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Dementia of the Alzheimer Type

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Dementia of the Alzheimer type is a progressive, fatal neurodegenerative condition characterized by deterioration in cognition and memory, progressive impairment in the ability to carry out activities of daily living, and a number of neuropsychiatric symptoms. This narrative review summarizes the literature regarding descriptive epidemiology, clinical course, and characteristic neuropathological changes of dementia of the Alzheimer type. Although there are no definitive imaging or laboratory tests, except for brain biopsy, for diagnosis, brief screening instruments and neuropsychiatric test batteries used to assess the disease are discussed. Insufficient evidence exists for the use of biomarkers in clinical practice for diagnosis or disease management, but promising discoveries are summarized. Optimal treatment requires both nonpharmacological and pharmacological interventions, yet none have been shown to modify the disease's clinical course. This review describes the current available options and summarizes promising new avenues for treatment. Issues related to the care of persons with dementia of the Alzheimer type, including caregiver burden, long-term care, and the proliferation of dementia special care units, are discussed. Although advances have been made, more research is needed to address the gaps in our understanding of the disease.

Alzheimer disease; dementia; drug therapy; review

Abbreviations: APOE, apolipoprotein E; DAT, dementia of the Alzheimer type; DSM-IV-TR, *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition text revision; MMSE, Mini-Mental State Examination; NINCDS/ADRDA, National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association.

INTRODUCTION

Dementia of the Alzheimer type (DAT) is a progressive, fatal neurodegenerative condition characterized by deterioration in cognition and memory, progressive impairment in the ability to carry out activities of daily living, and a number of neuropsychiatric and behavioral symptoms (1). DAT is the most common form of dementia among elderly persons and accounts for approximately two thirds of cases of dementia and between 60 percent and 70 percent of cases of progressive cognitive impairment in older adults (2, 3). The prevalence of DAT is expected to increase as the population ages (1).

In 2000, approximately 4.5 million people in the United States were living with DAT; by 2050, more than 13 million older Americans are projected to be afflicted with the condition if current trends persist and no preventive treatments become available (4). The cognitive, behavioral, and functional decline in patients with DAT places a considerable burden on the health care system and caregivers (5). DAT is therefore a growing medical, social, and economic problem.

Despite the urgency of the situation, many questions remain unanswered in DAT research. For instance, although advanced age, female gender, carrying the apolipoprotein E (APOE) *ε4* allele, current smoking, family history of DAT or other dementia, fewer years of formal education, lower income, and lower occupational status have been associated with an increased risk of developing the condition, the pathogenesis of Alzheimer's disease is still largely unknown (6–8). Although progress is being made in developing new therapies for DAT, no therapeutic interventions to cure or substantially modify disease progression currently exist.

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This review provides an update on the current state of knowledge on DAT. With a focus on findings generated from studies conducted in the United States, it describes the epidemiology of DAT, its characteristic clinical course, neuropsychiatric symptoms, factors associated with accelerated cognitive decline, characteristic neuropathological changes of Alzheimer's disease, diagnostic tools to assess DAT, and biomarkers and neuroimaging, and it provides an overview of pharmacological and nonpharmacological treatments. We also summarize the ramifications of DAT for caregivers and discuss long-term care.

DEFINITIONS

The following definitions were adapted from the position statement of the American Association for Geriatric Psychiatry (9):

Dementia is a clinical syndrome characterized by global cognitive decline with memory and one other area of cognition affected that interfere significantly with the person's ability to perform the tasks of daily life and meet the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition text revision (DSM-IV-TR) criteria.

Dementia resulting from Alzheimer's disease or DAT is characterized by decline primarily in cortical aspects of cognition (i.e., memory, language, praxis) and follows a characteristic time course of gradual onset and progression.

Alzheimer's disease is a specific degenerative brain disease characterized by senile plaques, neuritic tangles, and progressive loss of neurons, the presumptive cause of Alzheimer's disease.

GLOBAL INCIDENCE AND PREVALENCE OF DAT

Data documenting the incidence of DAT indicate that it is a global problem that will become more severe as the population ages. Table 1 summarizes population-based studies estimating the incidence and prevalence of DAT. Studies from different parts of the world (North America, Europe, Asia, and Africa) were selected if they were population based and large. The estimates from the Delphi Consensus Study are for dementia rather than DAT but were included because prevalence/incidence estimates were generated from a systematic review of population-based studies. Regardless of country of origin, age-specific incidence rates of DAT increase exponentially with advancing age. In the United States, the incidence rate of DAT is 1 per 1,000 person-years among individuals aged 60–64 years and 25 per 1,000 person-years among those older than age 85 years (10). Although DAT is not a normal part of the aging process, the prevalence of DAT also increases with advancing age. While less than 1 percent of individuals aged 60–64 years are deemed to be affected, it is estimated that up to 40 percent of those over the age of 85 years have the condition (11). Similar trends were observed in a population-based European study of persons aged 65 years or older. The age-standardized prevalence of DAT was 4.4 percent, and the prevalence increased with age (0.6 percent for those aged 65–69 years; 22.2 percent for those aged 90 years or older) (12).

In the United States, 12 percent of the population is at least 65 years of age (13). By 2020, 16 percent of the population will be 65 years of age or older, and adults over 80 years of age are expected to account for 3.7 percent of the population (14, 15). Growth will occur in all racial and ethnic groups (4). By 2050, the number of persons with DAT is expected to increase to 13.2 million, and it is estimated that more than 8.0 million cases will be older than age 85 years (4).

NEUROPSYCHIATRIC SYMPTOMS

Patients with DAT are likely to exhibit neuropsychiatric symptoms, also commonly referred to in the literature as behavioral and psychological symptoms of dementia, such as aggression/agitation, depression, apathy, anxiety, delusions, and hallucinations at some point during the course of the illness. Neuropsychiatric symptoms are common in all stages of dementia with prevalence estimates between 60 percent and 80 percent, depending on whether patients are community dwelling or institutionalized, and a lifetime risk of nearly 100 percent (16–20). The prevalence of neuropsychiatric symptoms in persons with DAT or dementia is greater than the background prevalence in the general population (16, 17, 21–24). Those symptoms most commonly seen in patients with DAT or dementia are apathy, depression, anxiety, aggression/agitation, and psychosis (delusions and hallucinations). The prevalence of apathy ranges from 20 percent to 51 percent and the 5-year prevalence is estimated as 71 percent (16, 18, 21, 23); the respective prevalences are 15–54 percent and 77 percent for depression (16, 18, 21, 22, 24–27) and 10–59 percent and 62 percent for anxiety (16, 18, 21, 23, 28). The prevalence estimates for aggression/agitation and psychosis range from 13 percent to 30 percent and from 12 percent to 74 percent, respectively (16, 18, 21, 29, 30). The considerable variation in the prevalence estimates results from the different operational definitions of dementia and neuropsychiatric symptoms, the different types of dementia studied, and the heterogeneity of the study populations. Other less-common and less-studied neuropsychiatric symptoms include irritability, elation, disinhibition, wandering, and aberrant motor behavior.

