Part I
Common Dementias

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Alzheimer's Disease

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History

In 1871, over 30 years before Alois Alzheimer published his seminal cases, James Crichton-Browne may have been among the first physicians to remark upon the relationship between "brain wasting" and "premature dotage" in a letter to Charles Darwin (Snyder & Pearn, 2007). Age-related mental deterioration as an entity had been recognized virtually for recorded history (Boller et al., 2007; Mandell & Albert, 1990). Emil Kraepelin, however, was one of the few 19th-century giants of medicine who recognized the connection between brain pathology and mental dissolution in the elderly (Stam, 1985). He referred to "Morbus Alzheimer" as early as 1908 and used the eponym in the 1910 edition of his textbook (Kraepelin, 1910). Over the next century plus, Alzheimer's disease (AD) has become the focus of one of the most intensive investigations in medical history. A Google search for AD now generates over 18 million hits.

Alzheimer examined 51-year-old Auguste D. in 1901 (Graeber, 2006). Her husband had noted a relatively sudden change in her behavior, dominated by panic, terror and suspicions of his having an affair with a neighbor. She neglected her housework, hid objects and fumbled in the kitchen. Over the next several months, she became increasingly restless and a disturbance to their neighbors. By the time of her admission to hospital, which she never left, she suffered from "weakening of memory, persecution mania, sleeplessness, restlessness," had an "amnestic writing disorder," was unable to perform any mental or physical work and was "rarely free from fear and agitation." Periods of calm cooperation alternated with physical aggression towards other patients, "groping their faces as if she were blind" (Page & Fletcher, 2006).

Alzheimer was met with silence when he first presented his case (Alzheimer, 1906) of "a distinct disease process" (Nair & Green, 2006). Following his initial publication

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of 1907 (Alzheimer, 1907), he issued his classic review article in 1911 (Alzheimer, 1911).

With a few exceptions and for several reasons (Nair & Green, 2006), "Alzheimer's disease" for roughly the next 50 years denoted "presenile" dementia and differed from the "normal" senility associated with old age, despite Alzheimer's assertion that there were no significant pathological differences between older and younger cases (Spielmeyer, 1916). Kraepelin as well opined that this illness is "a peculiar disease process that is largely independent of age" (Kraepelin, 1910).

Alzheimer described the now familiar distinctive pathology in his original 1907 article. Slides from two patients were rediscovered in 1992 and 1997, and those from Auguste D. clearly demonstrate numerous characteristic cortical plaques and tangles (Graeber, 2006).

Epidemiology of Dementia and AD

In virtually all developed countries, the oldest segments of society are increasing at the fastest rate and an epidemic of age-related diseases is already upon us. The dementia syndrome is largely a provenance of the elderly and is a major part of a looming public health crisis. The global prevalence of dementia of any cause in 2005 was about 24 million with yearly incidence of almost 5 million, tantamount to adding a new case every 7 seconds (Ferri et al., 2005).

AD accounts for about 55–70% of adult-onset dementia in the industrialized world (Lim et al., 1999), is the fifth leading cause of death in Americans older than 65, and, in contrast to the decreasing death toll attributable to other major diseases, that due to AD is on the rise (Mebane-Sims & Alzheimer's Association, 2009) (Figure 1.1).

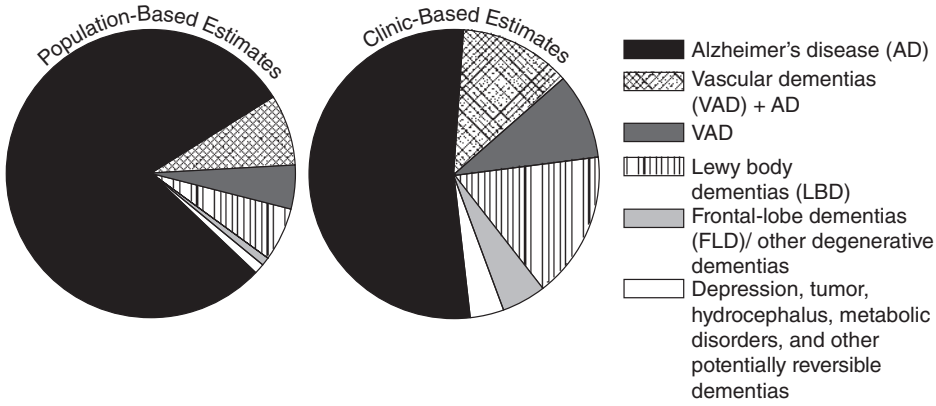

Figure 1.1 Population-based vs. clinic-based estimates of dementia
Source: Modified from Green, R.C. (2005). *Diagnosis and Management of Alzheimer's Disease and Other Dementias* (2nd edn.). Caddo, OK: Professional Communications, Inc., by permission

AD incidence is age related and doubles about every 5 years from age 65 through the 90s (Bachman et al., 1993; Berlau, 2007). The exact prevalence of AD is difficult to determine because, among other reasons, death certificates of people with end-stage AD often list infection or "cardiopulmonary arrest" as the proximate cause. Currently, over 5 million Americans have AD with incidence of a new case about every 70 seconds. In the United States, there will be at least 8.5 million people with AD by the year 2030, about 13 to 25 million in 2050 (a new case every 33 seconds) (Hebert et al., 2003; Mebane-Sims & Alzheimer's Association, 2009) plus an unknown number with other dementias. National direct and indirect monetary costs of caring for people with Alzheimer's disease alone is already at least $100 billion annually in the United States (Koppel, 2003), where nursing home cost per patient currently hovers around $50,000 per year, and over $300 billion per annum globally (Dartigues, 2009). We therefore need hardly emphasize the current and growing economic impact of AD, the "coming plague of the 21st century," on health systems worldwide. More specific epidemiological data are discussed in this and other chapters.

Dementia

Definition, evaluation, management, and treatment

Symptoms common to most dementias include forgetfulness, language deterioration, mood changes, impaired judgment, and loss of initiative. There is nevertheless no universally accepted definition of "dementia," which has been broadly characterized as a syndrome, as shorthand for unsuccessful aging, and as a specific diagnosis (Green, 2005), that is, as a synonym for AD. Within its multitude of definitions, diagnostic criteria have routinely included memory impairment, decline in social or occupational function (American Psychiatric Association, 2000), progressive deterioration, incurability, and irreversibility. Clinicians must nevertheless be aware that pathological processes underlying many causes of dementia are static and that a few are treatable. Furthermore, while the association between dementia and memory disorder is almost ubiquitous, significant amnesia is not a salient feature of every dementing disease. Evidence of *functional decline*, e.g., in personal hygiene, bill paying, housecleaning, personality, etc., is, at least for research purposes, currently the clinical marker separating "possible dementia" and "normal aging" from "dementia." Many factors can nevertheless mask or delay occupational or social incompetence and we favor a somewhat broader definition.

"Dementia," as used in this chapter, is a syndrome of *acquired persistent* intellectual impairments characterized by deterioration in at least three of the following domains: memory, language, visuospatial skills, personality or behavior, and manipulation of acquired knowledge (including executive function) (Cummings, 2004; Cummings & Benson, 1992; Cummings & Mega, 2003). According to this definition, mental retardation and acute confusional states (ACS; delirium) do not qualify, the

former because it is not acquired, the latter because multiple cognitive impairments associated with it by definition are temporary (see subsequent discussion of the ACS). The presence of a dementia is *supported* by a combination of a carefully obtained history, physical and mental status examinations, significant impairment on neuropsychological tests corrected for age and education, and a *change* in test scores over a 6–12-month interval (Mesulam, 2000).

This definition, like all the others, is not perfect. Persons with superior premorbid intellect and greater cognitive reserve (Roe et al., 2007) may suffer decline in occupational performance which nevertheless escapes even the most detailed clinical assessment and which results in no other objective functional impairment (Cummings, 2005a; Strub & Black, 2000). Some ultimately dementing disorders (Benson et al., 1988; Dubois et al., 2007; Mesulam, 2003) may manifest for years as gradual deterioration limited to a single cognitive domain which in turn can influence execution and interpretation of other cognitive functions (Mesulam, 2000).

"Dementia of the Alzheimer type" (DAT) refers to the *clinical syndrome* which by far is that most commonly associated with autopsy-proven (*pathologic*) AD.

Recognition and differential diagnosis of the dementia syndrome

Management and treatment of dementia begins with its recognition, which is reasonably straightforward either when the patient or an independent historian expressly raises cognitive (or behavioral) deterioration as an issue, or it becomes obvious in context with other medical issues (e.g., following hospital admission). Recognition is a not inconsiderable concern, however, because cognition and behavior are indeed not issues for many "community dwelling elderly" who are nevertheless already demented and just one fall, infection, change of address or assault of a spouse away from health system entry for these issues (Albert et al., 1991).

Recognition is further hindered because widespread neuropsychological testing, imaging and laboratory screening for asymptomatic elderly people is not economically feasible. Furthermore, many health professionals as well as lay people persist in believing that cognitive loss is an inevitable and "natural" consequence of aging rather than a reflection of brain damage. Although there is some longitudinal evidence that general cognition "normally" recedes in a person's mid-70s (Brayne et al., 1999), much of the decline previously attributed to age alone probably reflects the effect of mild unrecognized dementia. Studies of optimally healthy older adults who are evaluated each year suggest that overall cognitive function may slow somewhat but does not reflect a significant longitudinal decline for these persons (Schaie, 1989). Therefore, in the absence of disease, older adults can reasonably expect stable overall cognitive function and little or no interference with performance of everyday activity (Rowe & Kahn, 1987). This requires a fundamental shift in the approach to the aging patient, in that clinicians should not automatically attribute memory or cognitive problems that interfere with everyday activities to normal aging, and this should be communicated to the patient's family.

Among adults over 85 years of age, the definition of "normal" cognition is much more difficult to establish. Many neuropsychological tests have not been validated for this group of the "oldest old," and vision and hearing problems often interfere with assessment. Apparently unimpaired individuals over 85 are nonetheless at high risk of cognitive decline (Crystal et al., 2000; Howieson et al., 2003).

Most clinicians do not routinely test mental status in older individuals unless they receive complaints either from the patient or the patient's family. Many demented patients do not, however, so-complain and, on average, most family members do not seek medical attention for the patient until several years after onset of symptoms (if the dementia is progressive). Most patients with DAT, therefore, escape early diagnosis, particularly in primary care settings (Callahan et al., 1995; Cummings, 2004; Cummings & Mega, 2003; Dartigues, 2009; Petrovitch et al., 2001). Cognitive symptoms that are not associated with obvious functional impairment may be dismissed or minimized.

The prevalence of truly curable dementia in the community has been debated (Clarfield, 1995; Weytingh et al., 1995). The probability of finding a reversible cause for dementia has nevertheless likely declined greatly in the past 20 years (Clarfield, 2003; Mok et al., 2004). Prompt recognition of dementia remains important all the same because emerging diagnostic techniques and increasingly effective therapeutic interventions are altering the definition of "treatable" (Fagan et al., 2007). Advantages of an early-as-possible diagnosis of dementia are listed in Table 1.1.

Differential diagnosis of the dementia syndrome

Dementia is a syndrome of multiple possible causes. Like anemia, dementia is a differential diagnostic, not a diagnostic term. In other words, even though AD would for most demented persons be a correct diagnosis, the clinician should systematically consider other disorders. Drugs (polypharmacy!), depression, and

Table 1.1 Advantages of early diagnosis in dementing conditions

For every case
• Provide a diagnostic answer and education for the patient and/or family
For patients with reversible or static diseases (e.g., depression, stroke)
• Relieve the fear of an irreversible or progressive disease
• Treat the underlying disease
• Initiate prevention and/or rehabilitation strategies
For patients with irreversible and progressive diseases (e.g., Alzheimer's disease)
• Treat cognitive and behavioral symptoms
• Plan legal and financial future while patient is still competent
• Initiate management strategies that will postpone dependence and institutionalization

Source: Green, R. C. (2005). *Diagnosis and management of Alzheimer's disease and other dementias* (2nd edn.). Caddo, OK: Professional Communications. Professional Communications, Inc, by permission

metabolic disturbances are relatively common causes of the dementia syndrome (alone or in combination with AD) and are at least partially treatable if not frequently fully reversible (Clarfield, 1988). Important categories and diseases to consider are summarized in Table 1.2, many of which are further discussed in this and other volumes (Cummings & Benson, 1992; Cummings & Mega, 2003; Lerner & Whitehouse, 1994; Mesulam, 2000).

Depression, a very common ailment of the elderly, is worthy of special mention. Disturbances of thinking and memory frequently accompany depression and have led to the use of the misleading term "pseudodementia." Since depression can cause authentic, often but not always reversible functional cognitive impairment, a more appropriate designation would be the dementia syndrome of depression (DSD).

Application of the differential diagnosis assumes the examiner's clinical skills, competence and perseverance in gathering information, and recognizing patterns of neuropsychological impairments. A detailed mental status examination tutorial is beyond the present scope but following is a summary, and further guidance can be found elsewhere (Mandell, 2010; Strub & Black, 2000).

Dementia evaluation

The evaluation process includes physical and mental status examinations, ancillary studies and, most importantly, *history*. We cannot overemphasize the requirement for an *independent, reliable* historian, that is, someone other than the patient. Easily emphasized, this requirement is often not practical because elderly patients often live alone or are otherwise socially isolated. Furthermore, there is no guarantee that family members' or friends' histories are more reliable than that of the patient. For example, family members sometimes attribute actual cause to triggers such as fever, minor surgery, new stresses or a disorienting vacation because subtler symptoms have previously been missed or ignored. Some informants, including spouses, may be embarrassed or otherwise less than forthcoming about alcoholism, physical aggression or sexual indiscretions in the patient's presence; for this reason it's often helpful to interview the informant, particularly a spouse, separately. Other informants, including family members and business associates, may lie.

History taking often illuminates obvious functional impairments. Sometimes, however, there has been no significant activities of daily living (ADL) or occupational deterioration. The examiner should therefore attempt to determine whether the patient has had any consistent decline from his or her *usual* level of competence. For example, a university professor may complain that he or she can no longer teach a familiar class without notes, while someone working with fewer high-level cognitive demands may not notice problems in the workplace but may neglect paying the bills. A problem with evaluating the former is that of "ceiling effect": limited sensitivity to change by any test in very mildly impaired subjects. That is, even extensive neuropsychological testing may fail to detect significant deficits. Such people would not be classified as "demented" by most current criteria. Highly educated persons with minimal or no cognitive symptoms or signs may nevertheless harbor high plaque and tangle counts, enough to satisfy current pathological criteria

Table 1.2 Differential diagnosis of the dementia syndrome

Disease category	*Important examples*
Infections	Prion diseases, syphilis, Lyme disease, chronic meningidites, PML, HIV, Whipple's disease, hydrocephalus
Neoplasms	Primary or metastatic tumors, (particularly of the frontal lobe), paraneoplastic encephalitis, disseminated intravascular lymphoma, hydrocephalus
Traumatic brain disease	Chronic subdural hematoma, contusions, diffuse axonal injury, hydrocephalus, dementia pugilistica
Autoimmune diseases	Multiple sclerosis, primary CNS angiitis, lupus and other vasculidites, sarcoid
Metabolic disorders	Renal and hepatic failure, hyper/hypo-thyroidism/calcemia/natremia, Wilson's disease, metachromatic/adrenoleukodystrophy
	GM_2 and other gangliosidoses
	Pantothenate kinase deficiency
Toxic disorders	POLYPHARMACY
	Drugs: antidepressants, anxiolytics, sedatives, hypnotics, anticholingergics, neuroleptics, multiple cardiac and antihypertensive drugs, narcotics, lithium, antineoplastics, antiepileptics
	Metals (arsenic, thallium, lead, manganese)
	Industrial agents (CCl_4, CS_2, TCE, organophosphides)
	Radiation encephalopathy
	Alcohol and other drugs of abuse
Nutritional/Deprivation	B12/Folate and other vitamin deficiencies
	Wernicke–Korsakoff syndrome
"Degenerative" dementias	Alzheimer's disease
	Frontotemporal and Parkinsonian dementias
	Huntington's disease
	Neuronal ceroid lipofuscinosis
Vascular dementias	Multiple infarct dementia
	"Binswanger's disease"
	"Small vessel ischemic disease"
	CADASIL
Psychiatric disorders	Schizophrenia
	Dementia syndrome of depression
	Bipolar disorder
	Malingering
	Obsessive compulsive disorder

CCl_4 = carbon tetrachloride; CS_2 = carbon disulfide; CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CNS = central nervous system; HIV = human immunodeficiency virus; PML = progressive multi-focal leukoencephalopathy; TCE = trichlorethylene; pantothenate kinase deficiency = Hallervorden–Spatz disease

for AD. Their substantial "cognitive reserve" allows them to remain relatively asymptomatic despite extensive pathology although once (if) symptoms develop, they endure shorter duration of disease before death (Portet et al., 2009; Roe et al., 2008; Roe et al., 2007). Persons with limited education, in less demanding jobs, or those who were already significantly impaired prior to the onset of the dementing illness, in contrast, are vulnerable to "floor effect," a similar test insensitivity to change leading to overestimation of cognitive impairment.

If adequate information acquisition is possible, the following should be included:

- Present history – sudden versus insidious onset; precipitating event; relatively steady decline or remarkable fluctuations or prolonged periods of return to "normal" function; social skills, work, driving, hobbies, community activities, hygiene and eating behavior, housekeeping; sleep (nocturnal behavior; daytime somnolence).
- Past/Social history – alcohol or other substance abuse including tobacco; *all* current medications (including vitamin supplements); head trauma; psychiatric illness (particularly depression); surgical procedures; stroke and other vascular disease; cancer; sleep disorders.
- Family history – dementia; "senility"; "trouble with memory loss like his/hers when older"; "hardening of the arteries" and depression in any first-degree relative, if known.

