewart, 2000<sup>156</sup>) were fit



to numerous cognitive outcomes. These piecewise models estimated two slopes, permitting the knot of the spline (the change point) to vary across models in 1-month increments. Prior to the knot, time was parameterized as a function of chronological age (years since birth from each individual measurement). In contrast, following the knot, time was specified as a function of time to dementia diagnosis (years to diagnosis from each individual measurement). A profile likelihood method was then employed to select the best fitting change point spanning a range from 1 month to 10 years prior to diagnosis (eg, 3.1 years before diagnosis, 3.2 years before diagnosis, 3.3 years before diagnosis). These systematic model fit comparisons facilitated the identification of the average transition point that best differentiated between normative age-related cognitive decline and accelerated decline during the preclinical phase.

Thorvaldsson et al reported that the earliest preclinical deficits, around 9 years before diagnosis, were observed for cognitive correlates of dementia pathology (episodic memory) as well as more executively demanding tasks (eg, visuospatial ability, processing speed).<sup>155</sup> Notably, however, as nondemented elderly individuals also exhibited decline on these tasks, the relative magnitude of cognitive changes for the preclinical cases was only modestly incremented. Consistent with expectation, tasks that exhibited the earliest onset of cognitive decline did not also exhibit the fastest rate of change. Rather, the most precipitous estimates of decline were observed for tasks that are at least somewhat resistant to age-related decline such as category fluency – a knowledge-based task that incorporates both fluid and crystallized abilities. Such patterns suggest that tasks incorporating both fluid and well-preserved crystallized abilities may facilitate discrimination between preclinical cases vs noncases, but only in close proximity to incident diagnosis.

## Onset versus rate of change

In light of these findings underscoring that onset and rate of change in the prodromal period vary as a function of cognitive domain, another critical question concerns which characteristic to focus on for increasing sensitivity of detecting those at risk of dementing. As with most questions, the answer depends on whether an individual's emphasis concerns clinical practice or basic research. A general practitioner interested in the health of an individual patient should place more emphasis on early detection, and thus differentially focus on onset. Based on our findings, this would mean targeting early behavioral changes in process-based measures of cognition

(eg, episodic memory) that exhibit impairments up to 10 or more years prior to diagnosis. Of course, clinical detection of such onset in change requires knowledge of baseline performance and repeated within-person assessments, and even then may prove difficult to detect as normative age-related changes are also typically observed for these same measures. In the Thorvaldsson et al study, for example, episodic memory decline in the prodromal phase was only accelerated by a factor of 2 relative to decline observed during normal aging.<sup>155</sup>

In contrast, those focusing on more basic research (eg, targeting individuals at greatest-risk of converting to AD for use in clinical trials research, identifying candidates for aggressive pharmacological intervention) may differentially focus on accelerated rate of change (rather than onset) for select cognitive domains. In particular, our findings suggest that verbal fluency may be a particularly important measure for increasing sensitivity of detection for those at risk of dementing. Verbal fluency shows very little age-related change, but when change is finally manifest during the prodromal period within 6 years of diagnosis, performance decline accelerates by a factor of 5 or more relative to normal aging. Indeed, clinical trials research might consider adopting a *multivariate* approach where at-risk participants are selected on the basis of both onset (individuals exhibit early change in episodic memory consistent with AD etiology) as well as change (individuals with episodic deficit who also show accelerated decline in verbal fluency); such an approach is likely to improve sensitivity of identifying those at greatest risk of converting.

## Preclinical cognitive deficits and threshold models

Fundamental tenets of threshold models of cognitive impairment are consistent with both the Thorvaldsson et al findings, demonstrating inflection points that differentiate between normative age-related cognitive decline vs more accelerated decline during the prodromal period in proximity to diagnosis, and the Bäckman et al meta-analysis demonstrating that cognitive function is more strongly affected in proximity to diagnosis.<sup>147,155</sup> Further, the concepts of cognitive reserve as well as compression of morbidity are both consistent with initial trajectories of change that are gradual, followed by more pronounced cognitive decline in proximity to diagnosis.<sup>157–159</sup> For example, Stern's notion of cognitive reserve was developed to facilitate explanation on the modest association between the amount of underlying AD pathology and observed behavioral deficit.<sup>159</sup> Cognitive reserve is said

to reflect the amount of neuropathology that can be accrued prior to reaching a critical threshold beyond which cognitive deficits are manifest.<sup>159</sup> Educational attainment in particular has been viewed as an index of cognitive reserve, with recent findings clearly demonstrating the aforementioned threshold effects. Hall et al, for example, showed that those with more years of education (12+) did not exhibit cognitive decline onset until close proximity to dementia diagnosis relative to a low-educated group (less than 7 years) who would subsequently dement.<sup>157</sup> However, upon reaching their threshold for pathology burden, the rate of cognitive impairment was steeper for the high-educated group. Thus, later disease onset appears to be associated with greater disease burden, manifest as accelerated cognitive loss (ie, steeper prodromal slopes) once decline occurs.