Neuropsychiatric symptoms in DAT may be better captured by grouping individual symptoms into various clusters (20, 31–34). The motivation behind identifying symptom clusters is that they may form syndromes, with each DAT–neuropsychiatric symptom subtype having a different prevalence and time course as well as distinct biologic correlates and psychosocial determinants (32). If neuropsychiatric symptom clusters reflect differences in brain regions affected by the disease, pharmacological and nonpharmacological treatment opportunities could be optimized (20, 32). Neuropsychiatric symptoms in DAT may be classified into three groups: an affective syndrome, a psychotic syndrome, and other neuropsychiatric disturbances (20). Diagnostic criteria for DAT-associated affective disorder and DAT-associated psychotic disorder have been proposed (34). Other neuropsychiatric symptom classification systems, all of which have identified clusters of mood or psychotic neuropsychiatric symptoms, have also been advanced (17, 35–39).

NEUROPATHOLOGICAL FEATURES OF ALZHEIMER'S DISEASE

Alzheimer's disease can be definitively diagnosed only at brain autopsy or biopsy, when neuritic plaques reach a certain number in the most severely affected regions of the neocortex (40, 41). More stringent research criteria require the presence of neuritic plaques and neurofibrillary tangles in the neocortex (42–44).

Neuritic plaques consist of a central core of beta-amyloid peptides clumped together with fibrils of beta-amyloid, dystrophic neurites, reactive astrocytes, phagocytic cells, and other proteins and protein fragments derived from degenerating cells or liberated from neurons (45, 46). The accumulation of beta-amyloid seen in Alzheimer's disease brains may be the result of faulty beta-amyloid clearance (47), cleaving of the amyloid precursor protein by enzymes to yield free beta-amyloid peptides (48), or overproduction of beta-amyloid peptides caused by mutations in the amyloid precursor protein or the presenilins (49–54) or in the presence of the *APOE ε4* genotype (55, 56). Beta-amyloid fibrils aggregate and neuritic plaques form, triggering a locally induced, non-immune-mediated, chronic inflammatory response involving microglial cell activation and stimulation of a cerebral acute-phase reaction (57) (figure 1). Activated microglial cells release potentially neurotoxic proinflammatory cytokines (e.g., interleukin-6), reactive oxygen and nitrogen species, and proteolytic enzymes that may exacerbate neuronal damage (58, 59). Beta-amyloid fibrils also appear to exert direct neurotoxic effects (60–62).

Oxidative stress resulting from free radical damage may also be caused when soluble, aggregated amyloid fibrils are inserted into neuronal membranes, inducing lipid perioxidation, protein oxidation, and formation of reactive oxygen and nitrogen species (63). APOE may, in *ε4* allele carriers, exacerbate oxidative stress through its association with the catabolism of polyunsaturated fatty acids (63). Oxidative stress results in loss of cell potential, accumulation of excitotoxic molecules, and decreased neuronal viability (61).

Healthy neurons have microtubules stabilized by the *tau* protein; in Alzheimer's disease, this protein is hyperphosphorylated and aggregates as paired helical filaments, causing the dissociation of microtubules and the formation of neurofibrillary tangles that result in neurotransmitter deficits and neuronal cell death (45, 64–66). Beta-amyloid deposits may accelerate the formation of neurofibrillary tangles in brain areas associated with Alzheimer's disease (67, 68). Declining cholinergic function (69–71), reductions in synaptic density (71, 72), and the loss of neurons (71, 73–75) are also consistent features of Alzheimer's disease.

CHARACTERISTICS AND CLINICAL COURSE OF DAT

DAT is associated with increased mortality, but survival among those with the disease varies widely (76, 77). Estimates of mean survival time are hampered by lack of definitive onset-of-disease dates. In a study that followed persons with DAT for an average of 4 years, 54 percent were institutionalized and 49 percent died (78). Median survival is estimated at 11.8 years (standard deviation, 0.6) since retrospectively determined symptom onset and 5.7 years (standard deviation, 0.1) from initial clinic presentation (79). Baseline level of cognition may not predict mortality, but mortality is strongly related to rate of cognitive decline (76). Indeed, the lack of effective predictors of the rate of deterioration extends to the earliest stages of dementia (80).

In the early clinical stage, deficits occur in episodic memory, verbal abilities, visuospatial functions, attention, and executive functions (81). Sensory-motor performance and procedural memory seem to be intact, and only slight impairment may be seen in primary memory (81). Cognitive decline stems from unifunctional to global deficits (81). Performance falls off rapidly in all areas of cognitive functioning, but abilities thought to be subserved by the medial and lateral temporal lobes (episodic and semantic memory, respectively) appear to be substantially more impaired than those abilities thought to be subserved by the frontal lobes (82). Yearly cognitive decline varies from a loss of 2.7–4.5 points on the Mini-Mental State Examination (MMSE), 1.8–4.2 points on the Blessed Dementia Scale, and 12–13 points on the Cambridge Cognitive Examination to a gain of 2.6–4.5 points on the Blessed Test of Information, Memory, and Concentration (83).

The presence of one or more *APOE ε4* alleles is a significant predictor of the incidence of delusions during the course of DAT (84). The frequency and intensity of neuropsychiatric symptoms may increase with declining cognitive function in patients with DAT (76, 85–87) or may simply be correlated with duration of disease (88). Curvilinear associations between dementia severity and neuropsychiatric symptoms such as forgetfulness and emotional and impulsive behaviors have been reported (89, 90). Consensus has yet to be reached on whether the prevalence of individual neuropsychiatric symptoms remains constant at all stages of dementia or whether it varies systematically depending on the stage of the disease (21, 30, 91–94).

Some DAT patients appear to have neuropsychological deficits more prominent in one domain than in other domains (95). Language impairment in DAT may be associated with two distinct neuropsychological abnormalities: 1) a lexical/semantic impairment unrelated to onset or 2) progression of symptoms and a syntactic impairment that may be associated with earlier onset and more rapid progression of dementia (96, 97). The annual decline in language composite score was approximately 0.71 standard units, which did not differ by gender (98).

CORRELATES OF MORE RAPID COGNITIVE DECLINE IN DAT

Progressive cognitive decline is the principal clinical manifestation of DAT, and a faster rate of decline is strongly associated with mortality (76). The rates at which people decline, however, differ substantially between affected persons, are difficult to predict, and are still not well understood (76, 99).