Office testing of cognitive function should be performed on every person over the age of 65 in an attempt to distinguish demented from nondemented persons and thus inaugurate evaluation of the former. What constitutes "office testing" is often determined by the realities of practice type, time constraints and reimbursement. Many brief cognitive rating scales have been published in response to these realities, through which it is possible to get a reasonable notion of cognitive capacity ("mental status") (Mandell, 2010). These tests are simple to administer, require relatively little training, are in general valid for the functions being assessed, and usually boast good inter-rater and test–retest reliability.

Screening tests

All screening tests have their pros and cons since all are surrogates for more extensive neuropsychological testing. Some are highly verbal thus penalizing patients with relatively more profound language impairment or limited education. Some are directed to the patient, others are informant-based (generally more sensitive) (Tierney et al., 1996), some are dual purpose and all can be combined with elements from other tests to increase sensitivity and specificity (Galvin, Roe, & Morris, 2007), albeit at the expense of additional administration time. In general, all are relatively insensitive to mild cognitive and behavioral impairments and many are subject to educational, racial, cultural, and age biases. Some investigators have even recommended against screening in the absence of truly effective treatments for AD (Boustani et al., 2003).

The most commonly used brief rating scale is the Mini-Mental State Examination (MMSE) (Albert, 2008; Folstein et al., 1975; Mandell et al., 1994). Its advantages are its brevity, ease of administration, and accuracy in detecting moderate dementia. Used sequentially over several years, moreover, scores, in general, track cognitive decline, if any, reasonably accurately. Nevertheless, the MMSE suffers from insensitivity and both floor and ceiling effects, is very language dependent, culturally insensitive, and has limited value as a method to mark cognitive changes in people with AD in short clinical trials (Bowie et al., 1999; Clark et al., 1999).

A published brief informant-based test, the AD8 (Galvin et al., 2005), appears to distinguish dementia from nondementia reasonably well and may also be useful as a self-assessment tool in the absence of an informant, at least when dementia is mild (Galvin et al., 2007).

Other popular instruments include the Short Portable Mental Status Questionnaire (Pfeiffer, 1975), the Montreal Cognitive Assessment (www.mocatest.org) and 7-Minute Screen (Solomon et al., 1998).

Mental status testing

If you are the clinician to whom a patient has been referred specifically for neurobehavioral issues, however, these scales often are inadequate and office or bedside mental status evaluation, tempered in consideration of the patient's educational and cultural background, should include at least brief assessments of attention, language, praxis, visuospatial, memory, and executive functions. Assessment of attention is particularly important because the remainder of the mental status examination will be nonspecifically impaired by inattention. Also recognize that all of these domains are functionally interdependent. Copying a clock face, for example, requires sequencing ("executive") skill and attention as well as visuoperception. Selected tests include:

- Attention: digit span forwards, reciting months of the year in reverse, serial subtractions.
- Language: object and body part naming, assessment of spontaneous conversation (fluent or non-fluent speech), at least *auditory* comprehension, preferably reading comprehension as well; word-list generation and repetition (Green, 2005; Jorm et al., 2007; Knopman & Ryberg, 1989).
- Praxis: three or four transitive limb actions (hair combing, screw driving, teeth brushing, hammering, coin flipping), which are somewhat more sensitive than intransitive actions (waving goodbye, saluting) (Rapcsak, Croswell, & Rubens, 1989).
- Visuospatial: copy an analog clock face or a complex line drawing.
- Executive: clock drawing to command, proverb interpretation, similarities (e.g., between an apple and a grape, or a poem and a statue), coin switch test, cursive alternate writing of the letters "m" and "n" (Mandell, 2010).
- Memory: while assessment of orientation, delayed recall of several unrelated words, current events and verifiable biographical information are fine for overtly demented patients, we recommend adding the relatively brief drilled word span

and Three Words–Three Shapes (TWTS) (Weintraub, 2000) tests to mental status testing to capture more subtle memory deficits in dubious cases. Either adds several minutes to the encounter, but the information derived usually justifies the effort. The TWTS test is particularly useful because it assesses incidental learning (affected early in AD), both verbal and nonverbal episodic memory, and enhances encoding by minimizing the effect of inattention.

For descriptions and details of other brief cognitive tests, see Lezak (1995), Hebben (2002), Weintraub (2000) and other chapters in this book.

Ancillary testing for dementia

Time constraint, type or lack of insurance, availability of ancillary testing, and patient or family cooperation are important issues. A combination of neuropsychological, serologic, and spinal fluid testing is often employed, but these services are out of reach for many patients. Even when available, which tests should be performed depends on the source of the recommendation. Full batteries of laboratory tests and at least one brain magnetic resonance (MR) scan are recommended by many (Blennow et al., 2006; Cummings & Benson, 1992; Green, 2005; Knopman et al., 2001); others argue that this is a costly shotgun approach unlikely to determine a treatable cause in the vast majority (Clarfield, 1988; Siu, 1991).

Including B12, folate, and TSH levels, for example, is a point of some contention. Treatment of B12 encephalopathy, if instituted early, improves some functions, but not others, including memory (Freidenberg & Drake, 1990). Furthermore, high-dose B vitamin supplementation fails to slow cognitive decline in patients with presumed AD (Aisen et al., 2008). The American Academy of Neurology (AAN) Practice Parameter (Knopman et al., 2001), acknowledging that the association of B12 deficiency and hypothyroidism with dementia is not clear and that treatment of same in cognitively impaired people often yields no improvement, nevertheless recommends B12 (and TSH) measurement at *guideline* level.

If ancillary testing is available (and allowed), most clinicians still check, and we recommend: CBC, B12, TSH, liver and renal function. We also recommend brain MRI or, if not possible, at least a noncontrast brain CT scan (Knopman et al., 2001). MRIs in the elderly often demonstrate nonspecific "atrophy" and equally nonspecific scattered bright T2 white matter signals (leukoaraiosis; "microvascular white matter ischemic changes"). The aim of clinical neuroimaging is two-fold:

- to rule out (or in) significant abnormalities that are themselves treatable (e.g., chronic subdural hematoma, meningioma) or indicative of correctible underlying disorders (hypertension);
- to identify such specific perturbations as neoplasms, small or large infarcts, focal atrophy, infections which one could reasonably implicate as a cause of cognitive decline.

Serological testing for syphilis is recommended only if a patient has some specific risk factor or resides in an endemic area (Knopman et al., 2001). Consider additional tests (e.g., antiphospholipid antibodies; HIV) if history, physical examination or other studies warrant them.

Routine electroencephalography (EEG) in general is not useful in the routine dementia evaluation except when Creutzfeldt–Jakob disease (CJD) or subclinical seizures are strongly suspected, deterioration is rapid, or possibly in young (less than 60 years) persons. In AD, once clinically established, the EEG is diffusely but nonspecifically abnormal (Smith, 2005).

Occasionally, older patients with obstructive sleep apnea (OSA) can present with cognitive impairment or a confusional state, which may be reversible with proper treatment (Naegele et al., 1995). This underscores the importance of asking about the patient's sleeping habits, particularly daytime somnolence. Consider overnight polysomnography when OSA or other parasomnia is suspected from the history.

Lumbar puncture (LP) is indicated when data suggest neurosyphilis, CJD, any type of meningitis or vasculitis, demyelinating disease, or, again, when deterioration seems rapid. In general, LP is not useful for routine dementia evaluation. Cerebrospinal fluid (CSF) analysis is, however, assuming more importance in the specific diagnosis of AD (Li et al., 2007b), as we discuss later in the chapter.

Communication with the patient and family/caregivers

If you have diagnosed any type of dementia, should you inform the patient? One needs to consider each case individually, but in general, the answer is "yes," and this includes involved family members who collectively, in effect, become "the patient" (Mittelman et al., 2006). Patients and families must preferably be informed, if deterioration is expected, when the patient's comprehension and reasoning are optimal and he/she may be more willing to accept help with managing social needs, or consider therapeutic clinical trials. Driving can also be raised as an issue at this time (see later section). When patients have no support system, try to assist the patient in establishing support networks and relevant services (Grossberg & Desai, 2003).

Alzheimer's Disease

The conventional understanding of AD may be summarized:

- a degenerative brain disorder characterized by progressive intellectual and behavioral deterioration;
- symptomatically almost always heralded, and usually dominated by, memory disorder, with prominent visuospatial and language impairment in the context, at least early in the course, of preserved social skills;

- association with several neuropathological markers, the most distinctive of which are amyloid plaques and neurofibrillary tangles which appear initially in medial temporal limbic structures and then spread to neocortex (Braak & Braak, 1991);
- broad age range of clinical onset but usually after age 65;
- life span after diagnosis generally about 10 years, but can be as long as 20 years;
- motor and primary sensory disturbances are either not present or are late manifestations.

Diagnosis

Emerging diagnostic techniques for identifying persons prior to development of *any* symptoms are discussed later in this chapter and elsewhere in the book. In the absence of fully reliable biological markers for AD, major issues in clinical diagnosis are the trade off between sensitivity (the proportion of persons with AD-specific pathology who are accurately diagnosed in life as having the disease) and specificity (the proportion of persons without the disease who are accurately diagnosed as *not* having the disease), and what is meant by "disease."

As we go to press, AD remains a clinical diagnosis which for years has been based on criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM IV) (American Psychiatric Association, 2000) and the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 1984). As noted previously, the former require both memory disorder and deterioration in social function or in ADL. The latter do not require ADL debasement but specify insidious onset and demonstrable absence of other systemic or neurological diseases that might account for the cognitive deficits. NINCDS-ADRDA criteria designate AD as definite (clinical diagnosis with pathological confirmation), probable (typical syndrome without histopathology) and possible (atypical clinical features, no pathology but no other apparent diagnosis).

The good news is that when compared with histopathological gold standards (Braak & Braak, 1991; Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. The National Institute on Aging, and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease, 1997; Mirra et al., 1991), NINCDS-ADRDA criteria for probable AD are very good (over 90% sensitivity) (Galasko et al., 1994), even in early stages of the disease (Salmon et al., 2002). This means that when brains of demented patients are burdened with sufficient AD pathology, well-trained clinicians are almost always correct when matching clinical diagnosis with pathology. However, high sensitivity is paid for by low (~20–80%) specificity, which is even lower for the "possible AD" diagnosis (Varma et al., 1999).

Many Alzheimer brains prove not to have "pure" plaque and tangle pathology; most have significant vascular disease and many have abundant cortical Lewy bodies

even when parkinsonism was absent in life (Lim et al., 1999; Lopez et al., 2002; Olde Rikkert et al., 2006). Furthermore, most patients with pathologically proven non-Alzheimer frontotemporal lobar degenerations also fulfill NINCDS-ADRDA criteria (Varma et al., 1999). In other words, the criteria are better at predicting the presence of Alzheimer-type pathology (higher sensitivity), particularly as dementia worsens, than at accurately identifying patients with co-morbid pathologies (lower specificity) (Chui, 2002; Cummings, 2005b; Jellinger, 2002; Knopman et al., 2001; Strub & Black, 2000). For these reasons, major revision of the NINCDS-ADRDA criteria has been proposed (Dubois et al., 2007). For the present, since most cases incorrectly diagnosed as "just" AD have equally irreversible diseases, high sensitivity may be more important than high specificity as long as clinicians do not miss the minority of reversible disorders. The health consequences and economic costs of making false-positive or false-negative diagnostic errors will dictate whether higher sensitivity, higher specificity, or high values for both are required for a test or procedure to be clinically useful.

AD risk and protective factors

In epidemiological studies, the terms "risk factor" and "protective factor" should be interpreted cautiously since the observed risk or benefit can actually be due to known or unknown confounders. Several factors have nevertheless been consistently associated with greater or lesser risk of developing AD.

- Aging confers the greatest risk for dementia in general and AD in particular.
- Family history: No clear genetic pattern is evident in the vast majority (over 95%) of patients, who are said to have "sporadic" AD. Family history of AD increases relative risk three- to fourfold (at least up to age 80). An important figure for clinicians to know when they are asked by a family member about his or her own risk is this: The cumulative incidence of AD in first-degree relatives of individuals with AD is 41% by the ninth decade of life for white Americans, with even higher risks for dementia in African Americans (Cupples et al., 2004; Green et al., 2002) (Figure 1.2).
- Susceptibility genes: The genetics of heightened risk in sporadic cases has yet to be fully elucidated. Risk has been associated with at least 250 susceptibility (non-deterministic) genes, including *SORL1* (Bertram et al., 2007; Blacker & Tanzi, 1998; Rogaeva et al., 2007). The most robust risk by far is that associated with the APOE polymorphism on chromosome 19. This tri-allelic (ε2, ε3, ε4) gene codes for apolipoprotein E (ApoE), a remarkable protein involved in multiple normal physiological functions. The apoE2 isoform has been shown in multiple studies to confer at least some degree of protection against developing AD (Talbot et al., 1994). Possession of ApoE4, in contrast, increases risk for AD and several other disorders, including multiple sclerosis and obstructive sleep apnea (Gozal et al., 2007; Mahley et al., 2006), and to enhance other AD risk factors (e.g., head

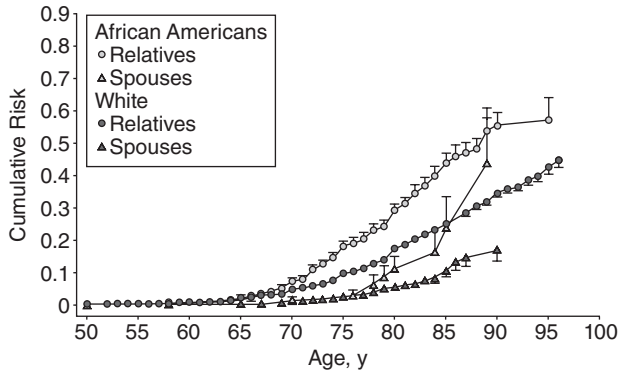

Figure 1.2 Cumulative risk of dementia in first-degree biological relatives and in spouses of probands, stratified by ethnicity of probands error bars indicate standard error (SE)
Source: Green, R. C., Cupples, L. A., Go, R., Benke, K. ., Edeki, T., Griffith, P. A., et al. (2002). Risk of dementia among white and African American relatives of patients with Alzheimer disease. *Journal of the American Medical Association, 287*(3), 329–336.

trauma). Inheritance of the ε4 allele significantly increases risk (3× for a heterozygote, about 15× for a homozygote) of developing AD, and at an earlier age.

Roughly 50% of sporadic AD victims do not possess the ε4 allele (Auguste D. was homozygous ε3) (Graeber et al., 1998), clearly indicating that other factors are involved (Hayden et al., 2009), and the strength of the association appears to vary in different ethnic groups (Farrer et al., 1997). For this and other reasons, APOE genotyping is currently not recommended for risk assessment except within controlled research studies (Green, 2002).

- Deterministic autosomal dominant transmission of AD resulting from multiple mutations on chromosomes 1, 14, 21 and likely others occurs in less than 5% of AD patients, in whom symptoms typically emerge quite young, sometimes as early as the third decade.
- Other putative, established, and in some cases *still-debated* risk factors include: traumatic brain injury (Guo et al., 2000); muscle weakness in old age (Boyle et al., 2009); systemic inflammatory activity (Holmes et al., 2009; Tan et al., 2007); low bone density in women but not men (Tan et al., 2005); midlife depression (Green et al., 2003; Ownby et al., 2006; Wilson et al., 2003); female gender; low serum docosahexaenoic acid (DHA) (Schaefer et al., 2006); isoflurane anesthesia (Xie et al., 2007); metabolic syndrome (Razay et al., 2007); low folate intake (Luchsinger, Tang et al., 2007); low thyroid stimulating hormone level (van Osch et al., 2004); obesity (Jagust et al., 2005; Kivipelto et al., 2005); obesity in younger but not older persons (Luchsinger, Patel et al., 2007); weight loss in women but not in men (Knopman et al., 2007); weight loss in the elderly (Fitzpatrick et al., 2009); vascular risk factors including hypertension (Launer et al., 2000; Petrovitch et al., 2000), smoking (Ford et al., 1996; Reitz et al., 2007; Rinne, 1989; Shalat

et al., 1987; Swan & Lessov-Schlaggar, 2007), not smoking (Ott et al., 1998), diabetes mellitus (Arvanitakis et al., 2004; Luchsinger et al., 2001), hyperhomocysteinemia (McMahon et al., 2006; Nilsson et al., 2002); low cerebral perfusion (Bradley et al., 2002); low educational achievement (Cummings, 2005b; Ngandu et al., 2007; Snowdon et al., 1996; Stern et al., 1994; Strub & Black, 2000); poor performance on verbal, visual memory and other learning tests (Blacker et al., 2007; Green, 2005; Jorm et al., 2007; Knopman & Ryberg, 1989); chronic psychological stress (Wilson et al., 2005); apathy (Bottiglieri et al., 1990; Robert et al., 2006; Starkstein et al., 2006); alcohol consumption (Paul et al., 2008) and many others.

- Possible protective factors include "mental exercise" (i.e., learning new skills in middle age and beyond) (Wilson et al., 2007); physical exercise (Boyle et al., 2009); *modest* alcohol consumption (Solfrizzi et al., 2007; Solfrizzi et al., 2009), especially red wine; caffeine consumption (women) (Ritchie et al., 2007); "healthy" diet including antioxidants (Galvin, 2007; Qin, Yang et al., 2006); increased physical activity (Mattson, 2008; Weuve et al., 2004); and diabetes (slower rate of cognitive decline) (Sanz et al., 2009).

Pathophysiology – The amyloid hypothesis

The cause of AD is not fully understood. By way of introduction, the "amyloid cascade" hypothesis is now generally accepted as at least a very important contributor, if not the sole explanation. In brief, both autosomal dominant and sporadic forms of AD likely result from the generation and accumulation of toxic fragments known as beta amyloid or amyloid beta (Aβ). Aβ fragments accumulate extracellularly, oligomerize and damage neuronal synapses, then precipitate eventually into misfolded neuritic plaques, which in turn seem to provoke inflammation, free radical formation, and, likely very early on, oxidative stress (Nunomura et al., 2001). This process kills neurons and disrupts neuronal networks.