## Future research

In light of the meta-analytic findings by Bäckman et al, it is apparent that prospective identification is not facilitated through solitary use of cognitive measures that exhibit large mean differences between dementia cases and controls years before diagnosis.<sup>147</sup> This is because the distributions between the two groups still overlap to a large extent (>40%) for individual cognitive domains such as episodic memory or executive functioning. To increase sensitivity of early detection, Small et al suggest that future research incorporates the following improvements.<sup>145</sup> First, these authors emphasize that multifactorial prediction models are required to improve early detection. Evidence suggests that early detection is improved considerably upon inclusion not only of episodic memory tasks, but also indicators of executive functioning and semantic memory.<sup>160,161</sup> Next, in service of better differentiating between cases and controls, future research should also supplement such cognitive markers with other markers linked to dementia incidence. These multivariate models and their corresponding interactions could include biomarkers such as brain volumetrics, amyloid deposition, and white-matter alterations, as well as genetic markers, subjective memory complaints, social isolation, and lifestyle factors such as lack of intellectual engagement or low physical activity levels.<sup>149,162–169</sup> A key challenge for future research will be to ascertain whether specific combinations of these biological, social, cognitive, genetic, and clinical markers increase identification of those at risk of dementia. To the extent that protective characteristics (eg, high education, active lifestyle) mask the early signs of AD and delay the clinical onset, effective multivariate (multistage) approaches for facilitating detection will be essential given

the reduced time window between onset of preclinical decline and subsequent diagnosis.<sup>170</sup> However, an alternate view is that delaying the clinical manifestation of AD by just 2 years could significantly reduce the total number of AD cases as well as helping to lower healthcare costs.<sup>171</sup> This latter view underscores the critical need to identify sensitive early indicators of those at risk, and then to target interventions such as health or behavior promotion strategies (eg, physical or cognitive lifestyle interventions), which may successfully delay (or prevent) onset of dementia. Finally, given the importance of understanding the natural history of AD progression, more sophisticated longitudinal designs should be adopted for the study of cognitive change during the preclinical period through to dementia onset. In particular, including multiple measurement occasions before diagnosis is required to better identify the onset of cognitive decline during the prodromal period, as well as to quantify the magnitude of acceleration. Multiwave datasets and linear mixed models may also identify whether select dementia correlates increase or decrease in importance in proximity to diagnosis.<sup>145</sup> Such differentiation may help differentiate between disease risk factors vs precipitating factors.

## Summary: toward a paradigm shift in dementia care for the 21st century

The preceding review highlights the many advances over the past few decades that aid our understanding of dementia epidemiology and its clinical presentation. It outlines various multidisciplinary treatments, including pharmacological and nonpharmacological treatment, and addresses significant management challenges. Demographic projections underscore the potential burden that the various dementias pose for healthcare in the coming 20 years. Dementia prevalence will continue to increase in concert with increased life expectancy and improved medical care. Unequivocally, clear advances have been made in dementia diagnosis, identification of associated risk factors, as well as management and care. However, effective pharmacological treatments that target the underlying neuropathology and alter the disease course remain elusive.

At least in the near term, we can argue that dementia is as much about social policy and governance as it is about medicine or neuropsychology. Given the progressive nature of the disease, it will be necessary to target preventive as opposed to reactive interventions. Improved policy initiatives should target public education documenting specific risk factors for dementia from early- and mid-life, as well as lifestyle interventions (eg, health or behavior promotion strategies)

that can potentially delay or prevent the disease. In the United States, for example, delaying the clinical manifestation of dementia by 2 years would reduce the total number of AD cases by approximately 600,000.<sup>171</sup> Based on increasing prevalence projections in Canada, the Alzheimer Society of Canada (2010) *Rising Tide* report projects the total economic burden of dementia to double each decade, increasing from approximately \$15 billion (CAD) per year in 2008 to \$153 billion (CAD) per year by 2038.<sup>172</sup> Clearly, delaying the onset of dementia by even several years would have considerable impact on both disease prevalence as well as associated healthcare expenditures. To realize such benefits, policy makers should place continued emphasis on dementia research, as well as renewed focus on public education initiatives (eg, increased as opposed to decreased emphasis on physical education programs in primary and secondary school) that promote protective and enduring lifestyle behaviors.

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