The *APOE ε4* allele, a strong genetic risk factor for DAT, is associated with a greater risk of developing DAT (odds ratio = 14.9, 95 percent confidence interval: 10.8, 20.6 for persons

TABLE 1. Summary of studies estimating incidence and prevalence of DAT* and dementia

Study	Population/study design	Measure of disease frequency
	Incidence studies	
North America		
Canadian Study of Health and Aging, Canadian Study of Health and Aging Working Group (291)	Population-based Canadian cohort study of 5,432 community-dwelling and 210 institutionalized persons 65 years of age or older	Women 65–69 years of age: 1.4 per 1,000 person-years (95% CI*: 0.1, 3.3); men 65–69 years of age: 0; women 85 years of age or older: 49.0 per 1,000 person-years (95% CI: 40.7, 57.2); men 85 years of age or older: 44.2 per 1,000 person-years (95% CI: 31.0, 57.5); women all ages: 7.4 per 1,000 person-years (95% CI: 4.4, 10.4); men all ages: 5.9 per 1,000 person-years (95% CI: 2.0, 9.8)
Cache County Study, Miech et al. (292)	US population-based cohort study of 3,308 persons aged 65 years or older	68 years of age or less: 2.2 per 1,000 person-years; 84–86 years of age: 57.9 per 1,000 person-years; all ages: 16.8 per 1,000 person-years
Monongahela Valley Independent Elders Survey (MoVIES), Ganguli et al. (293)	US population-based cohort study of 1,298 rural persons aged 65 years or older	65–69 years of age: 2.1 per 1,000 person-years (95% CI: 0.6, 7.8); 90 years of age or older: 50.9 per 1,000 person-years (95% CI: 23.3, 111.0); all ages: 11.6 per 1,000 person-years (95% CI: 9.5, 14.2)
North America/Africa		
Hendrie et al. (294)	2,459 Yoruba residents of Ibadan, Nigeria, aged 65 years or older; 2,147 African Americans residing in Indianapolis, Indiana, aged 65 years or older	Annual age-standardized incidence rate of DAT: Nigeria: 1.15% (95% CI: 0.96, 1.35); Indiana: 2.52% (95% CI: 1.4, 3.64)
Europe		
Fratiglioni et al. (295)	Estimates of DAT incidence in persons 65 years of age or older obtained by pooling population-based data from European population-based studies	65–69 years of age: 1.2 per 1,000 person-years (95% CI: 0.6, 2.3); over 90 years of age: 53.5 per 1,000 person-years (95% CI: 36.5, 55.8)
Neurologic Disorders in Central Spain Survey, Bermejo-Pareja et al. (296)	Population-based Spanish survey of 3,891 persons aged 65–90 years	65–69 years of age: 1.5 per 1,000 person-years (95% CI: 0.3, 4.4); 90 years of age or older: 52.6 per 1,000 person-years (95% CI: 31.7, 82.2); age-adjusted incidence rate: 7.4 per 1,000 person-years (95% CI: 6.0, 8.8)
Conselice Study of Brain Imaging, Ravaglia et al. (297)	Italian prospective population-based study of 927 persons aged 65 years or older	65–74 years of age: 11.3 per 1,000 person-years (95% CI: 7.1, 17.9); 85–94 years of age: 75.8 per 1,000 person-years (95% CI: 49.4, 116.2); all ages: 23.8 per 1,000 person-years (95% CI: 17.3, 31.7)
Rotterdam Study, Ruitenberg et al. (298)	Population-based Dutch study of 7,046 persons aged 55 years or older	65–69 years of age: 1.3 per 1,000 person-years (95% CI: 0.7, 2.3); 85–89 years of age: 34.8 per 1,000 person-years (95% CI: 27.7, 43.9); all ages: 7.2 per 1,000 person-years (95% CI: 6.4, 8.1)
Asia		
Li et al. (299)	Chinese cohort of 1,593 persons aged 60 years or older residing in Beijing	All ages: 5.4 per 1,000 person-years
Indo-US Cross-National Dementia Epidemiology Study, Chandra et al. (300)	Population-based Indian study of 5,126 persons aged 55 years or older	65–74 years of age: 1.2 per 1,000 person years (95% CI: 0.25, 3.57); 85 years of age or older: 24.8 per 1,000 person-years (95% CI: 5.1, 72.5); 65 years of age or older: 3.24 per 1,000 person-years (95% CI: 1.48, 6.14)

Table continues

homozygous for the *ε4* genotype; persons with only one copy of *ε4* are also at increased risk—odds ratio = 2.6, 95 percent confidence interval: 1.6, 4.0 for those with an *ε2*/*ε4* genotype; odds ratio = 3.2, 95 percent confidence interval: 2.8, 3.8 for those with an *ε3*/*ε4* genotype, relative to persons with an *ε3*/*ε3* genotype) (100). Earlier age at onset is observed in a dose-dependent fashion (the average age at onset for persons with genotype *ε4*/*ε4*, only one *ε4* allele, and no *ε4* allele is 68 years, 76 years, and 84 years, respectively) (101). These findings have led to the hypothesis that *APOE ε4* allele carriers may experience a more rapid degenerative process regarding development of DAT and that cognitive decline should progress more rapidly in these patients (102), but studies have provided conflicting evidence on whether the *APOE ε4* allele is associated with an accelerated rate of cognitive decline (102–107).

High educational attainment is also associated with an accelerated rate of cognitive deterioration in DAT patients (108, 109), and the cognitive reserve hypothesis has been proposed to explain this association. For instance, someone with a higher number of neuronal synapses or neurons could withstand a higher degree of neuropathological change