Autosomal dominant AD is a consequence of several mutations that generate abnormal species of *secretases,* which in turn cause aberrant cleavages of the transmembrane amyloid precursor protein (APP) into Aβ, particularly its very toxic 42 amino acid isoform. This may be an important mechanism as well for sporadic AD.

Aβ may also interfere with microtubule-associated proteins (MAPs) causing clumping of phosphorylated tau filaments into neurofibrillary tangles.

Dementia severity correlates more with tangle than with plaque load, leading some to claim that AD is primarily a tauopathy rather than an amyloidopathy. Another explanation for this correlation is that Aβ deposition reaches a "ceiling" early in the disease process, while tangle formation, synaptic loss and gliosis continue throughout the course (Giannakopoulos et al., 2003).

The exact role of amyloid accumulation in the pathogenesis of AD remains to be fully elucidated (Duara et al., 2009; Killiany, 2009), and there is increasing

speculation that a variety of exogenous factors, particularly infection by a variety of organisms, might ultimately underlie inflammation, oxidative stress, and other proposed pathogenetic mechanisms (Honjo et al., 2009; Kamer et al., 2008).

Pathology

In brief: The brain is grossly atrophic, most profoundly in frontal, parietal and temporal gyri, particularly entorhinal cortex and hippocampus, with commensurate ventricular enlargement. Brain weight and volume are usually markedly reduced. The major histopathological hallmarks of AD are:

- *Extracellular* neuritic (amyloid) plaques (NP), composed of neuronal and glial processes and Aβ, and distributed primarily throughout the association and limbic cortex as well as basal forebrain, substantia nigra, raphe nuclei, and locus ceruleus. Amyloid is also deposited in cerebral arterioles. AD is thus one of several disorders associated with cerebral amyloid angiopathy (Pardridge et al., 1987), a risk factor for lobar hemorrhage.
- *Intracellular* neurofibrillary tangles (NFT). Tangles can be found in the brains of nondemented older people and are a feature of other neurodegenerative diseases, but in AD have a relatively distinctive paired helical structure and are quantitatively highly correlated with dementia severity. The major components of NFTs are the hyperphosphorylated MAP *tau, and ubiquitin*. The intracellular deposition of tau and its disruption of the normal cytoskeletal architecture may be an important factor in neuronal death and is the target of several therapies discussed below (Iqbal et al., 2003).
- Widespread cortical neuronal loss and synaptic destruction. This loss is characteristically most obvious in hippocampus, temporal neocortex and in basal forebrain nuclei (nucleus basalis), but is also prominent in several subcortical structures including substantia nigra. Synaptic degeneration may be the major proximate cause of early cognitive decline.

Clinical features

AD is the prototypical "cortical dementia." Benson et al. formulated the cortical/subcortical dementia dichotomy in 1981 (Benson, 1983; Cummings, 1982). Controversy regarding the usefulness of this terminology notwithstanding (Brown & Marsden, 1988; Mandell & Albert, 1990; Mayeux et al., 1983), cortical dementia is code for a neuropsychological *pattern* suggesting multi-focal cortical damage, including amnesia, aphasia, agnosia, apraxia, prominent visuospatial impairment, and dysexecutive symptoms but, until late in disease course, normal gait, muscle tone, posture, speech volume and articulation, and lack of movement disorder (Cummings & Benson, 1992; Huber, 1990). Cortical dementias usually conform to

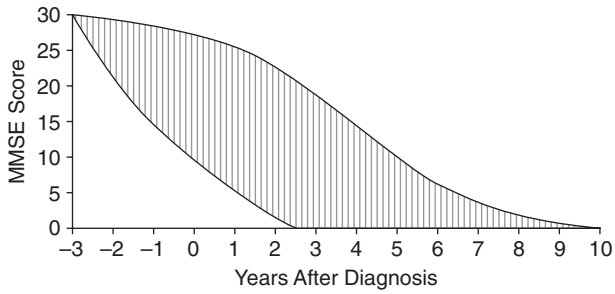

Figure 1.3 Deterioration in Mini-Mental State Examination scores over time
Source: Modified from Green, R.C. (2005). *Diagnosis and Management of Alzheimer's Disease and Other Dementias* (2nd edn.). Caddo, OK: Professional Communications, Inc., by permission

one of four "profiles" described by Mesulam (2000). These profiles reflect their dominant clinical features and include progressive language, comportmental/executive, and visual syndromes. Each clinical profile differs in its probability of association with specific underlying pathology.

Pathological AD has ultimately been associated with all of these profiles, but its signature syndrome is that of "progressive amnestic dysfunction" (sometimes referred to as progressive amnestic dementia), which henceforth will be referred to as "dementia of the Alzheimer type" (DAT). It is the most common dementia profile affecting the elderly. Although early executive, behavioral, visuospatial and language impairments are common in what proves to be pathological AD (Neary et al., 1986), until reliable biomarkers are readily available, lack of early and prominent memory impairment, that is, a non-DAT pattern, should raise at least some doubt regarding the diagnosis of AD (Mesulam, 2003).

The cognitive decline of DAT in general is inexorable (Figure 1.3): indolent in early stages, accelerating with disease progression (Morris et al., 1993), but can plateau (Bozoki et al., 2009).

DAT has for years been described as progressing through "stages." The staging formula relies on the relatively stereotypical evolution of symptoms and signs through three clinical phases variously termed initial, early, *mild* or stage I; intermediate, *moderate* or stage II; and advanced, *severe*, final or stage III disease (Table 1.3) (Cummings & Benson, 1992; Green, 2005; Hodges, 2006; Mesulam, 2000). Each stage denotes a characteristic *pattern* of functional losses (language, memory, social engagement) and abnormal gains (delusions, wandering, agitation), which collectively equate to severity.

There is nevertheless variation in time course of each stage among individual patients with DAT. One or more stages may be relatively prolonged for one patient compared with another, and for any given patient, duration of stages also is variable (Grady et al., 1988). There is overlap even when disease progression is orderly. The memory impairment usually ascribed to moderate stage disease, for example, may

Table 1.3 Clinical characteristics of dementia of the Alzheimer type

	MCI	*Mild*	*Moderate*	*Severe*
Memory				
Working	–	–/+	++	+++
Anterograde episodic	++	+++	+++	+++
Remote	–/+	–/+	++	+++
Semantic	–/+	+	+++	+++
Attention and executive	–/+	++	++	+++
Language	–	–/+	+	++
Visuospatial and perceptual	–	–/+	++	++
Praxis	–	–	++	++

– = absent; + = present; –/+ = variable; MCI = mild cognitive impairment
Source: Hodges, J.R. (2006). Alzheimer's centennial legacy: Origins, landmarks and the current status of knowledge concerning cognitive aspects. *Brain, 129*(Pt 11), 2811–2822. By permission of Oxford University Press

associate with language deficit more characteristic of mild stage (Storandt et al., 1986). Furthermore, day-to-day variability even in early DAT is common and dependent on factors such as intrinsic circadian rhythm (Volicer et al., 2001), blood glucose, pain severity (if any), sleep adequacy, drugs, and social stressors.

Once ADL dependence is fully established, worsening tends to accelerate. More severe memory impairment combines with fluent (usually) aphasia, apraxia, multimodal agnosias, attentional and reasoning disturbances, incontinence, and a variety of behavioral changes including wandering and pacing. Later, patients slow down, cognitive function cannot be assessed, communication becomes impossible, primitive reflexes often appear, and weight loss usually is prominent. In late stage, ambulation ceases, patients become bedridden, cachectic, and susceptible to infection. End of life is spent for months, sometimes for years, in a mute, tetraplegia-in-flexion state (Cummings & Benson, 1992).

Clinical neuropsychology of DAT

Following is a discussion of clinically pertinent neuropsychological features of DAT. Expanded analyses of domain-specific (frontal-executive, visuospatial, language, memory) functions and their clinical assessment are covered elsewhere in this book.

Memory

By definition, DAT is characterized primarily by progressive memory dysfunction. Clinically, memory impairment is manifest initially as inconsistent but more-than-before forgetfulness, particularly of names, phone numbers and recent conversa-

tions, and misplacement of personal belongings. Missing appointments and "forgetting to remember" events and tasks to occur in the future (prospective memory) is another very early feature (Huppert & Beardsall, 1993). Functional memory impairments nevertheless usually are few in mild-stage DAT. For example, housekeeping, most social and sporting activities, driving and, depending on the job, professional responsibilities are *usually* reasonably well maintained, particularly if other people "cover" for diminished capacity. At this point, clues, cues, and multiple choices usually improve retrieval and recognition of forgotten items. With worsening, forgetting becomes more persistent, resulting in repetitive iterations of the same questions and statements, often accompanied by irritable insistence that he/she is doing no such thing.

Memory deficit sufficient to constrict ADL signals moderate stage DAT. By this point, patients can neither store new information for more than a few minutes nor maintain a coherent stream of thought (Mesulam, 2000). The result is increasing dependence on a spouse or friend, who has by this time become a *caregiver*. Memory is difficult to characterize, much less to test, in severe DAT because of multiple other cognitive impairments. At this stage, even the most overlearned memories are starting to be lost or inaccessible, including recognition of close family or even of personal identity.

Many patients initially are acutely aware of their memory impairment and develop compensatory strategies such as list keeping, dependence on speed dialing, and asking a spouse for names in anticipation of personal encounters. Many become depressed about their forgetfulness and seek professional assessment. Not infrequently, however, they vociferously deny any cognitive problem, including memory, a consequence of anosognosia (lack of awareness of deficits), which at some point is virtually universal, although not always absolute (Grut et al., 1993; McGlynn & Kaszniak, 1991).

Neuropsychological testing demonstrates a variety of memory problems, the dissolution reflecting involvement of relatively distinct anatomical systems. Episodic memory, the ability to encode, retain and recall at will specific events and items, particularly those recently acquired, is the earliest and most affected, before behavior and language impairments become clinically manifest. If a patient can be tested at the earliest stage of DAT, intentional acquisition (encoding) of small amounts of new information is variable but fairly normal (Schachter & Kihlstrom, 1989). In contrast, poor delayed free recall even of subspan (two or three items) word lists after seconds-lasting distracting tasks is often apparent (Kopelman, 1985; Welsh et al., 1991), as is impairment of incidental learning (learning without awareness of doing so). Brief stories and nonverbal material also, in general, are poorly recalled (Weintraub, 2000) and soon become impervious to most cuing techniques and to repetition (Lezak, 1995). Recognition formats may show improvement over free recall but even then performance in most cases is significantly below established norms for age. Patients tend to contaminate their responses with irrelevant items from other lists or previous tests.

In contrast to recent memory, remote general and autobiographical information is *relatively* preserved (Piolino et al., 2003): "I can remember what I did in the army, but I can't remember what I ate for breakfast." Patients therefore tend to become preoccupied with the past. The dissociation between "recent" and "remote" memory preservation has, however, been exaggerated. Proper testing can demonstrate that, in mild DAT, patients perform poorly on tests even of autobiographical memory and that deficient naming, ostensibly a "language" impairment, likely has a semantic memory basis (Albert, 2008; Warrington, 1975). Implicit (unconscious) learning, including "procedural memory," at least for simple tasks, is usually spared well into the illness (Eslinger & Damasio, 1986; Harrison et al., 2007). The practical effect on ADL of a curious "rebound phenomenon," the ability of some early AD patients to recall stimuli better after three days' delay than at one day (Freed et al., 1989), is not clear.

Working memory (WM) is that needed for integrating the beginning of this sentence with its end, and for mentally manipulating small bits of information over several seconds. WM likely degrades with normal aging (Gazzaley et al., 2005). At least as assessed routinely by digit span testing, WM is spared in early DAT, as noted above, but acquisition of supraspan lists dwindles shortly after onset of overt memory disorder. Even in mild disease, working memory is demonstrably defective with tests of complex and divided attention (Becker, 1988; Grady et al., 1989; Perry & Hodges, 1999). Some early stage patients show significant deficits in all aspects of information acquisition (Lezak, 1995).

As a mater of differential diagnosis, the memory loss of DAT for years has been distinguished from that associated with microvascular ischemic disease ("vascular cognitive impairment"). This differentiation has recently been challenged (Reed et al., 2007).

Visuospatial and perceptual deficits

Associative visual cortex is an early locus of AD pathology (McKee et al., 2006, 2007). Not surprisingly, visuospatial dysfunction is an important component of DAT. It occurs early but in general is not clinically apparent until memory and attentional disturbances are fully established. The more subtle the deficit, the more rigorous the testing required to evoke it. For example, patients having little difficulty copying the MMSE intersecting pentagons may fail utterly when attempting to copy more complex line drawings (Rey, 1941) or to perform a block design test. Equally unsurprising, by the time perceptual deficits become a functional problem, differentiating "pure" visuospatial impairment from accompanying attentional, memory and executive perturbations is difficult. As with nondemented patients with other structural brain lesions (e.g., stroke), visuospatial dysfunction is referable mostly to right hemispheric damage.

Once apparent, clinical manifestations include:

- environmental and geographic disorientation: getting lost in familiar locations and when driving; aimless wandering;

- dressing disturbance ("apraxia"): inability to locate shirt sleeves or pant legs or to match socks;
- impaired contrast and figure-ground discrimination(Mendez et al., 1990): consistently missing the toilet when urinating, difficulty locating misplaced objects, inability to segregate clothes properly within a closet;
- construction disturbance: defective copy even of 2-D line drawings and poor judgment of line orientation (Finton et al., 1998);
- various visual agnosias: non-recognition of common objects and their use (eating utensils) and familiar faces, including one's own ("mirror sign"), inability to discriminate among members of a given class (e.g., different car brands, animal species);
- poor clock drawing (one of several reasons for this);
- defective imaging: tasks requiring mental rotation of objects, topography;
- Unique, AD-associated cataracts, macular degeneration, and glaucoma (Valenti, 2010).

Language

Aphasia (the acquired disturbance of language secondary to brain damage) is an important feature of DAT. Progressive and isolated language dissolution occasionally is *the* dominant clinical manifestation of what proves pathologically to be AD. In general, however, language impairment either parallels or follows that of memory, but language loss is not "global" until end stage; even then some patients who are otherwise mute retain minimal verbal responsiveness to their names or other audible stimuli (Volicer et al., 1997). Language characteristics for a given patient depend upon the severity of the dementia and loss in most cases occurs in a predictable sequence. Both output (speech and writing) and input (auditory and reading comprehension) are affected. Early, some linguistic functions are clearly better preserved than others, but, again, adequate testing almost always shows preservation to be relative when compared to properly matched normals.

Word-finding difficulty during everyday discourse is usually the earliest manifestation but auditory comprehension impairment can be demonstrated in some patients as well. Patients are often quite disturbed when searching for words and attempt to remedy conveyance via circumlocution. In some cases speech initiation becomes less spontaneous. Testing at this point usually demonstrates preserved confrontation naming but, in comparison, impoverished word-list generation. As patients become less engaged in conversation, parlance becomes "empty" as first nouns and then verbs elide from their lexicon and words without clear referents such as "thing/it/this" invade content and reduce meaning. At mid-stage, patients are significantly anomic in confrontation tasks and auditory comprehension deteriorates. If a patient cannot name a proffered item, most likely he/she will not be able to define it (Hodges & Patterson, 1995). Language remains fluent with preserved repetition while semantic (whole word) and neologisitic (non-word) paraphasias litter the output, a picture resembling transcortical sensory aphasia (Cummings et al., 1985). Basic language structure is nevertheless intact, that is,

"nouns are placed where nouns should go and verbs and other types of words are placed where they should go" (Bayles, 1988). Patients eventually become dysprosodic, failing both to charge speech with emotional tone and to recognize emotional content in the language of others (Allender & Kaszniak, 1989). A variety of reiterative speech disturbances such as echolalia (repeating others' words and phrases) and palilalia (repeating his/her own words and phrases) (Cummings & Benson, 1992) precedes terminal mutism; some patients become mute while still fully ambulatory.

Articulation often remains normal, basically as long as the patient speaks, although later in the course of DAT, dysarthria and stuttering are not unusual (Cummings & Benson, 1992).

Apraxia

Apraxia is a family of *cognitive* motor disorders that entail the loss or impairment of the ability to program motor systems to perform purposeful skilled movements in the absence of weakness, dystonia, tremor, other movement disorders, seizures, defects of sensory feedback or poor comprehension, agnosia or inattention (Heilman, 2003). This definition does not include entities such as constructional, dressing, and gait "apraxias" because these primarily are visuospatial or noncognitive motor disorders. Apraxia has often been described in association with DAT but its role as a symptom, that is, its clinical impact, has been confounded by imprecision of the term.

The two common types of apraxia, ideational (failure to pantomime correctly the sequence of events of a complex motor act, such as selecting and lighting a cigarette) and idiomotor (inability to do on command an act that can be performed spontaneously, such as brushing one's teeth) (Cummings & Benson, 1992) are usually demonstrable by mid-stage. Body part as tool substitution (using the index finger to brush teeth rather than pretending to hold a toothbrush) is a common manifestation of idiomotor apraxia (Rapcsak et al., 1989), but in advanced stages content errors (sawing wood instead of combing hair, or a nonsense action) also appear. Apraxia rarely can be an early disabling symptom of what proves to be AD (Green et al., 1995) but if specifically sought, it can sometimes be demonstrated even before other cognitive impairments are obvious (Heilman, 2003).