TABLE 1. Continued

Study	Population/study design	Measure of disease frequency
World estimates		
Delphi Consensus Study, Ferri et al. (301)	Estimates of annual incidence of dementia (per 1,000) in persons 60 years of age or older derived by using the Delphi consensus approach and guided by a systematic review of published work	North America: 10.5; Latin America: 9.2; western Europe: 8.8; eastern Europe: 7.7–8.1; North Africa and Middle Eastern Crescent: 7.6; Africa: 3.5; India and south Asia: 4.3; Indonesia, Thailand, and Sri Lanka: 5.9; China and developing western Pacific: 8.0; developed western Pacific: 7.0; world annual incidence: 7.5
	Prevalence studies	
North America		
Health and Retirement Study, Plassman et al. (302)	Nationally representative sample of the US population ($N = 856$) aged 71 years or older	71–79 years of age: 5.0%; 90 years of age or older: 37.4%; all ages: 9.7%
Framingham Study, Bachman et al. (303)	US population-based cohort study	Men: 1.17%; women: 3.01%
North America/Africa		
Hendrie et al. (304)	2,494 Yoruba residents of Ibadan, Nigeria, aged 65 years or older; 2,212 African Americans residing in Indianapolis, Indiana, aged 65 years or older	Age-adjusted prevalence in Nigeria: 1.41%; age-adjusted prevalence in Indiana for community-dwelling persons: 3.69%; age-adjusted prevalence in Indiana for persons living in the community and in nursing homes: 6.24%
Africa		
Farrag et al. (305)	Population-based Egyptian study of persons older than age 60 years	4.5% (95% CI: 3.6, 5.4)
Europe		
Lobo et al. (12)	Prevalence estimate for DAT in persons 65 years of age or older obtained by pooling population-based data from European population-based studies	Age-standardized prevalence: 4.4%; 65–69 years of age: 0.6%; 90 years of age or older: 22.2%
Rotterdam Study, Ott et al. (306)	Population-based study of Dutch persons aged 55 years or older	55–64 years of age: 0.20%; 85 years of age or older: 26.8%; all ages: 4.5%
Asia		
Gurvit et al. (307)	Population-based Turkish study of persons older than age 70 years	11.0% (95% CI: 7.0, 15.0)
Dong et al. (308)	Estimate of prevalence of DAT in China among persons aged 60 years or older derived from systematic analysis of work published between 1980 and 2004	1.6% (95% CI: 1.0, 2.7)
Zhang et al. (309)	Prevalence of DAT among persons 65 years of age or older across four regions in China: Beijing, Xian, Shanghai, Chengdu	4.8%
World estimates		
Delphi Consensus Study, Ferri et al. (301)	Estimates of prevalence of dementia in persons 60 years of age or older derived by using the Delphi consensus approach and guided by a systematic review of published work	North America: 6.4%; Latin America: 4.6%; western Europe: 5.4%; eastern Europe: 3.8%−3.9%; North Africa and Middle Eastern Crescent: 3.6%; Africa: 1.6%; India and south Asia: 1.9%; Indonesia, Thailand, and Sri Lanka: 2.7%; China and developing western Pacific: 4.0%; developed western Pacific: 4.3%; world prevalence 2001: 3.9%

* DAT, dementia of the Alzheimer type; CI, confidence interval.

before becoming symptomatic (45, 109, 110). If patients with higher educational levels also have a higher cognitive reserve, then, when DAT symptoms become apparent, the pathological burden will already be more severe and widespread, and, with the cognitive reserve depleted, the patient would appear to experience cognitive decline at a more rapid rate (45, 109). Rapid cognitive decline has also been observed among patients exhibiting neuropsychiatric symptoms such as aggression/agitation, depression, psychosis, delusions, and hallucinations (30, 78, 111–113), but these findings have been challenged (114–118). The neurobiology underlying the emergence of neuropsychiatric symptoms is far from being understood, as is the mechanism by which these symptoms may accelerate cognitive decline (119–123).

Antipsychotic medications, widely used to treat neuropsychiatric symptoms (124, 125), have also been identified

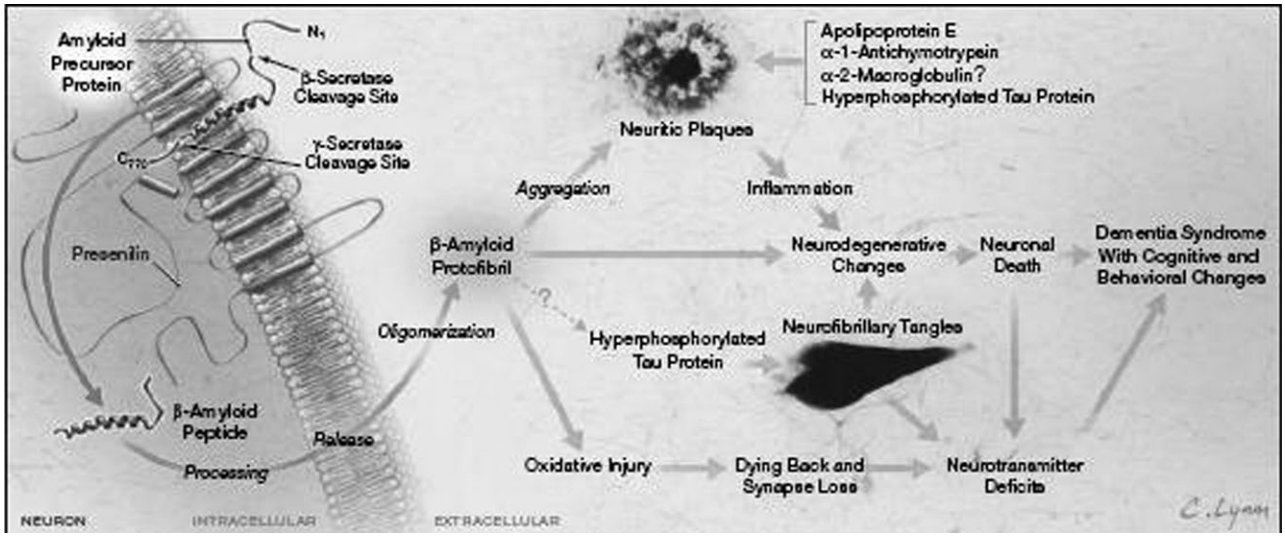

FIGURE 1. Cascade of neuropathological events leading to the behavioral and cognitive features of dementia. Reproduced with permission from primary author J. L. Cummings and from *JAMA* 2002;287:2335–2338. *Copyright © 2002, American Medical Association.* All rights reserved.

as a factor accelerating cognitive decline (114, 126). Although it is possible that antipsychotics could exacerbate cognitive deficits through their anticholinergic effects (117), some studies have failed to corroborate the findings that antipsychotic medications are associated with more rapid cognitive decline in DAT patients (117, 127–129). Although there is little information on the effects of other commonly used psychotropic medications on cognition in patients with DAT (125, 129), a positive association between certain psychotropic medications (sedatives and anxiolytics) and cognitive deterioration has been reported (129).

ASSESSMENT METHODS

In practice and in research, DAT is diagnosed by applying the DSM-IV-TR criteria (130) and/or those of the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) (40). Whereas the DSM-IV-TR criteria require the presence of memory impairment and cognitive deterioration in one other domain such as language, perception, or motor skills, or disturbances in executive functioning (130), the NINCDS/ADRDA criteria classify the likelihood of DAT into one of three categories: definite (clinical diagnosis coupled with a histologic confirmation of Alzheimer's disease), probable (clinical diagnosis without a histologic confirmation), and possible (atypical symptoms with no apparent alternative diagnosis in the absence of a histologic confirmation) (40). The NINCDS/ADRDA clinical diagnostic criteria, similar to those of the DSM-IV-TR, require a subtle onset and a gradual worsening of cognitive function and that other etiologies (e.g., thyroid diseases) be ruled out. Studies validating the NINCDS/ADRDA and DSM-IV-TR against a variety of ''gold standards'' have found that the sensitivity ranges from 65 percent to 96 percent and that the specificity of these criteria for DAT against other dementia ranges from 23 percent to 88 percent (131–139).

Table 2 briefly summarizes the screening instruments used to determine the need for further evaluation. The MMSE (140), consisting of a brief assessment of language, memory, praxis, and orientation, is the most widely used and has been the most extensively studied with respect to its accuracy and validity (141–146). MMSE scores are affected by gender, educational attainment, age, and cultural background (143, 147, 148); the sensitivity of the MMSE is poor for patients with mild dementia (2, 149); the instrument is considered too time-consuming to administer in routine clinical practice (150, 151); not all changes in MMSE scores necessarily reflect true clinical improvement or decline (152, 153); and the MMSE exhibits floor effects in patients with severe impairment and ceiling effects in those who are mildly impaired (154). Modifications, alternatives, and supplements to the MMSE such as the modified version of the MMSE (155); the Montreal Cognitive Assessment (156); the Memory Impairment Screen (157); the Blessed Test of Information, Memory, and Concentration (158) and its abridged version, the Short Blessed Test (159); the One-Minute Verbal Fluency Test for Animals; and the Clock Drawing Test (160) have been advanced.

Although the lines between screening instruments and neuropsychological battery tests are sometimes blurred, generally the former are much less time-consuming and detailed than the latter; battery tests often combine multiple screening tests so that more cognitive symptoms in DAT can be covered in one assessment; and battery tests may allow for discrimination between DAT and other illnesses affecting cognitive function. One of the most commonly used neuropsychological instruments in clinical trials of antidementia medications in the United States is the Alzheimer's Disease Assessment Scale-Cognitive Subscale (161, 162).

TABLE 2. Summary of commonly used DAT* screening instruments

Instrument	Cognitive domains assessed	Advantages	Disadvantages
MMSE* (140)	Language, memory, praxis, orientation	8–13 minutes in duration (310), covers a wide variety of cognitive domains in a brief test, reliable (149, 311)	Sensitivity poor in those with mild dementia (2, 149); performance affected by age, educational attainment, gender, and cultural background (2, 143, 148); too long to administer routinely in clinical practice (150, 151); ceiling effects in mild impairment and floor effects in severe impairment (154)
Modified MMSE (155)	Language, memory, praxis, orientation, executive functioning, visuospatial abilities	10–15 minutes in duration (310), samples a broader variety of cognitive domains than the MMSE (155), enhanced reliability and validity relative to the MMSE (155, 312)	Takes longer to administer than the MMSE
Montreal Cognitive Assessment (156)	Language, memory, praxis, orientation, visuospatial abilities, attention, concentration, executive functioning	High specificity and sensitivity for mild cognitive impairment and mild DAT (156), can detect mild cognitive impairment (156), reliable (156)	Useful primarily for mild cognitive impairment and mild DAT (156), longer to administer than the MMSE (156)
Memory Impairment Screen (157)	Memory	4 minutes in duration (310); performance not affected by age, education, or gender (313)	Covers few cognitive domains in DAT patients, sensitivity influenced by severity of dementia (157)
Blessed Test of Information, Memory, and Concentration (158)	Orientation, concentration, memory	Performance not correlated with educational background (151), does not require a specific form to administer	Covers few cognitive domains in DAT patients, demonstrates intermediate sensitivity (151)
Short Blessed Test (192)	Orientation, concentration, memory	5 minutes in duration (310), reliable (314, 315), can differentiate between mild cognitive impairment and normal subjects (159), highly sensitive and specific for dementia (313), high correlation with the MMSE (163, 314)	Covers few cognitive domains in DAT patients, should be used in conjunction with other screens
One-Minute Verbal Fluency Test For Animals	Language, semantic memory	1 minute in duration, less time-consuming than most screens, correlates well with the MMSE (163), demonstrates good discrimination between persons with dementia and normal controls (316), does not require a specific form to administer	Covers few cognitive domains in DAT patients, demonstrates intermediate sensitivity (151), should be used in conjunction with other screens
Clock Drawing Test	Praxis, executive functioning, attention, visuospatial abilities	2 minutes in duration (310), less time-consuming than most screens, high interrater reliability (317)	Covers few cognitive domains in DAT patients, subjective interpretation of clock drawing, intermediate sensitivity and specificity (313, 317), should be used in conjunction with other screens

* DAT, dementia of the Alzheimer type; MMSE, Mini-Mental State Examination.

This instrument assesses memory, language, praxis, and orientation with a total score ranging from zero (no impairment) to 70 (severely impaired). The Neuropsychological Battery of the Consortium to Establish a Registry for Alzheimer's Disease (163) consists of seven tests, including the MMSE and three others adapted from the Alzheimer's Disease Assessment Scale-Cognitive Subscale (162) and measures memory, language, praxis, and orientation. Other neuropsychological tests used in dementia include, but are not limited to, the Syndrom-Kurztest (164) (assessing memory, attention, naming, and object arrangement), the Seven-Minute Neurocognitive Screening Battery (165) (assessing memory, orientation, visual abilities, praxis, and language skills), the Addenbrooke's Cognitive Examination (166) (assessing orientation, attention, memory, language, and visuospatial abilities), and the Cambridge Cognitive Examination (167) (assessing orientation, language, memory, praxis, calculation, and perception). Screening instruments, particularly the MMSE, and more in-depth neuropsychological tests are also often used to chart the rate of cognitive decline.

BIOMARKERS AND NEUROIMAGING

Disease-modifying drugs are likely to be more efficacious in the early or preclinical stage of the disease (168, 169). Promising biomarkers and neuroimaging could have a substantial public health impact if new drug candidates, such as beta-amyloid immunotherapy or beta-sheet breakers, were found to have disease-arresting effects (170). Evidence is currently insufficient to support or direct the use of biomarkers (table 3) in usual clinical practice for dementia diagnosis or disease management purposes.