Attention

What often is referred to as "attention" is of particular interest. Like memory and language, a network of anatomical areas underlies attention, which has been described by several models and has several subcomponents: selective, sustained, and divided attention (Grady et al., 1989; Perry & Hodges, 1999). If by attention one is referring essentially to vigilance (sustained attention), it is preserved in early DAT even when new learning is clearly impaired, at least when assessed by tests such as digit span, reciting months in reverse, serial 3s or 7s subtractions or the "Trail Making A" test. In the absence of significant aphasia, poor performance on these tests should suggest another or at least additional disorder (e.g., hypoglycemia). As

DAT worsens, patients eventually become distractible and are often described as having poor concentration. We often hear patients complain that reading for pleasure has become too difficult because "I can't concentrate."

Dysexecutive syndrome

The domain of *executive* ("frontal executive") *functions* has been increasingly recognized. This term refers to a variety of abilities ranging from planning, manipulation of information, and initiation and termination or inhibition of behavioral responses, i.e., social judgment (Hebben, 2002). Lezak posits four executive components: volition; planning; purposive action; and effective performance (Lezak, 1995). All are necessary for appropriate, socially responsible adult conduct. *Dys*executive syndromes are often attributed to "frontal systems" damage, but they may result from diffuse and extra-frontal focal brain lesions (Cummings, 1993; Stokholm et al., 2006).

An entire chapter of this book is devoted to the description and testing of executive impairments. For now, a few statements are in order. Executive deficits, as with visuospatial dysfunction, are demonstrable in most DAT patients at mild stage (Albert, 2008; Stokholm et al., 2006).

Assessment of executive dysfunction is, nevertheless, not easy. The examiner usually determines the goals, directions, materials, and timing of any given test. Executive function testing, in contrast, requires transferring "goal setting, structuring, and decision making from the clinician to the subject within the structured examination" (Lezak, 1995). Although in general not an overt disabling feature of early DAT, deficits in executive function influence performance in multiple cognitive domains. "Working memory," for example, essentially is an executive function, and poor organizational strategies can affect verbal learning and impede retrieval of "remote" memories. Even a relatively simple test of language comprehension, *executing* a three-step command, demands maintenance of serial order. Executive disturbances likely, in fact, underlie the ADL impairments at a stage when memory disorder is the only obvious symptom (Grady et al., 1989; Hodges, 2006; Perry & Hodges, 1999).

Neuropsychiatric issues

Behavioral aberrations are core features of DAT, were very prominent early in Alzheimer's original patient, and eventually arise in all patients. Manifestations are protean, are roughly severity-specific, but occur earlier in some patients than in others. Once established, some evolve, some remain stable, some recede. Behavioral deterioration may be triggered suddenly by an acute systemic perturbation, a change in environment, or any other stressor. Changes range from apathy and social withdrawal ("pseudo-depressed") to disinhibition, agitation, eating disorders, and frank psychosis ("pseudopsychopathic") (Cummings, 1982).

In early DAT, personality and social behavior in general are broadly preserved (Galton et al., 2000). Subtle indifference and emotional detachment are common (Petry et al., 1988) but frequently either go unnoticed or may even be welcomed

(Mesulam, 2000). Many individuals thus continue to function well socially, leading others to underestimate or excuse memory, language or executive impairments until, for example, sudden disruption in routine leaves the patient unable to deal with a novel situation (Cummings & Benson, 1992). The tolerance for personality change, however, usually is less than that for insidious memory loss, which for most people is a "normal part of aging." Patients with overt personality change therefore are referred, or dragged into, an evaluative process soon after onset.

Apathy (lack of motivation relative to the patient's baseline state) is common in many brain disorders and is worthy of special consideration. Ranging from mild passivity and loss of interest to abulic immobilization, and difficult to evaluate, apathy is the most common neuropsychiatric manifestation of AD and a source of considerable caregiver stress (Marshall et al., 2007). Although prevalence increases with severity of cognitive impairment (Bózzola et al., 1992; Landes et al., 2005; Mega et al., 1996), noticeable apathy may appear when cognitive impairment is minimal (Onyike et al., 2007), when it can be misdiagnosed as depression. This misdiagnosis is understandable since low mood and apathy frequently go hand in hand. Apathy and depression nevertheless are separate phenomena with different neuroanatomic substrates, and at least half of apathetic DAT patients are not depressed (Geldmacher, 2007; Hodges, 2006; Levy et al., 1998). The distinction is clinically important because generally well-tolerated drugs such as selective serotonin reuptake inhibitors (SSRIs) may worsen apathy (Barnhart et al., 2004).

Apathy is a double whammy for patients and their caregivers because it is also strongly associated with anosognosia and executive dysfunction (McGlynn & Kaszniak, 1991; McPherson et al., 2002): "They don't know and they don't care." This combination underlies the poor hygiene and inappropriate dressing so common in mid-stage DAT. Apathetic patients are more ADL-dependent than those without apathy at a similar level of cognitive impairment, are more likely to manifest other abnormal behaviors (Chow et al., 2009), and, even when functional impairments are not yet an issue, have double the risk of progression to overt DAT (Starkstein et al., 2006). Apathy is difficult to treat, given the probability that the patient already will have been prescribed several other medications, but ameliorative effects of cholinesterase inhibitors have been shown (van Reekum et al., 2005; Wynn & Cummings, 2004).

Apathy very often is replaced by or mixed with a variety of disruptive behaviors as the dementia worsens. These include psychomotor agitation, aggression, resistance, delusions and hallucinations, repetitive vocalizations, shadowing, and frank psychosis. Disruptive behaviors are common and usually late manifestations of AD although agitation occurs in a significant percentage of even mildly demented patients (Cummings, 2005a). When evident early in the course, delusions and hallucinations (usually visual) in particular predict more rapid cognitive and functional decline (Scarmeas et al., 2005), are more likely to prompt institutionalization than even incontinence, and are associated with longer hospital stays (Wancata et al., 2003). Delusions are more common than hallucinations and usually are persecutory, involving fears of personal harm, property theft, and spousal

infidelity. Capgras syndrome (a belief that someone, often a spouse, has been replaced by an identical imposter) and other reduplicative phenomena also occur (Rubin, 1992).

Behavioral problems in general become more common and more severe as cognitive abilities deteriorate, although the pattern changes. Delusions and hallucinations tend to decline as the disease proceeds from moderate to severe stage, while agitation, aggression, and inappropriate shouting increase (Cummings, 2005b).

There appear to be both cultural-dependent similarities and differences in behavior patterns at similar stages (Binetti et al., 1998; Ortiz et al., 2006). Particular aberrant behaviors possibly correlate with pre-morbid personality traits, although findings among various studies have been mixed (Archer et al., 2007). Persons with at least one copy of the ApoE ε4 allele may be more likely to become agitated (Craig et al., 2004). Behavioral symptoms, depending on specific type, have been correlated with both right medial frontal lobe damage (Rosen et al., 2005; Senanarong et al., 2004) and with left frontotemporal hypoperfusion, regardless of dementia etiology (Hirono et al., 2000).

Virtually every patient with a progressive dementia develops agitation, wandering, sleep difficulties, or other behavioral problems at some point in the course of the disease. The clinician should be mindful that behavioral symptoms are manifestations of an older, diseased brain that will usually be far more vulnerable to the side effects of psychiatric medications than the brain of a younger or nondemented patient. In practice, patients will often have combinations of these symptoms or linked symptoms (e.g., a patient who paces due to anxiety). Agitation and aggression, for example, are provoked by:

- confusion due to cognitive, memory, or language impairments;
- delusions;
- depression in a patient too impaired to express distress in another manner;
- sleep disturbance;
- pain (fall injury, decubitus ulcers, arthritis, renal colic, etc.);
- infections, metabolic perturbations, and drug interactions and changes;
- trivial environmental changes including recent travel and bathing (Corey-Bloom et al., 2006; Press & Alexander, 2007).

Depression often accompanies DAT. Depression is common among the elderly. It is still not clear whether DAT patients suffer depression with greater frequency compared with age-matched nondemented people (Rubin et al., 1991; Wilson et al., 2003).

Degenerative brain diseases, including AD, often coexist with depression in the same patient and symptoms overlap. Agitation, apathy, eating disorders, weight loss, and sleep disorders are common to both, rendering interpretation of these symptoms difficult (Riviere et al., 2002). Confirming depression in a patient presenting with cognitive impairment is not easy since patients may not complain of mood disturbance. Instead, they frequently present with somatic symptoms

and sleep problems as well as memory difficulties. Overt depressive symptoms nevertheless can occur prior to manifest dementia and at nearly any point in DAT and are more common when there is a family history of mood disorder (Strauss & Ogrocki, 1996).

Late-onset depression without significant cognitive abnormalities is a risk factor for later development of DAT (Green et al., 2003; Reding, Haycox, & Blass, 1985) although major depression fulfilling DSM-IV criteria is unusual, and the mechanism may be independent of plaque and tangle burden (Wilson et al., 2003). In most but not all persons with DAT, depressive symptoms decrease as the dementia worsens (Teri & Wagner, 1992). Since depression in the elderly may present atypically and may worsen the cognitive impairments that are already present due to underlying neurodegenerative disease, it is not always easily recognizable and many clinicians prescribe antidepressants empirically to cognitively impaired persons with vague somatic symptoms. A six- to eight-week treatment trial of one of the serotonin reuptake inhibitors is relatively safe (but see above regarding apathy) and sometimes provides considerable and even unexpected improvement. In our clinical experience, an impressive improvement in mood or anxiety may be seen with antidepressant treatment, while the cognitive impairment remains relatively unchanged.

Other manifestations

Sleep disruption occurs in more than half of community-dwelling patients with DAT and is one of the most disturbing behavioral symptoms associated with AD, creating exhaustion and despair among caregivers (McCurry et al., 2009). In at least one study, sleep disturbances and night wandering were considered among the most intolerable of the behavioral symptoms and thus a major precipitant of institutionalization (Sanford, 1975). Several studies have demonstrated that the average nursing-home resident may never sleep for a full hour, nor be awake for a full hour, throughout the entire 24-hour day (Jacobs et al., 1989). Sleep disruption is not only a prominent behavioral problem in patients with AD and other dementias but it may also exacerbate daytime confusion or agitation.

Sundowning is a widely used term for a clinical phenomenon that is neither medically defined nor biologically well understood. In general, sundowning may be characterized by the onset or exacerbation of agitation, restlessness, panic, intensified disorientation, and verbal or physical outbursts in the afternoon or evening. In some studies, disease-related abnormalities of the sleep–wake cycle have been implicated as potential causes of sundowning, although it is clear that patient agitation may contribute to sleep problems as well (Reynolds et al., 1988).

Epilepsy can complicate DAT (Hauser et al., 1986; Hesdorffer et al., 1996). Old age is itself a risk factor for epilepsy through multiple mechanisms (most commonly, stroke), and differentiation between epileptic and non-epileptic events can be difficult among the elderly demented. Whether or not epilepsy is a complication

of AD per se, independent of other risk factors, is not completely clear. Risk factors for seizures are more advanced dementia in some studies (Amatniek et al., 2006; Romanelli et al., 1990), focal EEG abnormalities, race and younger age in others (Amatniek et al., 2006; Scarmeas, Honig et al., 2009). Seizures provoked by AD pathology alone are likely uncommon, but more common compared with age-matched persons in the general population (Scarmeas, Honig et al., 2009). Recent animal studies suggest that subclinical seizures may contribute to Aβ-induced deficits (Palop et al., 2007) and may even account for some cases of wandering (Palop & Mucke, 2009).

Treatment of epilepsy in DAT doesn't differ much from that of younger patients. Enzyme-inducing drugs such as phenytoin, carbamazepine (CBZ) should be avoided, if possible, in view of their drug interactions, reduced protein binding and, in relatively younger persons, their osteopenic effect. Valproate (VPA) is often too sedating. Nevertheless, any anti-epileptic drug may interact differently within a demented host than within an otherwise normal person, so one prescribes what is ultimately necessary to control seizures with the least side effects (Palop & Mucke, 2009). CBZ and VPA may even ameliorate disruptive behaviors in a few patients.

Myoclonus, or brisk irregular involuntary muscle contractions, occurs in 5–25% of AD patients, mostly as a late manifestation (Hauser et al., 1986). Creutzfeldt–Jakob disease (CJD) is therefore not the only dementia associated with myoclonus. Since AD is much more common than CJD, it is probably a more common cause of dementia associated with myoclonus. Pathological AD has been reported to be a rare cause of the progressive myoclonus epilepsy syndrome in young adults (Melanson et al., 1997).

Sexual behavior. Actual hypersexuality or aggression almost never occurs although inappropriate sexual comments and increased interest may in some cases be early manifestations. When this occurs, redirection usually suffices in halting what for many partners has become unwelcome attention. Badgering of the spouse is unusual, but can occur. In general, sexual interest and activity are diminished (Kumar et al., 1988).

Clinical heterogeneity in AD

DAT is by far the most common manifestation of pathological AD. However, AD is phenotypically a heterogeneous disorder that doesn't always generate the DAT syndrome. The very earliest indication that something is wrong, i.e., that determined by the patient, family, or close friends to be worthy of reporting, may not be a memory problem (Galton et al., 2000; Hodges, 2006; Johnson et al., 1999; Lambon Ralph et al., 2003; Oppenheim, 1994). To the extent that autopsy can "confirm" AD, pathologically verified cases sometimes clinically don't conform to the standard DAT blueprint, and *clinically* "pure" cases, as previously noted, often harbor other, sometimes unexpected, pathologies (Lim et al., 1999; Lopez et al., 2002).

AD as pathologically defined sometimes symptomatically manifests as one of the other cortical dementia syndromes (Mesulam, 2000) and begins with isolated language, visuospatial, or, as with Auguste D., executive/comportmental deterioration. Striking focal motor, cerebellar (Piccini et al., 2007), or sensory symptoms rarely may even dominate the entire clinical course (Crystal et al., 1982; Jagust et al., 1990), particularly when AD is caused by autosomal dominant presenilin mutations (Marrosu et al., 2006). AD should therefore be considered in a wide spectrum of focal cortical syndromes, including both fluent and non-fluent progressive aphasia and progressive personality dissolution (Galton et al., 2000), but should not be the assumed cause of all cortical dementia syndromes (Tang-Wai & Mapstone, 2006). Indeed, some persons with pathological AD according to multiple established criteria show no signs of cognitive impairment prior to death (Erten-Lyons et al., 2009; Roe et al., 2007; Snowdon et al., 1997) and, rarely, brains of patients with typical DAT show no pathology at all (Crystal et al., 2000; Howieson et al., 2003).

Pathological AD, the prototypical "cortical dementia" syndrome, has been associated with a variety of motor disturbances, especially parkinsonism, which can predate the dementia and have been described in cases of mild cognitive impairment (Louis et al., 2005; Portet et al., 2009; Richards et al., 1993).

Is, therefore, AD *per se* a valid nosological concept? The received wisdom is that "Alzheimer's disease" exists, it has a recognized pathology with a recognized anatomical distribution, and this anatomical and chemical pathology leads to a characteristic clinical syndrome. What if this received wisdom is wrong? What would the alternatives be? Once this question is asked, the options open and multiply. One option is that there are different etiologies of Alzheimer's disease and they have different underlying pathophysiologies but overlapping clinical phenomenology (Grossberg & Desai, 2003; Hardy, 1997). There is little difference, for example, in plaque and tangle distribution and morphology between early-onset and late-onset Alzheimer brains. Plaque and tangle load is, however, more severe and correlates much better with dementia severity in the former versus the latter (Prohovnik et al., 2006). Pathophysiologically, early- and late-onset AD may not, in fact, represent the same, unique disease (Blennow et al., 2006; Licht et al., 2007).

One can argue that overlapping but nevertheless different clinical clusters with different natural histories represent Alzheimer "variants" (Blennow et al., 1994; Holtzer et al., 2003; Mayeux et al., 1985). One could also argue that, as fundamental neurobiological research exposes brain–behavior relationships in health and disease, the various forms and patterns of underlying mechanisms that lead to the common clinical presentation currently labeled AD will emerge, and each of these forms and patterns would thus be given its own name (Albert, 2008; Graham et al., 1996; Neary et al., 1986). The reader should keep in mind, especially when consulting older citations, that many current (and for that matter, future) staining techniques (e.g., ubiquitin, synuclein, AT8) were not available as recently as the early 1990s. The "pathological Alzheimer's" of circa 1990 and before differs in many ways from what

neuropathologists are now confirming as "Alzheimer's disease" (Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. The National Institute on Aging, and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease, 1997).

Mild cognitive impairment

Many older adults, both those with and without cognitive complaints, enjoy substantially uncompromised ADL and do not meet DSM-IV clinical criteria for dementia, yet show impairments, if tested. The overall prevalence of this condition has been estimated at 19% up to age 75 and about 29% for age 85 or older (Lopez et al., 2003). These people have for years been described by a variety of terms such as "cognitive impairment not demented" (Di Carlo et al., 2007; Ebly et al., 1995), "age associated memory impairment" (Crook et al., 1986), "benign senescent forgetfulness," and most recently and most often by mild cognitive impairment (MCI) (Flicker et al., 1991; Negash et al., 2008; Petersen et al., 2009; Petersen, 2007; Petersen et al., 1999; Winblad et al., 2004).

MCI refers to people with subjective *and* objective cognitive symptoms "greater than expected for an individual's age and education level but that do not interfere notably with activities of daily life" (Gauthier et al., 2006; Petersen, 2007), i.e., a transitional state between "normal aging" and dementia.

MCI was originally described as isolated subjective and objective memory impairment without functional decline (Petersen, 2007; Petersen et al., 1999). Cognitive loss in other domains was added to MCI criteria in response to criticism that they were insufficiently inclusive of the non-amnestic problems that often occur in elderly persons, i.e., not sufficiently accountable for MCI heterogeneity (Winblad et al., 2004) (Figure 1.4).