TABLE 3. Summary of the rationale and the disadvantages of selected CSF* and plasma biomarkers

Biomarker	Rationale	Disadvantages
CSF beta-amyloid	Decreased levels of beta-amyloid in CSF may reflect increased deposition of beta-amyloid in the brain (171).	Requires a lumbar puncture; invasive and uncomfortable procedure; despite availability of a commercial test with high sensitivity and specificity, this biomarker is underutilized (318).
CSF total *tau*	*tau* is released from dying neurons, so total *tau* concentration in the CSF is thought to reflect the intensity of the neuronal damage and degeneration (168).	Requires a lumbar puncture; invasive and uncomfortable procedure; nonspecific for Alzheimer's disease because elevated levels of *tau* are observed in other degenerative CNS* conditions (168); despite the availability of a commercial test with high sensitivity and specificity, this biomarker is underutilized (318).
CSF hyperphosphorylated *tau*	Concentration of phosphorylated *tau* in the CSF may reflect the formation of tangles in the brain because there is no increase in phosphorylated *tau* in other diseases with intense neuronal degeneration (e.g., Creutzfeldt-Jakob disease) (168).	Requires a lumbar puncture; invasive and uncomfortable procedure; despite the availability of a commercial test with high sensitivity and specificity, this biomarker is underutilized (318).
Plasma beta-amyloid	Beta-amyloid is produced in the brain and cleared to the plasma via the CSF and the blood brain barrier (319).	Plasma beta-amyloid levels do not correlate well with biochemical or pathological measures of cerebral beta-amyloid deposition (181); there is broad overlap in the plasma levels of beta-amyloid peptides in persons with DAT* and controls, making discrimination of persons with and without Alzheimer's disease difficult (171).
Plasma amyloid-beta autoantibodies	Antibodies against neuritic plaques may protect against Alzheimer's disease (320, 321).	Titer of beta-amyloid antibodies has been found to be significantly higher in healthy controls than in patients with DAT (322); some studies have found no correlation between antibody titer and prevalence of DAT (323); immune response to beta-amyloid 40 and tolerance of beta-amyloid 42 occurs naturally in humans and is not related to the neuritic plaque burden in the brain (171).
Plasma APOE*	The *APOE ε4* allele is associated with increased neuritic plaque load and elevated levels of beta-amyloid in the brain (324–326); the *APOE ε4* allele is associated with less APOE protein in plasma (327).	Studies of levels of APOE in DAT have been contradictory; some have reported elevated APOE levels in DAT (328), no difference (329–331), or reduced (332, 333) levels compared with controls.
Plasma isoprostanes	Increased levels of lipid oxidation in the Alzheimer's disease brain support a role for oxidative stress in DAT (171); free-radical-mediated peroxidation of polyunsaturated fatty acids creates isoprostanes (171).	Isoprostanes appear to be elevated in DAT patients relative to controls (334), but these findings have been challenged (335).
Inflammatory molecules such as interleukin-6	Amyloid deposition in the Alzheimer's disease brain elicits a range of inflammatory responses (57, 336); interleukin-6 is a cytokine implicated in inflammation.	Many of the proteins involved in the inflammatory response do not cross the blood-brain barrier (188); controversy exists regarding the levels of cytokine and acute-phase reaction reactants in the blood following an inflammatory response (187); findings from studies comparing the levels of plasma interleukin-6 in people with DAT and in healthy controls have been inconsistent (182, 185, 186, 337).

* CSF, cerebrospinal fluid; CNS, central nervous system; DAT, dementia of the Alzheimer type; APOE, apolipoprotein E.

Beta-amyloid 42, a more aggregate-prone peptide derived from the amyloid precursor protein, a key molecule in Alzheimer's disease pathology (171), total *tau*, and phosphorylated *tau* in the cerebrospinal fluid are biomarkers with high diagnostic sensitivity and specificity for Alzheimer's disease (172, 173). The decrease in beta-amyloid 42 in the cerebrospinal fluid, presumably a result of its decreased clearance from the brain into the cerebrospinal fluid (174), has recently been added as one of the supportive features of the proposed revisions of NINCDS/ADRDA criteria for Alzheimer's disease (131). Cerebrospinal fluid biomarkers may be able to identify preclinical Alzheimer's disease even before the onset of mild cognitive impairment (175–177).

Plasma levels of beta-amyloid peptides in persons with DAT overlap those found in controls (171, 178–180) and do not reflect neuropathological or neurochemical measures of the levels of beta-amyloid deposition in the brain (181). Some studies reported increased levels of interleukin-6, a cytokine implicated in inflammation, in serum and plasma of persons with DAT (182, 183), whereas others did not (184–186). Cytokine and acute-phase-reaction reactant levels in the plasma or serum remain controversial (187), and many of these proteins do not cross the blood-brain barrier (188). Cerebrospinal fluid measures of beta-amyloid, total *tau*, and hyperphosphorylated *tau* are currently the best biomarkers available.

Within the medial temporal lobe, the disease consistently manifests itself through atrophy of the hippocampus and parahippocampal gyrus (189), which can be visualized by using structural magnetic resonance imaging (190). Magnetic resonance imaging measurements of the medial temporal lobe include the qualitative appraisal of atrophy in the hippocampal formation (191) as well as quantitative techniques analyzing tissue segmentation and computing cerebral volume (192). Sensitivity ranges from 80 percent to 100 percent (193–195) and specificity is over 90 percent (194) when magnetic resonance imaging–based estimates of the volume of various regions of the medial temporal lobe are used to discriminate between patients with Alzheimer's disease and normal controls. Functional magnetic resonance imaging may also allow for earlier detection of Alzheimer's disease (189).

Single-photon emission computed tomography has been used to measure regional cerebral blood flow, which correlates well with severity of DAT (196, 197) and prognosis (198), although its diagnostic accuracy for distinguishing between DAT and non-DAT in studies including healthy controls is quite low (pooled weighted sensitivities ranged from 65 percent to 71 percent with a specificity of 79 percent) (199). Computed tomography, the oldest technique for scanning the brain, is generally used to exclude other causes of dementia (e.g., subdural hematomas) (189) but is worse than cognitive screening in identifying dementia (200).

Positron emission tomography can assess hypometabolism and hypoperfusion and, when conducted with fluorodeoxyglucose, can measure the regional cerebral metabolic rate of glucose (201). Approved in the United States as a diagnostic tool, fluorodeoxyglucose−positron emission tomography is highly sensitive and specific in detecting Alzheimer's disease in its early stages (202). Positron emission tomography techniques in combination with use of an amyloid-specific tracer may also provide in vivo visualization of neuritic plaques. Studies using the Pittsburgh Compound B, a molecule that binds preferentially to beta-amyloid fibrils (203), demonstrated that brains of DAT patients had a two- to threefold greater Pittsburgh Compound B retention on positron emission tomography scans relative to cognitively intact age-matched controls, and retention was consistent with Alzheimer's disease pathology (204–206). Pittsburgh Compound B–positron emission tomography imaging of amyloid deposits may have the potential to increase diagnostic accuracy of DAT and could serve as a tool for monitoring the changes in beta-amyloid pathology over the course of DAT (206).

TREATMENTS FOR DAT

Optimal treatment of DAT requires both nonpharmacological and pharmacological interventions (207). Given the progressive nature of the illness, interventions must be periodically reviewed and revised to meet the changing needs of the patient.