Individuals with memory-only cognitive decline are a small proportion of the total MCI population (Kramer et al., 2006; Lopez et al., 2003). They are said to have the "amnestic single domain" form of MCI (aMCI), although whether or not memory is the only impaired system in these people has been questioned (Dudas et al., 2005). Most research has nevertheless been focused on this cohort of MCI patients (Guillozet et al., 2003; Markesbery et al., 2006; Petersen et al., 2006; Whitwell et al., 2007). The pathological substrate putatively reflects the entorhinal and hippocampal changes asserted frequently to be the earliest change of AD (Whitwell et al., 2007), but both this assertion and the necessary association between medial temporolimbic degeneration and memory impairment in AD have been challenged (Galluzzi et al., 2005; Lim et al., 1999; McKee et al., 2000; Nestor et al., 2006; Scheff et al., 2007; Snowdon et al., 1997; Vinters, 2006).

The reported "conversion" rate of aMCI to overt DAT ranges from 8–33% over two years (Aisen et al., 2003; Cummings, Doody, & Clark, 2007), generally about 15% for patients evaluated in specialized memory clinics (Tuokko et al., 2003), which is much higher than the incidence rate of DAT in the general population.

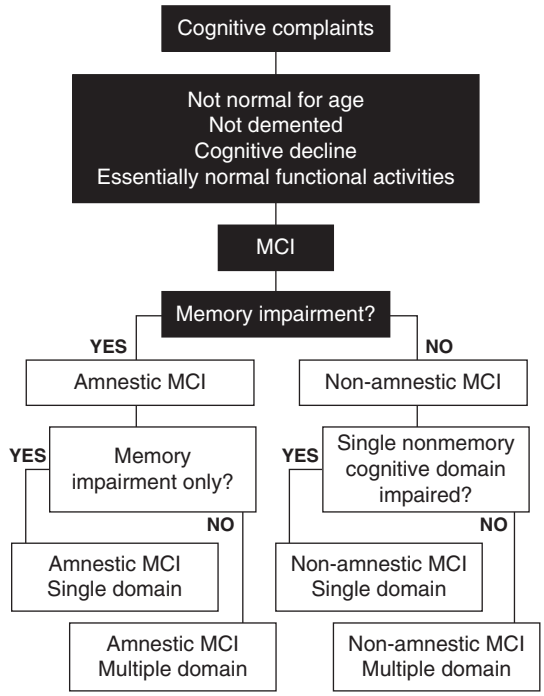

Figure 1.4 Flow chart of decision process for making diagnosis of subtypes of mild cognitive impairment
Source: Petersen, R.C. (2004). Mild cognitive impairment. *Continuum, 10*, 9–28. Taylor & Francis

If MCI is applied to non-(overtly) demented patients with a clear history of progressive memory impairment, the one- and two-year conversion rates are 41% and 64%, respectively (Geslani et al., 2005). Nevertheless, in a study having interpretive implications of therapeutic trials, 30% of aMCI patients who "converted" did not meet neuropathological criteria for AD (Jicha et al., 2006): not all patients with deteriorating MCI turn out to have AD. As of this writing, there is no clear evidence that pharmacological treatment of MCI has any efficacy (Doody et al., 2009).

Discrepancies in conversion rates, that is, the heterogeneity of prognosis, are reflective of the heterogeneity of MCI (Albert, 2008; Chetelat & Baron, 2003). Variability is due to the manner in which patients are recruited to studies, the use of different testing measures to operationalize the MCI construct, differing outcome measures and statistical modeling, quality of information (i.e., history) available to clinicians and researchers, and insufficient consideration of co-morbid conditions that can affect cognition (Cummings, Doody et al., 2007; Dubois et al., 2007; Geslani et al., 2005; Lopez et al., 2003; Petersen, 2007). Some people with MCI do not worsen significantly over time, a minority improve, and persons with non-amnestic MCI (naMCI) can develop DAT as well as other types of dementia (Mesulam, 2000).

Of those who do convert from MCI to DAT, risk factors for so doing have been addressed. ApoE ε4 carrier status very likely is important (Blacker et al., 2007; Petersen et al., 1995; Tervo et al., 2004). Some studies indicate that those with amnestic-multiple domain MCI (aMCI-MD), rather than those with pure aMCI, are at highest risk, likely because such people have more advanced pathological AD (Chen et al., 2000; Tabert et al., 2006; Whitwell et al., 2007). Others conclude that conversion to clinical DAT (Storandt et al., 2006) or even other dementing disorders is independent of MCI "type" (Fischer et al., 2007).

Poor prognostic conversion indicators of variable strength and specificity also include neuropsychiatric symptoms (Copeland et al., 2003; Palmer et al., 2007), lack of awareness of subtle functional impairments (Tabert et al., 2002), subjective complaints versus no complaints (Geerlings et al., 1999; Reisberg et al., 2005), suboptimal performance on a variety of cognitive measures (Arnaiz et al., 2004; Blacker et al., 2007; Fleisher et al., 2007; Galvin, Roe, & Morris, 2007; Petersen, 2007), particularly delayed recall (Arnaiz et al., 2004; Ivanoiu et al., 2005), and MRI atrophy of limbic and association cortices (Whitwell et al., 2007; Whitwell et al., 2008).

Many dementia experts accept MCI as a useful concept, and its inclusion into DSM V is under consideration (Negash et al., 2008). Others continue to debate its validity (Gauthier et al., 2006; Gauthier & Touchon, 2005), *to the extent that MCI has been eliminated in the proposed revision of the NINCDS-ADRDA research criteria for AD* (Dubois et al., 2007). For Petersen and Morris (2005) "mild cognitive impairment is an evolving construct" but "the heterogeneity reflects a refinement of the entity rather than a weakness."

Indeed, it is now evident that the pathogenetic processes underlying AD begin decades before development of any clinically recognizable symptoms. *Subjective* impairments, for example, remembering names and recalling where one has placed things, in the absence of any objective cognitive deficit, have collectively been termed "subjective cognitive impairment" (SCI) (Reisberg et al., 2008). This ultimately is the focus of large biomarker research trials such as the Alzheimer's Disease Neuroimaging Initiative (ADNI), and others listed below, and the National Institute on Aging Alzheimer's Disease Centers Program for the Uniform Data Set (Jagust, 2008; Mueller et al., 2005).

MCI is a concept in transition, a subject of intense investigation and competing models of characterization (Gauthier & Touchon, 2005; Grundman et al., 2004; Petersen & Morris, 2005).

DAT without MCI

Recognizable DAT is almost always preceded by MCI, but sometimes AD and other dementing diseases are akin to a falling tree heard by no one until its crash. That is, for a significant cohort of "community dwelling elderly," in which multiple systemic illnesses, multiple causes of dementia (Schneider et al., 2007), and polypharmacy are common, and in whom cognitive reserve has about been exhausted, the trigger for entry into the health care system may not be MCI or equivalent. Rather,

such people, either having lived alone or been assisted by ever more attentive associates, often present to emergency departments in an acute confusional state (ACS; delirium). A declaration, "he was sharp as a tack until . . ." is not uncommon (Dembner, 2007).

The core feature of the ACS, which has a differential diagnosis as diverse as that of the dementia syndrome (Lipowski, 1987), is impairment of attention, which disrupts all other cognitive domains. Markedly reduced digit span and inappropriate responses to extraneous stimuli are salient characteristics, which often are accompanied by some combination of delusions, hallucinations, myoclonus, asterixis, and disturbances of the sleep–wake cycle. The gross disturbance of attention of the ACS should facilitate its differentiation from otherwise uncomplicated DAT, in which, at least in mild stage, attention as commonly assessed is preserved. However, about 25% of elderly patients admitted with a delirium harbor an underlying dementing disease, often pathological AD with or without significant cerebrovascular disease. The message: a dementing process should be suspected in elderly people in an ACS, and dementing diseases, including AD, render persons more vulnerable to developing it (Jackson et al., 2004). In such cases, even when underlying causes are identified and treated, recovery to baseline is usually slow, frequently incomplete, in part genetically determined (Ely et al., 2007), and associated with prolonged hospital stays (Erkinjuntti et al., 1986).

Emerging Developments in the Diagnosis of AD

Recall that recommendations from the preceding paragraphs reflect many years of clinical practice. Clinical evaluation remains the gold standard of diagnosis, differential diagnosis, and assessment of the success of therapeutic interventions but has several disadvantages, including insensitivity to pathology during the preclinical phase and the variability of the host (cognitive reserve) in which the disease process occurs (Cummings, 2005a; Deary et al., 2004; Strub & Black, 2000). Principal goals of AD research have been to develop methods for diagnosis, predicting risk, and tracking effects of therapy. We are at the threshold of realizing these goals in the form of reliable biomarkers and their employment in a proposed revision of the NINCDS-ADRDA criteria (Craig-Schapiro et al., 2009; Duara et al., 2009; Dubois et al., 2007).

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to therapy (Cummings, 2005b; Strub & Black, 2000) and comes in three varieties (Fox & Growdon, 2004):

- State markers – also known as diagnostic markers, reflect intensity of disease process and indicate that the pathology of concern (in this case, of AD) indeed is present. In general, these suffer from suboptimal specificity, i.e., distinguishing AD from other causes of the dementia syndrome (Blennow & Hampel, 2003).

- Rate or stage markers (surrogate endpoints) – track disease progression or detect response (or lack thereof) to therapeutic interventions. Quantitative measurement of hippocampal and other medial temporal atrophy, and rating scales are examples.
- Trait (genetic) markers – predict likelihood of developing a disease or indicate susceptibility to it, e.g., APOE genotype or presenilin mutations.

Biomarkers for AD can also be classified as direct (e.g., measuring Aβ in CSF or with neuroimaging) or indirect (quantifying cerebral atrophy, clinical assessment), according to which step in the putative pathophysiological cascade they are associated with (isoprostanes Π oxidation; PIB PET Π Aβ plaque burden) (Cummings, 2005a; Strub & Black, 2000), and by which body compartment (CSF, brain, serum) is scrutinized. Biomarkers also include a variety of neuroimaging techniques, particularly positron emission tomography (Jagust et al., 2007), which are covered in detail in other chapters of this book.

The ideal biomarker should be convenient, safe, non-invasive, inexpensive, at least 80% sensitive and specific even in preclinical AD (the population for which biomarkers are mostly intended), feasible to perform, and validated by neuropathology (Borroni et al., 2006; Silver et al., 1998). Currently available biomarkers satisfy many of these requirements, but remaining limitations render them not yet ready for clinical use. Most of them require measurement at research or custom laboratories and there is insufficient standardization of assays and collection procedures (e.g., type of conveyance into which specimens are collected). Effects of circadian rhythms on biomarkers, likely an important factor, have not been well studied. It is, moreover, difficult, time consuming, and very expensive to follow a cohort of asymptomatic or minimally symptomatic individuals, even those enriched with higher-at-risk persons, long enough to associate the biomarker with subsequent development of DAT (Borroni et al., 2006; Fagan et al., 2005; Galasko, 2005). For the foreseeable future, no single biomarker is likely to fulfill all ideal criteria. The real, as yet untapped, potentials for biomarkers are in pre-symptomatic identification of at-risk individuals and in tracking persons with DAT in clinical therapeutic trials. Once they are readily available, convenient and precise, combinations of several CSF, plasma and neuroimaging markers likely will prove useful (Hansson et al., 2006). Several biomarkers have been chosen for the ADNI study (Mueller et al., 2005). The usefulness of which biomarkers, in which combinations, have yet to be determined (Frisoni et al., 2009).

Biomarkers are discussed in detail in many recent reviews (Blennow & Hampel, 2003; Borroni et al., 2006; Craig-Schapiro et al., 2009; Cummings, 2005a; Fagan et al., 2005; Strub & Black, 2000). In summary:

- Plasma biomarkers: High plasma $A\beta_{42}$ levels are found in *some* cognitively normal first-degree relatives of AD patients (Ertekin-Taner et al., 2007), and are a risk factor for developing AD, but this marker is still insufficiently sensitive and

specific for reliable early diagnosis. Plasma $A\beta_{42}/A\beta_{40}$ ratio may be a better indicator (Graff-Radford et al., 2007).

Platelet APP isoform ratio (130 kDa band/110 kDa band) is reduced in persons with clinically diagnosed AD, correlates with declining MMSE scores (Baskin et al., 2000), and may predict conversion from MCI to DAT. This ratio, in combination with measurement of platelet β and α-secretase may increase accuracy of early diagnosis (Borroni et al., 2006).

- CSF biomarkers: Low $A\beta_{42}$ level appears to predict conversion of MCI to DAT but reduced level is also found in many other neurological diseases, and CSF Aβ levels appear to be time of day and activity dependent (Bateman et al., 2007).

  The same is true for increased total CSF tau (t-tau); high CSF phosphorylated tau (p-tau) is more specific for AD but does not distinguish those with and without cortical Lewy bodies (Sjogren et al., 2001).

  Measuring CSF $A\beta_{42}$/t-tau or $A\beta_{42}$/p-tau$^{181 \text{ and/or } 231}$ ratio has improved diagnostic sensitivity and specificity in some but not all studies.

  Low CSF $A\beta_{42}$/p-tau^{181} ratio nonetheless has accurately predicted conversion not only from MCI to DAT but also from normal (CDR 0) cognition to dementia, and correlated with PIB-PET brain amyloid burden (Fagan et al., 2007). Abnormal CSF $A\beta_{42}$ and p-tau^{181} concentrations in cognitively intact middle-aged persons also correlate with FDG-PET hypometabolic areas known to be affected in early AD (Petrie et al., 2009).

  F2-isoprostanes, a marker of oxidative stress, are elevated in CSF, blood and urine in early AD and are potentially useful for monitoring effects of antioxidant therapy but, again, there is discrepancy among studies regarding sensitivity and specificity (Flirski & Sobow, 2005; Ringman et al., 2008).

Many other fluid biological markers, including CSF cytokines, as well as techniques employing mass spectrometry (proteomics) are in various stages of development and validation (Craig-Schapiro et al., 2009; Cummings, 2005a; Ma et al., 2009; Strub & Black, 2000).

Treatment

We begin with a discussion of the pharmacological treatment of DAT. We stress, however, that DAT is a family-systems disease, causing tremendous upheaval and morbidity for the patient and for everyone in the patient's family. At every stage of the disease, the patient's deterioration requires increasing resources. At every stage of the disease, the family requires new information and access to new services. The focus of care must expand from diagnosis and specific management to include the patient's caregiver, and supportive care ideally begins at the time of diagnosis (Cummings & Benson, 1992). Nonpharmacological assistance is addressed in a subsequent section.

The therapeutic goal ultimately, of course, is intervention with disease-modifying agents at multiple points within the pathophysiological cascade during the years-lasting *preclinical* phase of AD, when pathological burden is low (primary prevention). Once symptoms have developed, however, one should expect that early and persistent pharmacotherapy for AD will result in less behavioral, functional, and cognitive deterioration over a period of time than one would expect in the absence of pharmacotherapy (secondary prevention). Thus, treatment success includes not only short-term improvement of symptoms but also less decline over the long term (Geldmacher et al., 2006).

Identifying these phases is *the* challenge to effective treatment and is addressed later in this chapter, elsewhere in this book, and in other articles (Cummings, Doody et al., 2007). Distinguishing, for example, between a substantial epoch of "natural" memory stability in MCI (Smith et al., 2007) and treatment effects (when memory change is a principal outcome measure) may prove very difficult.

In this chapter, we distinguish among symptomatic therapies, such as the cholinesterase inhibitors (ChEIs) and *N*-methyl-D-aspartate (NMDA) receptor antagonists (Figure 1.5, left), disease-modifying therapies (DMT) that may prevent the onset or slow the progression of the disease, such as antioxidant drugs (Figure 1.5, right), and adjunctive medications for neuropsychiatric symptoms (Table 1.4).

The confounding problems of clinical trials in need of overcoming include accurate detection of placebo responses, the difficulty of differentiating between symptomatic and disease-modifying effects, especially for drugs that harbor both

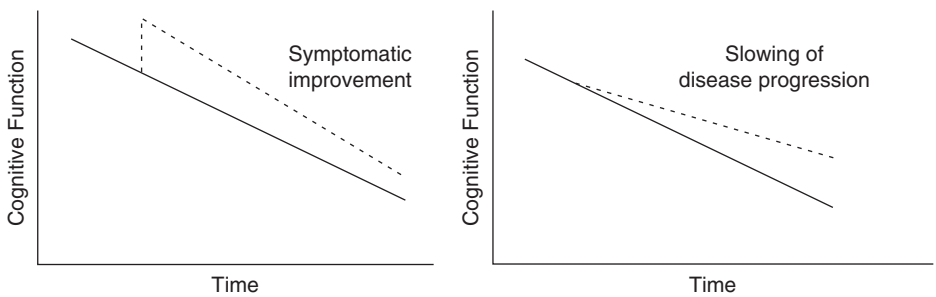

Figure 1.5 These figures suggest how different pharmacological treatments may affect the downward course of symptoms of AD and show the distinction between a treatment that improves symptoms and one that slows disease progress. The ChEIs have been shown in many studies to provide symptomatic improvement but not to modify disease progression. As discussed in the text, several new possibly disease-modifying compounds are in phase III trials

Source: Modified from Green, R.C. (2005). *Diagnosis and management of Alzheimer's disease and other dementias* (2nd edn.). Caddo, OK: Professional Communications, Inc., by permission

Table 1.4 Pharmacological treatment of Alzheimer's disease

DISEASE SPECIFIC	*ADJUNCTIVE*	
Symptomatic	*Disease-modifying*	
ChEIs	Immunotherapy	Antipsychotics
Memantine	Secretase inhibitors	Antidepressants
Herbals	Selective Aβ lowering drugs	Opioids
Muscarinic receptor agonists	Anti-Aβ aggregation agents	Anti-epileptics
Nicotinc receptor agonists	Hormonals	β-Blockers
	NSAIDs	Anxiolytics
	Statins	Tau inhibitors
	Metal chelators	Diet/Nutrition
	Antioxidants	NMDA receptor antagonists?
	Small peptides	

properties, and circumventing insufficient trial durations (Cummings, 2009; Doody, 2008; Kennedy et al., 2007). Furthermore, the people who take these drugs are likely to have other age-related medical disorders that directly (in the case of vascular disease) or indirectly influence symptoms and treatment. It is common, for example, for patients with DAT also to be taking a variety of anticholinergic medications for bladder control, "dizziness," insomnia, and, particularly, depression (tricyclics). These often worsen cognition and precipitate neuropsychiatric symptoms and should be avoided. Confusional states are associated with many cardiovascular agents (calcium channel and beta-blockers, amiodarone, ACE inhibitors) and particularly with narcotics, benzodiazepines and sedative-hypnotics, all of which should be prescribed with circumspection, if at all. Optimal management of polypharmacy and frequent co-morbid medical illnesses, including depression, remain a significant challenge for most clinicians.

There have been separate trials with some drugs (donepezil, anti-inflammatory agents, hormone replacement therapies) to explore the possibility of both symptomatic and disease-modifying properties (Hashimoto et al., 2005). DMT and symptomatic treatments may not, in fact, be fully dichotomous (Doody, 2008). Rather, they may reflect opposite ends of a treatment continuum: symptomatic drugs possibly alleviating downstream effects (neurotransmitter deficits), DMT theoretically disrupting early events such as $A\beta_{42}$ or hyperphosphorylated tau overproduction. If by 2012 drugs could delay the onset of AD by about seven years, its prevalence would decline by approximately 40% by 2050 (Sloane et al., 2002), reducing the national cost by trillions of dollars.

The distinction between symptomatic and DMT is frequently misunderstood by both clinicians and families, leading to unrealistic expectations. Since every medication choice weighs the anticipated benefits against the side effects and financial costs of that therapy, it is particularly important that clinicians inform patients accurately. Providing accurate information is a key step in the treatment protocol for the use

of pharmacological therapies in AD. Ideally, one should expect that the patient who is treated early and persistently with medication for AD will show less evidence of behavioral, functional, and cognitive deterioration over a period of time than one would expect in the absence of pharmacotherapy.

What, precisely, "accurate information" is, is still unsettled. ChEIs, for example, are currently the standard of care for the treatment of mild, moderate, and severe AD (Doody et al., 2001). We use them, and believe that they are underutilized and that every patient/family should have access to them. We have, furthermore, previously referred to several articles and studies indicating that ChEIs provide real symptomatic benefit to patients with DAT. There are nonetheless issues relating to their use.

A recent meta-analysis concluded that the scientific evidence for their use is highly questionable (Kaduszkiewicz et al., 2005). The National Institute for Health and Clinical Excellence in the UK (Technology Appraisal TA 111, 2006) argues that the modest benefits of ChEIs for mild dementia do not justify their cost (Corey-Bloom et al., 2006), an opinion that has been challenged by the drug companies (Dyer, 2007). There is both supportive and contrary evidence (Birks & Flicker, 2006; Feldman et al., 2007; Petersen & Morris, 2005) that cholinesterase inhibition delays progression of MCI to manifest DAT.

Symptomatic treatment

The AD pathophysiological process affects nearly all neurotransmitter systems, including noradrenergic neurons in the locus ceruleus, serotonergic cells in the dorsal raphe, and glutamate, dopaminergic and multiple polypeptide networks necessary for normal synaptic function (Coyle et al., 1983). Current treatment, however, rests mostly on the "cholinergic hypothesis": a central nervous system (CNS) drug-induced cholinergic blockade causes reversible cognitive impairment. Degeneration in AD of presynaptic cholinergic neurons in the basal forebrain results in widespread cortical and hippocampal depletion of acetylcholine (ACh). Several studies support an association between memory and other cognitive impairments on the one hand and basal forebrain cholinergic neuronal loss and virtual absence of cortical choline acetyltransferace in AD brains on the other (Terry & Buccafusco, 2003). In theory, cholinergic replenishment would partly counteract the insufficiency associated with AD neuropathology. Other studies indicate lack of such an association (Kaduszkiewicz et al., 2005). Disappointing results in many cases with cholinergic therapy are not particularly surprising.

Therapeutic trials commenced in the 1980s with ACh muscarinic precursors such as lethicin and oral choline. All studies concluded with either too small drug versus placebo differences or high incidences of side effects. More recent research has focused on cholinergic muscarinic and and nicotinic agonists. Either side effects, lack of efficacy, or conflicting and insufficient evidence render the role of these drugs presently unclear, and none is commercially available.

Acetylcholinesterase inhibitors

ChEIs are FDA-approved and are recommended by the American Academy of Neurology as standard (Doody et al., 2001) for the symptomatic treatment of mild-to-moderate AD. These drugs block, through a variety of mechanisms, the degradation of ACh at surviving presynaptic neuronal terminals, thereby prolonging its action and partially compensating for postsynaptic ACh depletion.

ChEIs have all shown measurable but modest improvements in cognition and ADL function. When treatment has been discontinued in many ChEI trials, cognitive and global ratings for the treatment groups have rapidly declined to levels that were not significantly different from those of the placebo group, suggesting that the beneficial effects of ChEIs rely upon continued administration. Hake (2007) suggests as prolonged a trial as possible, with ChEIs and with memantine, because "no difference" in fact could reflect benefit in view of the progressive nature of the disease, although improvement, if any is noticed, occurs mostly within three months.

The average cost of ChEI treatment is $1200–$1800 per year and pharmacoeconomic studies suggest that, if initiated early and continued for two years, the drug cost can be recouped by savings through reduced care costs (transportation, daycare, remunerated private supervision) and delayed nursing home placement (Cummings, 2003). Cost has also been justified in custodial settings (Volicer, 2001). Nevertheless, these and most other pharmacological treatments remain financially out of reach for many patients and their families (Matthews et al., 2006).

Few studies have focused upon when to begin these treatments, how to choose optimal dosing, when and how to change drugs, and how long to continue treatment. Reliable data are not yet available on the long-term efficacy of ChEIs after one year, although there is evidence that donepezil transiently slows the deterioration of cognitive function in amnestic MCI patients for at least one year (Petersen et al., 2005) and stabilizes severely demented patients with DAT (Black et al., 2007). No distinctive subpopulations (age, gender, APOE genotype) of patients have been identified that show greater benefit with ChEIs than others. Many of the trials evaluating ADL, caregiver burden, and patient behavior were either not randomized or were uncontrolled.

To repeat, the actual benefits, duration (anywhere from six months to five years) of meaningful improvement or clinical stability of these drugs, even when started early, and their effects on severely demented patients, remain to be firmly established (Blennow et al., 2006; Corey-Bloom et al., 2006; Cummings, 2004). Whatever their effect, most studies are in agreement that any benefit wanes over time. Our bias nonetheless is to encourage their use when finances are not a significant issue.

Three approved ChEIs are currently available: donepezil, rivastigmine, and galantamine. They differ in their structure, mode (competitive or noncompetitive), and specificity (CNS vs. GI) of inhibition, metabolism, half-life, and duration of action.

All are indicated for mild-to-moderate DAT. Only donepezil is FDA approved for severe DAT. All three have pretty much the same efficacy. Nevertheless, in the event of clear non-efficacy (worsening) or of side effects, switching from one ChEI to another is a reasonable strategy and can be done without a washout period for those who have not responded to the first ChEI, or with a washout period of five to seven days for those who had significant side effects on the first ChEI. Donepezil 10 mg/day and galantamine extended release (ER) 16 mg/day, are, for example, equivalent.

Having hopefully established realistic expectations for treatment benefits and side effects, there are two approaches to long-term continuation:

- Continue therapy until the patient's quality of life is too impaired to justify the potential benefit or financial cost.
- Continue as long as function appears to be stabilized. If cognition declines, reduce the dose of the ChEI and observe for accelerating deterioration. If yes, restart ChEI. If discontinuing treatment has no effect, ChEI can be stopped (Green, 2005).

Words of caution regarding "stabilization": as if there were no other management conundrums, caregivers and clinicians must be circumspect and take into account length of observation period before concluding that any given treatment is ineffective. As previously discussed in the Clinical Manifestations section, cognitive and behavioral deterioration tend to accelerate over time, but there is considerable variation in rate of change both among patients and within individuals even in the absence of intercurrent illnesses, drug side effects, environmental effects, etc. Reports from caregivers of "good days" (or even weeks) and "bad days" for mildly or moderately demented patients are not unusual. Reliability of reported change increases in proportion to the length of the observation. This underlies the importance of developing and accessing reliable surrogate endpoints (Cummings et al., 2008).

Practically, the main differences among the ChEIs are in their titration schedule and dosing regimen (Corey-Bloom et al., 2006), and, to a certain extent, their tendency to cause adverse effects. Administration is summarized in Table 1.5.

As with any drug, multiple side effects and drug interactions are possible. Overall, ChEIs are safe and well tolerated. Side effects generally are limited to gastrointestinal symptoms, in roughly this order of frequency: nausea, anorexia, dyspepsia, diarrhea, and vomiting. Uncommon side effects include insomnia, vivid dreams and nightmares, leg cramps, diaphoresis, headache, confusion, rarely seizures. The FDA has issued an alert concerning galantamine, for which there is a small risk of increased mortality (www.fda.gov/cder/drug/InfoSheets/HCP/galantamineHCP.htm).

Donepezil should be used with caution in patients with significant liver or renal disease; it may adversely interact with paroxetine (Dooley & Lamb, 2000), and can worsen patients with frontotemporal dementia (if AD diagnosis is incorrect)

Table 1.5 Prescription of cholinesterase inhibitors

	Donepezil (Aricept®)	*Rivastigmine (Exelon®)*	*Galantamine (Razadyne®) IR*	*Galantamine (Razadyne®) ER*
Doses per day	1	2	2	1
How supplied	5 mg, 10 mg, 23 mg tablets. (5 & 10 mg oral disintegrating tablets available)	1.5 mg, 3 mg, 4.5 mg, 6 mg tablets. Also available as patch 4.6 mg/24 hr, 9.5 mg/24 hr	4 mg, 8 mg, 12 mg tablets	8 mg, 16 mg, 24 mg capsules
Initial daily dose/ titration schedule	5 mg per day HS or AM/Increase to 10 mg after one month (23 mg for select patients with severe AD after 3 months on 10 mg)	1.5 mg B.I.D./Increase each dose by 1.5 mg every month 4.6 mg/24 hr to 9.5 mg/24 hr after 1 month	4 mg BID/Increase each dose by 4 mg every month	8 mg AM/Increase by 8 mg every month
Recommended daily dose	10 mg per day, HS or AM	6 mg B.I.D.	12 mg B.I.D.	24 mg AM
Take with food	Unnecessary	Yes	Yes	Yes

HS = bedtime

(Mendez et al., 2007). Usually taken at bedtime, morning administration is indicated for patients experiencing nightmares or insomnia. In our experience, gastrointestinal intolerance is most likely with oral rivastigmine but we have nevertheless successfully switched some patients intolerant to donepezil or galantamine to rivastigmine. Rivastigmine differs somewhat from the other ChEIs in that its metabolism does not require the cytochrome P450 system; theoretically this means less possibility of drug interactions. A rivastigmine trans-dermal patch, which may improve treatment efficacy and compliance, is commercially available (Cummings, Lefevre et al., 2007). Galantamine ER 24 mg might confer additional benefits (over, for example, donepezil 10 mg/day), if tolerated.

NMDA receptor antagonism

The rationale for using NMDA receptor antagonists rests on the theory that "excitotoxicity" plays a pathogenetic role in AD. Glutamate, a major excitatory neurotransmitter, acts on the NMDA receptor. Sustained NMDA stimulation, possibly resulting from NMDA receptor/Aβ interaction (Mattson & Rychlik, 1990), leads to prolonged calcium ion influx which can then trigger a cascade of neuronal injury and death. NMDA antagonism theoretically blocks low, tonic levels of glutamate-mediated excitation ("noise") while still allowing at least some normal NMDA responses ("signal").

Memantine is a low affinity NMDA receptor antagonist. It is approved for mid and late stage DAT. The biological basis for its therapeutic effect is not well understood. Large-scale, double-blind, six-month placebo-controlled trials of memantine in patients with moderate-to-severe dementia (Wilcock et al., 2002; Winblad & Poritis, 1999) and moderate-to-severe DAT (Reisberg et al., 2003) have demonstrated significant but modest improvements in cognition, but its effects on ADL have been inconsistent.

Memantine has a long history of extensive use in Europe and has been available in the United States since 2004. It has no significant drug interactions and improves patients with moderate-to-severe DAT who are already on a stable donepezil dose (Tariot et al., 2004). It can be taken with or without food and, in clinical trials, was not associated with any greater discontinuation of drug or any more side effects than seen in the placebo arms. Among patients who stop memantine because of side effects, the most common are headache, confusion, dizziness, and hallucinations, although these tend to dissipate with continued treatment. Recommended initial dosage is 5 mg per day, then increase the dose by 5 mg increments at least one week apart to the target dose of 10 mg B.I.D. Memantine is clinically used in conjunction with ChEIs besides donepezil.

Numerous other transmitter modulators are either in clinical or pre-clinical development, some already with discouraging results (Chappell et al., 2007; Jacobsen et al., 2005). Each is anticipated similarly to provide more symptomatic than disease-modifying effect.

Disease-modifying treatment (DMT)

The most fruitful areas for pharmacological treatment concern compounds that prevent AD in cognitively normal persons, or slow the progression of mild cases, such as those with MCI. Despite a wealth of epidemiological evidence about drugs or lifestyle interventions that might be helpful, the trials necessary to demonstrate clear efficacy are arduous and expensive. This is a rapidly moving field, but no treatments currently are available that either unequivocally protect normal individuals against developing AD or significantly slow the degenerative process. All agents discussed in this section are still in the investigative stage.

DMT is an attempt either to translate the advances in the molecular pathogenesis of AD into therapeutic strategies or to develop pharmacological treatments based on epidemiology. The former is represented mostly by drugs aimed at preventing and/or reducing accumulated brain Aβ or tau, the latter essentially by putatively neuroprotective agents. The success of most of these agents depends ultimately on the extent to which the amyloid cascade hypothesis is correct and whether transgenic mouse models are suitable in vivo surrogates for AD. Keep in mind that treatments successful in markedly reducing brain Aβ burden in murine models do not necessarily improve cognitive function in patients with DAT or MCI (Blennow et al., 2006). Other review articles relating to DMT are available (Davis et al., 2008; Doody, 2008; Duara et al., 2009; Salloway et al., 2008), as are summaries of ongoing and completed phase II and III trials (Sabbagh, 2009; Schneider & Sano, 2009).

Neuroprotection

So far, neuroprotective approaches, as reflected in multiple primary prevention studies, have been disappointing (Kaye, 2009). Following is a brief discussion of those that have generated most interest.

1 Anti-inflammatory drugs. This strategy is based on observations that AD plaques are routinely accompanied by inflammatory changes (McGeer & McGeer, 1995), on increasing evidence that CNS inflammation may precede or even promote the development of neuritic plaques (NPs) and neurofibrillary tangles (NFTs) (Rosenberg, 2005; Tan et al., 2007), and on animal (van Groen & Kadish, 2005) and epidemiological studies indicating reduced incidence of AD in chronic users of nonsteroidal anti-inflammatory drugs (NSAIDS) (in 't Veld et al., 2001; Szekely et al., 2004). In animals, ibuprofen reduces microglial activation and production of $A\beta_{42}$ peptides (Lim et al., 1999), suggesting an effect at an early stage of plaque development. These drugs may safely promote a shift from $A\beta_{42}$ to less toxic $A\beta_{40}$ production (Weggen et al., 2001).

Clinical trials with rofecoxib and naproxen and with prednisone, however, have either not substantiated significant amelioration of cognitive decline (Aisen et al.,

2000; Aisen et al., 2003), or were hampered by unacceptable gastrointestinal or cardiac toxicity (Burns et al., 2006) due to their inhibition of cyclooxygenase 1 (COX 1).

A large multicenter primary prevention trial testing the efficacy and safety of naproxen and celecoxib for the primary prevention of DAT, the ADAPT study (Martin et al., 2002), was suspended due to cardiovascular safety concerns. Primary analyses have now shown no effect on the incidence of milder cognitive syndromes and an inconclusive trend toward *increased* DAT incidence with either NSAID (Group et al., 2007). One explanation for inefficacy in all trials is that NSAID consumption was tardy with respect to the putative inflammatory mechanisms. It is possible that NSAIDs may, in fact, be effective but only when taken many years before onset of symptoms, particularly for those who have one or both ApoE ε4 alleles (Hayden et al., 2007). Another reason for failure is that naproxen and celecoxib do not lower $A\beta_{42}$ production; the wrong drugs may have been chosen! Mechanisms other than their anti-inflammatory properties may explain their still-possible neuroprotective effect. With few exceptions, clinical evidence currently does not support routine prescription of anti-inflammatory agents for the prevention and treatment of DAT. Continued masked follow-up of the ADAPT cohort is necessary.

2 Antioxidants. There is evidence that oxidative damage may be the earliest event in the pathogenesis of AD (Nunomura et al., 2001). Free radicals, the byproducts of metabolic processes such as oxidative metabolism, may accumulate, leading to excessive lipid peroxidation, nitration, and free carbonyls (Pratico et al., 2002). Observational and case-control studies suggest that supplemental intake of antioxidants such as vitamins E and C, or MAO inhibitors, can reduce risk, that is, act as neuroprotectors (Zandi et al., 2004). Most supplement studies have focused on vitamin E. Sano et al. (1997) conducted a large, randomized placebo-controlled study of large dose vitamin E and the MAO inhibitor selegiline. Neither drug yielded cognitive improvement over two years, although all treated groups, after statistical adjustment to equate initial severity of dementia, showed less decline on an ADL scale when compared with placebo. More vitamin E patients suffered falls.