Nonpharmacological methods are appropriately used throughout the severity spectrum of DAT and are used alone or in combination with pharmacotherapy (208). Despite frequent use in clinical practice, few have been studied in controlled trials. Much of the published evidence is characterized by a number of limitations such as inadequate sample sizes, short study duration, use of nonstandardized evaluation methods, and lack of information on persistence of treatment effects (209). Although short-term adverse consequences of nonpharmacological interventions, such as agitation and catastrophic reactions, have been reported in some studies, these outcomes have not been a focus of research (210).

The 2007 American Psychiatric Association guidelines for treatment of patients with DAT and other dementias categorize nonpharmacological or psychosocial treatments into four broad areas: emotion oriented (reminiscence therapy, validation therapy, supportive psychotherapy, sensory integration, and simulated-presence therapy), stimulation oriented (recreational activities, art therapies, exercise), cognition oriented (reality orientation, cognitive retraining, skills training), and behavior oriented (211). The growing interest in newer, nonpharmacological interventions such as cognitive rehabilitation and retraining techniques in the early stages of DAT is focused on developing therapies that enhance present capabilities and possibly augment the effects of cholinesterase inhibitors (212, 213). While some studies have reported treatment-related improvements in specific cognitive domains, well-designed, randomized trials of these interventions are lacking, and the effect on real-life skills, required for independent living, is largely unknown (214).

Nonpharmacological interventions for dementia-related neuropsychiatric symptoms have been more widely studied and target predominantly neuropsychiatric symptoms in mild to moderate stages of dementia (e.g., communication techniques, environmental alterations) (215). Studies of patient-centered behavioral interventions such as sensory stimulation or music therapy have reported positive, but short-lived effects on agitation and other symptoms (216). Caregiver interventions may have long-term benefits because several well-designed trials of psychoeducation programs for caregivers of persons with dementia reported a decrease in the frequency of neuropsychiatric symptoms and a delay in the time to institutionalization (217, 218).

The currently available DAT pharmacotherapeutic agents are symptomatic rather than disease-modifying treatments. Symptomatic treatments such as cholinesterase inhibitors and memantine, an *N*-methyl-*D*-aspartate receptor antagonist, may stabilize or slow the progression of DAT, but these effects are lost after discontinuation (219, 220). Disease-modifying therapies are being designed to target various aspects of DAT neuropathology and confer benefits that persist beyond the course of treatment. The three broad investigational classes of disease-modifying treatments are antiamyloid agents, neuroprotective agents that reduce or protect against neuronal injury associated with amyloid deposition, and neurorestorative strategies such as nerve growth factors and cell transplantation (221). Experts in the field have theorized that the most effective DAT medication regimens of the future will combine symptomatic and disease-modifying agents (221, 222).

Cholinesterase inhibitors have been the cornerstone of contemporary DAT pharmacotherapy for over a decade and were developed based on the cholinergic hypothesis

of memory dysfunction (223). Degeneration of cholinergic neurons in the basal forebrain and declining levels of choline acetyltransferase, the enzyme responsible for acetylcholine synthesis, are associated with progressive decline of cholinergic transmission in the cerebral cortex and hippocampus (223). Cholinesterase inhibitors block the degradation of acetylcholine and are associated with modest benefits in the domains of cognition, function, and behavior in DAT clinical trials (224). Two drugs in this class, donepezil and galantamine, inhibit acetylcholinesterase, whereas tacrine and rivastigmine block both acetylcholinesterase and butyrylcholinesterase, an enzyme that plays a lesser role in the breakdown of acetylcholine (225). Galantamine is also an allosteric nicotinic receptor modulator and enhances the effect of acetylcholine on nicotinic receptors (226). Donepezil, rivastigmine, and galantamine have supplanted tacrine because of more convenient dosing, greater tolerability, and the absence of significant hepatotoxicity (224).

A recent meta-analysis of 13 double-blind, placebo-controlled trials using donepezil, rivastigmine, or galantamine treatments for 6 months to 1 year in patients with mild, moderate, or severe DAT reported improvements over placebo in cognition averaging 2.7 points (95 percent confidence interval: −3.0, −2.3) on the 70-point Alzheimer's Disease Assessment Scale-Cognitive Subscale and 1.37 points (95 percent confidence interval: 1.13, 1.61) on the 30-point MMSE scale (227). Modest, but statistically significant benefits were also observed for global clinical ratings, activities of daily living functioning, and neuropsychiatric symptoms. More patients dropped out of cholinesterase inhibitor treatment groups because of adverse effects (29 percent) than placebo-treated patients (18 percent), and fewer patients experienced adverse events with donepezil compared with rivastigmine.

Despite the structural differences between various cholinesterase inhibitors, there is no evidence to suggest clinical differentiation in efficacy trials (227, 228). Of the four cholinesterase inhibitor comparative clinical trials that have been conducted, there is only one double-blind study: a 2-year comparison of donepezil with rivastigmine in patients with moderate DAT (range of MMSE scores: 10–20) (229). No significant treatment differences were observed between donepezil and rivastigmine regarding ratings of cognitive function, activities of daily living performance, and neuropsychiatric symptoms (229). However, compared with rivastigmine-treated patients, fewer donepezil patients discontinued treatment (odds ratio = 0.64, 95 percent confidence interval: 0.50, 0.83) (229).

More recently, dysregulation of glutamatergic neurotransmission in DAT was hypothesized to play a role in abnormal information processing, storage, and retrieval (230). Memantine, a low-to-moderate-affinity, noncompetitive, *N*-methyl-D-aspartate glutamate receptor antagonist, blocks excitotoxic neuronal toxicity associated with excessive release of glutamate (230). Memantine has been used in the treatment of a variety of neurologic disorders for more than 25 years in Europe and, in 2003, was approved in the United States to treat moderate-to-severe DAT.

Studies of memantine in patients with more advanced DAT have reported favorable treatment effects; randomized, controlled trials of mild-moderate disease, however, have failed to show conclusive evidence of benefit (231, 232). In a 6-month, placebo-controlled, monotherapy trial, memantine was associated with improvements in cognition and function (233). In addition, memantine or placebo added to a stable regimen of donepezil resulted in significant treatment effects favoring memantine in cognitive, functional, neuropsychiatric, and global outcomes over a 6-month period (234). To our knowledge, no head-to-head trials comparing memantine monotherapy with cholinesterase inhibitors therapy in moderate-to-severe DAT have been conducted. Adverse-effect rates from placebo-controlled dementia trials indicate that memantine is generally well tolerated (233, 234).

Considerable debate over the value of the pharmacological treatment of DAT continues and is fueled by difficulties in translating the modest effects observed in controlled trials into meaningful clinical and economic benefits (235). The United Kingdom's National Institute for Health and Clinical Excellence recently revised its previous position and approved the use of cholinesterase inhibitors for moderate-stage DAT only (235). Memantine is not recommended as a treatment for DAT under the guidelines, except for patients participating in clinical trials. Without solid evidence to elucidate the optimal duration of therapy, the impact of treatment on outpatient and institutional caregiver burden, and the effects of therapy on patient and caregiver quality of life, payers will continue to question the utility of treating DAT with the currently available agents.