Other trials have shown no effect of supplemental vitamin E either on delay of symptoms or rate of progression in MCI (Petersen et al., 2005), and increased mortality with this and other antioxidants (Bjelakovic et al., 2007).

There is now little to support vitamin E as either prevention or therapy of DAT although some authors believe that the *form* of vitamin E is as important as the dose, that further studies are justified (Dunn et al., 2007), and, as with the NSAIDs, results of an adequate (i.e., early-enough) prevention trial could be very different from the results of a treatment trial.

Ginkgo biloba, available widely as an "herbal supplement" is also believed to act as an antioxidant. Again, the data are mixed. Some studies have shown modest cognitive improvement in patients with DAT (Le Bars et al., 1997), but it is likely ineffective (DeKosky et al., 2008; Doody et al., 2001). Questions regarding this

treatment, and, more importantly, the stucture and design of all primary prevention trials, nevertheless remain (Kaye, 2009).

Curcumin, a component of tumeric, has antioxidant and anti-inflammatory properties and inhibits formation of amyloid fibrils in vitro (Kennedy et al., 2007).

As of this writing, evidence is insufficient to recommend antioxidants as treatment for or prevention of AD and there are warrants against it (Burns et al., 2006).

3 Hormonal treatment (HRT). Estrogen and testosterone therapy have both been advocated for prevention and treatment of DAT on the basis of epidemiological studies. Here again the data are inconsistent (Burns et al., 2006). Although one small study showed possible benefit for young, fertile women (Henderson et al., 2005), several controlled estrogen trials with both normal and cognitively impaired post-menopausal women, with and without progesterone, have shown either no benefit, increased risk of dementia, or worsening of dementia (Henderson et al., 2000; Mulnard et al., 2000; Shumaker et al., 2003). There is evidence that age-related increase in leutenizing hormone (LH) "may be a fundamental instigator responsible for the aberrant reactivation of the cell cycle that is seen in AD" (Casadesus et al., 2006). This has prompted clinical trials with leuprolide acetate, a gonadotropin-releasing hormone agonist that lowers LH levels (Casadesus et al., 2006; Christensen, 2007). The preponderance of the evidence at present indicates that estrogen therapy is ineffective and should not be used.

Testosterone levels and cognition seem to be correlated in healthy older men (Yaffe et al., 2002). The benefits of testosterone supplementation for prevention or treatment of MCI and DAT are at present not clear. Some studies have shown no change, others, modest but measurable improvements in quality of life, if not cognition (Lu et al., 2006). Future trials may yet indicate testosterone treatment for DAT, but as of now this also cannot be recommended unless there are other indications for treatment.

4 Statins. Statins (HMG-CoA reductase inhibitors) are effective treatments, among those that tolerate them, of hyperlipidemia and are effective for the prevention of stroke and heart disease. Some case-control epidemiological studies have suggested that statins, at least some of them, may reduce the risk of developing DAT (Green et al., 2006; Rockwood et al., 2002; Wolozin, 2004; Wolozin et al., 2000), independently of their cholesterol-lowering property. Atorvastatin (80 mg/day) slowed rate of cognitive decline but did not affect other outcome measures in a recent one-year study of patients with mild to moderate DAT (Sparks et al., 2005). Activation of the α-secretase pathway, inhibition of tau phophrylation, and moderation of inflammatory cascades have been proposed as mechanisms (Kennedy et al., 2007; Li et al., 2007). More recent prospective trials have not supported significant risk reduction, or changes in plasma or CSF $A\beta_{42}$ (Arvanitakis et al., 2008; Hoglund et al., 2005; Zandi et al., 2005). As with the NSAIDs, early treatment, before significant neuronal degeneration has occurred, may abate one or

more pathological processes leading to clinical AD (Li et al., 2007). Additional long-term trials are in progress.

5 Diet. There is increasing evidence that "healthy" eating, e.g., Mediterranean diets (Scarmeas et al., 2006; Scarmeas, Stern et al., 2009; Solfrizzi et al., 2006), any diet high in omega-3 fatty acids, or even calorie restriction (Qin, Chachich et al., 2006) reduces risk of all types of dementia, and may even reduce mortality in AD (Scarmeas et al., 2007). Multiple possible mechanisms are possible, including antioxidant effects. Additional nutritional studies are ongoing. Diet and other risk-factor modification seems, not surprisingly, a promising avenue of primary prevention at least for dementia, if not specifically for AD (Middleton & Yaffe, 2009).

6 Other investigational DMTs. An enormous number of strategies are under investigation for their potential as treatment or preventive agents in persons with or at risk for AD. Drugs have included opiate antagonists, GM_1 ganglioside, clonidine, thiamine, somatostatin replacement, and guanfacine. All have proven disappointing. Nerve growth factor treatment is promising but it does not cross the blood–brain barrier, so an effective, non-invasive delivery system is an important issue (Christensen, 2007).

Treatments directed at amyloid and tau

The likely role of Aβ and tau in the pathogenesis of AD has led to many novel therapeutic strategies targeting the mechanisms of plaque and tangle formation. Some of the most promising therapies are those designed to alter the production, deposition, or clearance of Aβ. These include the APP β and γ secretase inhibitors, Aβ vaccine, selective Aβ lowering and anti-aggregation agents, and drugs directed at tau protein. The hope is that one or more of these compounds will slow or stop the neurodegeneration characteristic of DAT.

Aβ immunotherapy

Active immunization of older transgenic mice with aggregated $A\beta_{42}$ both reduces amyloid plaque burden and improves function (Schenk et al., 1999). Multiple studies have suggested several possible mechanisms for these effects (Klafki et al., 2006; Walker et al., 2005). These comprised the rationale for trials with the Aβ vaccine AN1792. A phase II trial was halted because 18 of 300 patients developed meningoencephalitis. T-cell attack on the C-terminal of the Aβ peptide (Nicoll et al., 2003; Schenk et al., 2004) and polysorbate supplementation of the vaccine (Gilman et al., 2005) may have been responsible. Autopsies on several study participants suggested reduced neocortical Aβ plaque and dystrophic neurite burden, but no change in NFT concentration or amyloid angiopathy (Bombois et al., 2007; Klafki et al., 2006).

About 20% of patients mounted an antibody response. In general, differences in cognition or functional ability were not great between antibody responders and nonresponders, but response correlated with improvement on some memory

subscales, and mean total CSF tau concentration was lower in responders than in the placebo group. Conversely, responders with high antibody titers showed whole-brain volume reduction and ventricular enlargement compared to nonresponders and those with less robust antibody production (Koepsell et al., 2007), although these effects did not correlate with cognitive decline (Gilman et al., 2005). A recent animal study raises further concern that $A\beta_{42}$ immunization increases vascular amyloid and microhemorrhages (Wilcock et al., 2007).

The upshot is that results have been encouraging enough to warrant additional studies, including trials of Aβ immunoconjugates composed of its N-terminal part in the hope of producing a more specific antibody response (Schenk et al., 2004).

Passive immunotherapy, which bypasses the need for active antibody formation, is also under evaluation. This approach may be more beneficial for older patients, whose immune response is relatively impaired. Anti-Aβ fragments to APP, monoclonal antibodies, and human intravenous immunoglobulin in several trials have all shown promise and reasonable safety and are in various stages of development (Kennedy et al., 2007; Klafki et al., 2006). Most interest is now focused on the humanized monoclonal antibody bapineuzumab. A phase II trial has not shown efficacy in primary outcomes (Salloway et al., 2009). We and others are in the midst of a large phase III trial (ICARA). The human immune system likely represents significant untapped potential in the treatment of DAT (Mohajeri, 2007).

Secretase modulators

Elucidation of the roles of APP α-, β-, and γ-secretases in the pathogenesis of AD has spurred development of agents targeting them as therapeutic substrates. The goal is either to augment α-secretase or to inhibit β- and γ-secretase activity, safely.

The promise of anti-β-secretase treatment derives from the observation that BACE1 (β-secretase converting enzyme) knock-out transgenic mice produce only very small amounts of Aβ yet have no apparent behavioral or cognitive impairments (Roberds et al., 2001). The difficulties with β-secretase inhibitors are that they are large molecules that do not cross the blood–brain barrier and the relationship between their activity and Aβ formation is nonlinear. The first difficulty has encouraged synthesis of so-called "natural binding partners," such as reticulons, that would allow β-secretase inhibition in vivo. Reticulons negatively modulate BACE1, decreasing both $A\beta_{42}$ and $A\beta_{40}$ secretion in a dose-dependent manner without changing their intracellular ratio (Bornebroek & Kumar-Singh, 2004). However, BACE1 inhibition may as well disrupt peripheral nerve function (Willem et al., 2006). As with many of the other investigational agents, additional preclinical studies are necessary (Skovronsky & Lee, 2000).

Stimulating α-secretase activity in the hope of shifting APP processing toward the non-amyloidogenic pathway (see *Pathogenesis* section) is another approach. Clinical development of this type of drug has also proven difficult because of concern that α-secretase might also increase peripheral $A\beta_{42}$, which can then be

taken into the brain via receptor-mediated uptake from the vascular compartment (Bornebroek & Kumar-Singh, 2004). Clinical trials are nevertheless underway with several agents. The anticancer drug, bryostatin, a protein kinase C activator, enhances α-secretase activity and reduces $A\beta_{42}$ concentration in transgenic mice (Blennow et al., 2006; Etcheberrigaray et al., 2004).

Finally, the search is on for safe and effective γ-secretase inhibitors. Animal studies have demonstrated that they lower CSF $A\beta_{42}$, and that this reflects lowering of brain oligomeric Aβ (Barten et al., 2005). Phase I and II testing of mild to moderate AD patients with the drug LY450139 has so far been disappointing. CSF Aβ dropped in both active drug and placebo patients but cognitive effects were not impressive (Siemers et al., 2006). Safety is also an issue because γ-secretase inhibitors are nonspecific. In addition to blocking APP processing, they also block physiologically essential substrates, notably the Notch signaling protein, which modulates many cellular functions including proliferation of T cells and gastrointestinal goblet cells (Christensen, 2007; Gandy, 2005; Kennedy et al., 2007). A multicenter phase III study (the IDENTITY study) to demonstrate safety, CNS specificity, and efficacy is ongoing. This drug class nevertheless remains an attractive therapeutic strategy.

Selective Aβ lowering agents

Another means of modifying the disease process, if not to interfere with AD pathogenesis, involves selective $A\beta_{42}$ lowering agents (SALAs). These drugs lessen $A\beta_{42}$ production by allosterically altering the active core of γ-secretase, "in essence moving the site of action on APP to produce shorter, less toxic Aβ fragments" (Kennedy et al., 2007). These drugs do not *inhibit* γ-secretase, therefore do not interfere with essential substrates such as Notch.

Tarenflurbil (Flurizan®), the pure R-enantiomer of flurbiprofen, was the first SALA to enter clinical trials. It has no significant COX I or II activity and is therefore virtually devoid of gastrointestinal side effects. It reduces plaque burden and preserves learning and normal behavior in Alzheimer transgenic mice and lowers $A\beta_{42}$ levels in human cell lines. In a phase II trial, a subgroup of patients with mild AD (MMSE 20–26) declined more slowly in ADL and global function, and showed a trend toward cognitive improvement in those treated with a higher dose (800 mg twice daily). The patents with the highest R-flurbiprofen levels deteriorated least (Christensen, 2007; Kennedy et al., 2007).

In yet another demonstration of the necessity of circumspection when extending results of animal trials to humans, however, final results of a very large and well-conducted phase III trial of tarenflurbil on patients with mild DAT confirmed inefficacy – at any drug dose – on either cognitive or ADL primary endpoints (Green et al., 2009).

The disappointment with tarenflurbil hopefully will be tempered by results of an ongoing phase III study of docosahexaenoic acid (DHA), a deriviative of fish oil, which itself has been the subject of multiple investigational trials (Cunnane et al., 2009). Low plasma DHA levels are clearly associated with cognitive decline in

elders, although its association with AD specifically is less robust (Cunnane et al., 2009; Schaefer et al., 2006). In various animal models and using a variety of experimental protocols, DHA exerts a protective effect against neuropathological signs of AD, including Aβ accumulation, synaptic marker loss, and hyperphosphorylation of tau. It appears also to have anti-inflammatory activity and may reduce oxidative stress.

Anti-Aβ aggregation agents

Aβ-derived diffusible ligands (small oligomers) are likely just as toxic as deposited Aβ, if not more so (Lambert et al., 1998; Walsh & Selkoe, 2004) and are associated with very early cognitive impairments (Lacor et al., 2004). There is increasing evidence that, if the amyloid hypothesis is at all correct, brain damage occurs well before plaque formation (Gandy et al., 2007; Kaye et al., 2007). Preventing aggregation of Aβ fibrils into plaques, or enhancing clearance of soluble Aβ, is another anti-amyloid treatment in development and has shown modest promise. Strategies include small molecule inhibition, glycosaminoglycan mimetics, proline-rich polypeptides, and copper chelators.

Small peptides can interfere with the conformational change of soluble Aβ to β-sheet structure but in general lack sufficient steric bulk to prevent interactions between larger peptides. Small peptides can, however, bind with larger "chaperone" molecules which can still bind with Aβ and increase their anti-aggregation power (Gestwicki et al., 2004; Kelly, 2005). They have been the subject mostly of animal studies.

An exception is dimebolin hydrochloride (latrepirdine) (Dimebon), an orally active small molecule originally marketed in Russia as a nonspecific antihistamine. Dimebon appears to act through a variety of mechanisms, including neuroprotection, anti-amyloid, serotonergic, adrenergic and NMDA receptor blockade, mitochondrial permeability, and inhibition of butyrylcholinesterase and acetylcholinesterase (Bachurin et al., 2001). On the basis of several studies showing improvement in several outcome measures in AD patients (Doody et al., 2008), Dimebon was the subject of an ongoing phase III efficacy and safety study (CONCERT) (Hung, 2008) that was recently suspended due to lack of efficacy (March 2010).

Sulfated glycosaminoglycan (GAG) binds to Aβ and allows polymerization into amyloid plaques. GAG mimetics compete for GAG binding sites, hinders fibril formation, and may reduce soluble Aβ. Preclinical studies with tramiprosate (3-amino-1-propanesulfonic acid [3APS]; Alzhemed®), a GAG mimetic competing for Aβ binding sites, reduced plaque burden in animals but yielded no clear cognitive or behavioral improvements. In phase II trials 3APS significantly lowered CSF Aβ although there were no significant clinical effects after three months (Aisen et al., 2004; Aisen et al., 2006). A phase III trial showed no effect compared with placebo (Sabbagh, 2009) and development of the drug was discontinued.

Colostrinin (O-CLN), another Aβ anti-aggregant, is a proline-rich polypeptide complex (PRP) from sheep pre-milk colostrum. Colostrinin and other PRPs are

cytokine-like molecules that induce interferon gamma, regulate the secretion of cytokines, and inhibit nitric oxide and apoptosis in cell cultures (Bacsi et al., 2007; Leszek et al., 2002; Zablocka et al., 2005).) Limited (phase I and II) testing with several doses so far indicates reasonably good tolerance with modest but unsustained cognitive improvement.

Putative DMTs

Pioglitazone and peroxisome proliferators-activated receptor-gamma (PPAR-gamma) antagonists, are prescribed for type II diabetes although safety issues are a significant concern (Home et al., 2007). They reduce Aβ, plaque deposition, and microglial-mediated inflammation in transgenic mice. Phase II studies of several daily doses administered to mild–moderate AD patients over six months discerned no differences in cognition or global function between active drug and placebo groups. However, ApoE ε4 negative patients receiving rosiglitazone 8 mg per day showed significant improvement in cognitive testing scores whereas ApoE ε4 carriers did not improve and some even declined (Risner et al., 2006). Pioglitazone trials in animals have yet to suggest any utility. More studies are needed.

Metal chelators have been used previously for the treatment of AD with findings of interest (Crapper McLachlan et al., 1991). Clioquinol (PBT-1), a quinolone antibacterial and antifungal agent, interferes with copper and zinc homeostasis. Copper is enriched in amyloid plaque and is bound by APP. Clioquinol apparently reduces extracellular copper availability, interrupting $A\beta_{42}$ production and facilitating the clearance of soluble Aβ. A phase II trial showed marginal cognitive improvements in moderately severe AD patients (Ritchie et al., 2003) but further clinical trials have been halted because of toxic impurities during production. Clinical trials with a similar drug (PBT-2) are in progress (Blennow et al., 2006). In general, side effects associated with metal chelators prohibit their widespread use.

Lithium and valproate, drugs not particularly useful for neuropsychiatric symptoms of DAT (Sink et al., 2005), have been investigated as disease-modifying agents in preclinical studies. Lithium limits formation of hyperphosphorylated tau by inhibiting glycogen synthase kinase-3 (GSK-3β) (Iqbal et al., 2005; Noble et al., 2005). Inhibition of a single kinase is probably insufficient to reverse tau hyperphosphorylation since this process is regulated by the balance between multiple kinases and phosphates (Blennow et al., 2006). Both lithium and valproate modify Aβ processing (Su et al., 2004) and tau hyperphosphorylation can also be limited by their increasing the activity of phosphatases such as protein phosphatase 2A (Bornebroek & Kumar-Singh, 2004). Limited clinical studies of both drugs have yet to yield particularly promising results.

On the horizon is the isolation and restoration of enzymes, likely deficient in Alzheimer brains, that degrade Aβ (Press & Alexander, 2007; Yamin et al., 2007). Table 1 in the article by Jacobsen et al. summarizes many of the studies currently underway with these and other drugs (Jacobsen et al., 2005). Many promising drugs other than those specifically discussed above are in clinical development.