Another area of controversy in DAT pharmacotherapy is what constitutes appropriate treatment of neuropsychiatric symptoms. Pharmacological treatment of neuropsychiatric symptoms may be warranted when nonpharmacological interventions fail or when the nature or severity of neuropsychiatric symptoms endangers the safety of the patient or others (211). Before considering any pharmacological therapy to treat neuropsychiatric symptoms, it is essential that physiologic (hunger, thirst, need to void) and medical causes of the behavior be investigated and treated because these antecedents can trigger or exacerbate neuropsychiatric symptoms (236, 237).

Pharmacotherapeutic management of neuropsychiatric symptoms poses complex challenges for clinicians and caregivers because an increasing body of evidence has revealed that the potential ''cost'' in the form of adverse effects may offset marginal therapeutic benefits for many patients (238). A recent meta-analysis of antipsychotic, antidepressant, and anticonvulsant clinical trials for dementia-related neuropsychiatric symptoms concluded that these medications offer modest benefits and a considerable risk of adverse effects (239). No medication has been approved by the US Food and Drug Administration to treat dementia-related neuropsychiatric symptoms.

The second generation of antipsychotics, atypical antipsychotics, is the best-studied and most commonly prescribed class of psychoactive medications for neuropsychiatric symptoms. A number of recent placebo-controlled clinical trials of atypical antipsychotics for neuropsychiatric symptoms have reported small treatment effects coupled with adverse effects at rates that exceed those observed among placebo-treated

patients (238, 240). Results from some randomized controlled trials in dementia and subsequent meta-analyses have identified an increased risk of mortality and cerebrovascular-adverse events associated with atypical antipsychotic treatment (241, 242). Conventional antipsychotics may not be safer than atypical antipsychotics; subsequent analyses have reported an elevated risk of mortality associated with the use of older antipsychotics in patients with dementia and other psychiatric illnesses (243, 244). These developments have fueled an ongoing debate over the appropriate prescribing of antipsychotics (242, 245).

Better understanding of the safety issues associated with antipsychotic therapy and the lack of safer and more effective alternatives have stimulated interest in the effects of dementia-specific medication on neuropsychiatric symptoms. Modest reductions in neuropsychiatric symptoms have been reported from trials of cholinesterase inhibitors, memantine monotherapy, and combined memantine-donepezil in DAT patients (227, 246). Studies of small numbers of patients in open trials of cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and in one double-blind, placebo-controlled trial with rivastigmine have reported varying degrees of improvement of neuropsychiatric symptoms and psychosis in dementia with Lewy bodies (247). Delusions, hallucinations, apathy, and agitation/aggression are the symptoms most likely to show significant improvement in trials of DAT or dementia with Lewy bodies (246), but there is considerable intertrial heterogeneity in neuropsychiatric symptoms domains showing the greatest response to treatment. Current treatment guidelines suggest a trial of a cholinesterase inhibitor and/or memantine in the management of nonacute neuropsychiatric symptoms (211, 239).

A substantial number of patients with dementia experience severe and persistent neuropsychiatric symptoms that may require the use of medication for varying periods of time throughout the course of DAT (248). The optimal treatment of neuropsychiatric symptoms is an essential research focus. More thoughtfully designed randomized controlled trials of pharmacological agents as monotherapy and in combination with innovative nonpharmacological interventions are urgently needed.

CAREGIVING AND LONG-TERM CARE

As persons with DAT become more cognitively and functionally impaired, many lose the ability to care for themselves and become dependent on others for their care (249). The majority of informal DAT caregivers are caring for a relative, usually a parent, because the spouse of a DAT patient may be deceased or unable to provide the level of care needed without substantial help from his or her children (250, 251). The burden of care is often borne by one individual (252).

Caregiving generally requires a significant investment of time, energy, and money that often needs to be sustained over a period of years (252, 253). The number of hours per week spent providing care increases from 13.1 for patients with mild dementia to 46.1 for those in the more advanced stage of the illness (254). Increasing dependency, personality changes, and neuropsychiatric symptoms such as aggression/agitation and depression are also highly distressing to the caregiver (255, 256). Providing assistance to a loved one afflicted with DAT comes at a considerable emotional, psychological, and physical cost to the caregiver. Informal caregivers report higher levels of depression and anxiety (255–259), lower overall life satisfaction (257, 260), and engaging in fewer preventive health behaviors (261), and they are at increased risk of illness (262–265) and mortality (266). Informal caregivers also often experience social isolation (256), financial strain (251, 259, 267), employment complications (258, 268), and disruption of relationships (258). Research has predominantly focused on the negative and deleterious aspects of caregiving, but some studies have found that caregivers of persons with dementia perceive their caregiving as providing them with positive and satisfying experiences (269–272).

The decision to institutionalize a loved one afflicted with DAT is difficult and complex but has been found to be associated with the patient's manifestation of neuropsychiatric symptoms, caregiver exhaustion, and the increased need for patient supervision (273–276). As many as 90 percent of patients with dementia will be institutionalized before death (277). Among new admissions to nursing homes, the prevalence of dementia is nearly 70 percent (278); in 1999, approximately 214,200 nursing home residents were living with DAT (279).

In the last few decades, there has been a rapid proliferation of dementia special care units in nursing homes (280). Approximately 10 percent of nursing homes had a special unit for people with dementia in the 1990s; this figure has risen to 20 percent (281, 282). There is no consensus definition of what constitutes ''special care'' for dementia, but a modified physical environment, special programs for residents and families, and additional staff training and coverage have become standard features (283). Studies evaluating the impact of living in a special care unit on improved resident outcomes (slower cognitive and functional decline and fewer neuropsychiatric symptoms) have been contradictory (284–287). In contrast, research has shown that the use of psychotropic medications is higher among residents of special care units (288–290).

CONCLUSION

Alzheimer's disease is a complex neurodegenerative illness, but much progress has been made in understanding it. Research on the use of neuroimaging and biomarkers is promising and may allow for earlier and more accurate detection of Alzheimer's disease cases. Most studies across the world indicate that the incidence and prevalence of DAT are increasing. The majority of persons afflicted with DAT will exhibit neuropsychiatric symptoms, but symptom-specific prevalence estimates vary widely and it is unclear how and if stage-specific prevalence of individual symptoms changes. Current pharmacological treatments for DAT appear to slow progression of the disease but are not disease modifying. Further research on disease-modifying therapies

is needed if the prevalence and clinical course of the condition are to be altered. This review underscores that much more needs to be done before the mystery of DAT is unraveled.

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