Pharmacotherapy for behavioral problems

Cholinesterase inhibitors

For most patients with access to adequate health care, ChEIs are not the initial drugs of choice for behavioral symptoms since they likely have already been prescribed for cognitive deterioration. Several studies nonetheless indicate that ChEIs may improve or delay onset of neuropsychiatric symptoms for patients with mild AD (Gauthier & Touchon, 2005; Suh et al., 2004; Terry & Buccafusco, 2003; Trinh et al., 2003). Effects generally are modest (Ballard et al., 2005). If cost is not an issue, a trial is not unreasonable. The same assertions are valid for memantine (Ballard et al., 2005; Cummings et al., 2008; Cummings et al., 2006).

Antipsychotic drugs

As the incidence of disruptive behaviors increases with disease progression, so does prescription of antipsychotic drugs, which are administered to at least 25% of nursing home patients, the majority of whom are demented (Katz et al., 1992). Pharmacological treatment of neuropsychiatric disorders is expensive, accounting for about 30% of the direct costs of caring for AD patients (Beeri et al., 2002).

It is now generally agreed, if not universally practiced, that older ("typical") antipsychotics (butyrophenones, phenothiazines) should be avoided. These agents are more likely than other adjunctive drugs to cause side effects (Lee et al., 2004), representing for many patients and caregivers a cure worse than the disease. Side effects, in part dependent on the specific drug, include sometimes irreversible parkinsonism, acute and tardive dyskinesias, dystonias, sedation, orthostasis, gait disturbance, weight gain, and falling. Worsened agitation, cognition, and confusion are also particularly common, even at low doses, for neuroleptics with anticholinergic properties.

Are they effective? Differences in methodologies and quality among the few controlled studies of these drugs account for variable conclusions. For example, one controlled study indicated that haloperidol, especially at higher doses, reduces agitation (Devanand et al., 1998), another demonstrated amelioration of both agitation and aggression (Allain et al., 2000), and another clearly showed improvement in psychosis (albeit at a cost of increased "anergy") (Tariot et al., 2006). A Cochrane review, however, concluded that haloperidol might alleviate aggression but not agitation or other neuropsychiatric symptoms (Lonergan et al., 2002). Studies with other typical antipsychotics have likewise indicated improvements in some but not other disruptive behaviors, but practically all have also shown that side effects are a significant cost of any improvement, and there is no conclusive evidence that any one of these drugs is better than the others (Sink et al., 2005; Teri et al., 2000).

The fact, however, is that symptoms such as pervasive shadowing, aggression, and persistent yelling are very stressful to caregivers and usually so resistant to other strategies (pharmacological and nonpharmacological) that antipsychotic drugs may

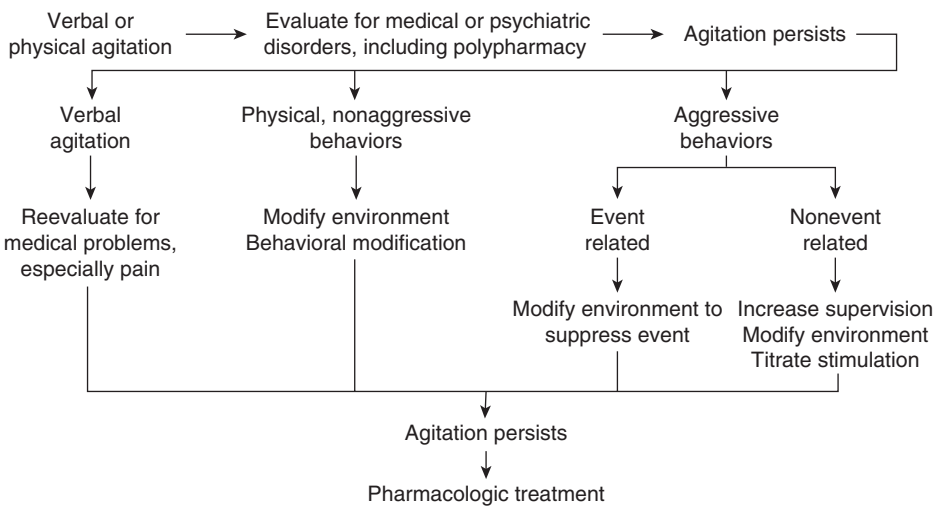

Figure 1.6 Diagnosis and treatment of agitation in the demented elderly
Source: Modified from Green, R.C. (2005). *Diagnosis and management of Alzheimer's disease and other dementias* (2nd edn.). Caddo, OK: Professional Communications, Inc., by permission

represent the only alternative, and we use them judiciously. As is the case with any other treatment, risk/benefit analysis is essential. Analysis requires data. Whether the patient is living in the community or in an institution, there is no substitute for collecting a careful history of the behavioral symptoms prior to formulating treatment (Figure 1.6). Determine, whenever possible, whether:

- the caregiver's complaint truly reflects the patient's behavior;
- the behavior in question is an isolated occurrence or a frequent event;
- some fundamental feature of the patient's environment or health has changed;
- the behavior represents a danger to the patient or to those caring for the patient.

For patients who are unable to communicate adequately, the clinician should specifically consider coincident medical conditions causing increased confusion or pain, particularly occult infections, constipation, hunger, or discomfort from falls.

"Atypical" neuroleptics are the current agents of choice for severe disruptive behaviors and are widely used although they are not FDA-approved for use in demented patients. Particularly when patient behavior is dangerous to him/herself or to others, a trial is reasonable once risks and limited expectations are discussed with family or other caregivers.

Does efficacy override a drug's known side effects? Again, quality of trials and conflicting results are issues. The atypicals (risperidone, quetiapine, olanzapine, clozapine, aripiprazole, ziprasidone) are in general perceived as better tolerated than older neuroleptics and a recent cohort study suggests that cognitive deterioration

may not be as much of a risk as previously demonstrated (Livingston et al., 2007). Studies have shown modest reduction in psychotic behaviors with risperidone, aripiprazole, quetiapine, and olanzapine compared with placebo (Lee et al., 2004; Schneider et al., 2006; Sink et al., 2005). Experts vary in their preferences for specific drugs. On the basis of several small trials, the American Academy of Neurology recommends atypicals at *guideline* level (Doody et al., 2001).

Atypicals are nevertheless far from problem-free and for many patients, risks ultimately outweigh their possible benefits. Potential adverse effects are multiple, common, and in general dose-related (Lee et al., 2004; Sink et al., 2005). Table 3 from Schneider et al. (2006) summarizes side effects associated with three commonly prescribed atypicals. Quetiapine is less likely to cause parkinsonism than the others and for this reason is the favored agent for many practitioners, but inconsistent efficacy is likewise an issue (Tariot et al., 2006). A principal side effect of the atypical neuroleptics is sedation, but this may in some cases be useful in treating nighttime agitation. We avoid using clozapine because of its epileptic potential and the risk of agranulocytosis, which requires frequent monitoring of white blood cell counts.

Like typical antipsychotics, atypicals are associated with increased mortality (Ellul et al., 2007; Schneider et al., 2005) on account of which they are under an advisory by the FDA. Several but not all studies report increased risk of stroke (Brodaty et al., 2003; Sink et al., 2005). In the aggregate, trials so far suggest that for a majority of patients with DAT, there is no significant clinical benefit from atypical antipsychotics compared with placebo and that side effects limit their overall effectiveness (Ballard et al., 2005; Kurlan et al., 2007; Schneider, 2007; Schneider et al., 2005; Schneider et al., 2006; Sink et al., 2005).

Antipsychotic drugs are clearly effective, however, for some patients. If these drugs are prescribed and are salutary, the goal is short-term treatment with the lowest possible dose and their indication should frequently be reassessed. No response after two to four weeks is an indication for discontinuing treatment or switching to another drug. In the absence of greatly effective DMT, clinicians quite rightly desire adjunctive drugs that reliably alleviate psychotic behavior with minimal side effects. No such "magic pills" are currently available (Sink et al., 2005).

Antidepressants

As previously noted, depression is common in the elderly, it coexists or is part and parcel of many dementing diseases in which it may have "atypical" features, and it may initially be the salient symptom of AD. If depression is evident clinically, pharmacotherapy is often effective. SSRIs are generally safe, even in older persons, and can be quite effective for elevating or stabilizing depressed or labile mood. It is often helpful to initiate antidepressant treatment in the face of fragmentary symptoms of depression even if the full syndrome is not present. We initiate these drugs at the lowest starting dosage recommended (or lower) and gradually increase to a typical, but low, antidepressant dosage. For example, we often start a patient on sertraline

12.5 mg daily, very gradually increasing to 50 mg daily, and if necessary, increasing further to 100 mg per day. Citalopram, escitalopram, and duloxetine are reasonable alternatives. Some practitioners regard agitation and aggressiveness as surrogate behaviors for underlying depression, but with the possible exception of citalopram, these drugs have not shown particular efficacy against neuropyschiatric symptoms other than relatively clear-cut depression (Sink et al., 2005).

We have had success with trazodone for the treatment of agitation, particularly if sleep problems are involved although one controlled study failed to demonstrate its efficacy (Teri et al., 2000). We typically begin with a low dose of 50 mg at bedtime and increase slowly, up to 100 mg b.i.d. We add the morning dose only to impact daytime agitation, and if the problem is largely restricted to nighttime, increase only the evening dose. Trazodone can in most cases be combined safely with other SSRIs.

All of these medications have potential side effects, including gastrointestinal distress, sexual dysfunction, sedation, and orthostasis. While generally well tolerated, for some patients antidepressants are not necessarily safer than neuroleptics (Rabins & Lyketsos, 2005; Schneider, 2007).

We avoid tricyclics and paroxetine because of their anticholinergic properties, and fluoxetine because of its long half-life and many drug interactions. Venlafaxine, mirtazapine, and bupropion may also be useful but information regarding their efficacy and safety in DAT is scant, and they may interfere with sleep.

Other drugs

Benzodiazepines, mood stabilizers (including antiepileptic drugs), beta-adrenergic blocking agents, and buspirone have all been used as adjuncts for neuropsychiatric symptoms. Valproate (long or short acting) is possibly useful for short-term use (Porsteinsson et al., 2001) and has been advocated in review articles (Corey-Bloom et al., 2006; Rabins & Lyketsos, 2005), but a contemporaneous review (Sink et al., 2005) and a comprehensive placebo-controlled trial in nursing home patients (Tariot et al., 2005) indicate that it is not effective. Evidence is insufficient to recommend carbamazepine, an enzyme-inducing drug that should be avoided whenever possible, as well as gabapentin, lamotrigine, and levetiracetam. Beta-blockers, particularly propranolol and pindolol, have also been used with some success to treat physical aggressiveness and motor restlessness in demented patients, but efficacy is less well documented and the risk of adverse effects makes these a less favorable choice (Peskind et al., 2005).

Opioids have been reported to control agitation (Manfredi et al., 2003; Sink et al., 2005), and melatonin for the treatment of sleep disruption (Singer et al., 2003). Some clinicians use benzodiazepines (e.g., short-acting lorazepam) for acute agitation. They may be useful for severely demented institutionalized patients. We typically avoid them as they are not only sedating but also can lower inhibitions, worsen gait, and add to confusion and agitation. Buspirone, in general better tolerated than benzodiazepines, may be useful for repetitive and stereotyped behaviors (Helvink & Holroyd, 2006).

Nonpharmacological treatment

Nonpharmacological strategies (Gray, 2004; Teri et al., 2002) should always be considered prior to using medication, but bear in mind that timing is an important issue. An important lesson of DAT management is that, practically, it's a very different disease at different stages and management approach must be tailored accordingly. Once the patient is dependent on the caregiver (if there is one), general recommendations for reducing the impact of cognitive impairment include: providing predictable routines; dressing patient in his/her own clothing; explaining procedures many times, in simple language; simplifying all tasks as much as possible and providing instructions for each step. For neuropsychiatric disorders, the following recommendations are often useful:

- determine precipitating factors;
- avoid environmental triggers;
- don't make significant changes to the environment (e.g., moving furniture);
- use distraction and redirection for problem situations;
- if possible, anticipate unmet needs.

Successful interventions are often symptom specific. Consider the stress associated with bathing demented people. There are several strategies one can employ, for example, using "person-centered bathing" (Corey-Bloom et al., 2006): provide sponge baths when the patient is strongly averse to bathing; raise room temperature and have towels ready in advance to create a warm environment; offer a favorite food after the bath; and play soothing background music that the patient likes. Whatever the symptoms, pharmacotherapy in general is unwarranted if the behavior is not disturbing to either the patient or the caregiver(s). When drugs are employed, nonpharmacological strategies should be continued.

Caregiver issues may be, as previously noted, depression, anxiety, loss of autonomy, and their own deteriorating health. Other common caregiver problems include unease over role reversal, helplessness, guilt about even considering nursing home placement, anger and frustration with the patient's ever increasing limitations, and concern about continuation or lack of sexual relationship (Cummings & Benson, 1992).

Typically, families look to their primary medical clinician to be their interpreter and referral source – someone to prioritize and guide them through the maze of issues they may be facing for the first time.

The often-frustrating management of DAT begins with an alliance between clinicians and family members and other caregivers responsible for the patient (Cummings, 2004). Some families are unprepared for a diagnosis of AD and may refuse offers of assistance, or may be unwilling to share their difficulties during an office interview. This reaction impedes the clinician's ability to get an accurate assessment of the patient's functional status and makes recommendations for sup-

portive measures difficult. Most families and caregivers, however, are grateful for appropriate referrals to education and support services and the clinician's coordination of information with other medical specialists.

Caregivers should receive:

- An explanation of the diagnostic process and the disease itself, i.e., what to expect at each stage of the illness including possible behavioral symptoms and increasing levels of dependency.
- A general description of the prognosis and what to expect in terms of cognitive decline, possible behavioral symptoms, and increasing levels of dependency.
- An overview of available pharmacological treatments, including their medical benefits, financial costs, and possible side effects and a treatment recommendation.
- Referral to the local Alzheimer's Association for further education and caregiver support and introduction to educational materials.
- Information about local social workers, lawyers specializing in the management of elders with cognitive impairment, and home-based care services.
- Encouragement to caregivers to take care of their own emotional and health needs. Neglecting their own health reduces their ability to care for the patient and renders them more vulnerable to depression.

Family education and reducing caregiver burden

Nonpharmacological and supportive interventions are extremely important to patient management, if they can actually be executed. In most families, a spouse or adult child assumes the role of the primary caregiver, an unanticipated and demanding job that often continues even after nursing home placement. Almost 90% of caregivers interviewed in one study reported fatigue, anger, and depression as a consequence of caring for a demented family member (Rabins et al., 1982). Younger, less financially secure, and more poorly educated caregivers are at especial risk of depression (Covinsky et al., 2003). The majority of caregivers of patients are female family members who provide care informally, with little outside assistance, and without pay ("no salary, benefits, sick days, or vacations") (Cummings & Benson, 1992). Men are more likely to delegate duties and use professional services for both household and patient management (Corcoran, 1992). The needs of both the patient and the caregivers should at least be addressed, if not totally satisfied.

"Burden" refers to the extent to which caregivers perceive their emotional or physical health, social life, and financial status as suffering as a result of caring for their demented friend or relative. The level of caregiver burden is not directly related to the degree of patient impairment (Hadjistavropoulos et al., 1994). Availability of social support, caregiver finances, and coping are important co-determinants. Burden is lessened when other family members share in the caregiving and facilitate respite periods for the primary caregiver (Cummings & Benson, 1992).

Recommendations are easy enough to print, but, for an increasing number of involved individuals, difficult to execute. Evidence that education programs and

community support services reduce caregiver perception of burden and depression, enhance well-being, and sometimes delay nursing home placement, is mixed. Examples of interventions include structured interactions between the caregiver(s) and an AD expert, short-term community occupational therapy (Graff et al., 2006), counseling, and intensive long-term education and support programs (Doody et al., 2001). Families who have had formal instruction in custodial care and recommendations for simple home modifications to encourage independent patient function may need less assistance within the home (Gitlin et al., 2005). Professional counseling in management of behavioral problems may also aid the caregiver (Guerriero Austrom et al., 2004; Mittelman et al., 2004), but pharmacotherapy, in itself problematic, usually also is necessary (Weiner et al., 2002).

These services are often effective for those with access to them, and should be offered. However, they are time consuming and for many families not readily available (Graff et al., 2006; Mittelman et al., 2006), particularly in underprivileged communities. It is not clear, for example, whether interventions that have been designed for primarily white populations attending AD specialist clinics are as effective for minority families who receive their care, if at all, mostly in a primary care setting, and who are more inclined to rely on extended networks of family and friends (Dilworth-Anderson, 2001; Green, 2005; Guerriero Austrom et al., 2006; White-Means & Thornton, 1990). Many minority individuals perceive even the screening process, during a regularly scheduled primary care visit, as harmful (Guerriero Austrom et al., 2006).

Specific issues

Safety Almost any behavior can pose a risk to a demented individual. Examples of potentially dangerous events include leaving the house alone, wandering, dressing inappropriately for the cold, becoming lost, using a toaster or a stove improperly, and eating spoiled food. Even when the demented person can perform routine activities without difficulty, confusion may hamper his or her ability to respond appropriately to an unexpected or dangerous situation, such as an electrical problem in the home or a simple fall. Persons with cognitive impairment can easily become the victims of financial scams or be taken advantage of by unscrupulous family members. As the dementia worsens, the simplest, but sometimes most difficult, intervention is to increase direct supervision. A few key safeguards should always be considered:

- reducing fire hazards by putting timers on stoves and ovens;
- reducing medication errors by counting pills into pillboxes;
- ample lighting, locks on cabinets and ovens, unplugging dangerous appliances;
- reducing falls by adding handrails and changing loose rugs;
- reducing and stopping patient driving.

Incontinence Along with disruptive behaviors, sleep disturbances, and withdrawal of a paid caregiver, incontinence is a major precipitator of institutionalization.

Urinary incontinence occurs in about half of ambulatory dementia patients and fecal incontinence is common among those with frequent urinary incontinence (Cummings & Benson, 1992). As with hallucinations and agitation, there are multiple noncognitive causes including fecal impaction, drugs, urinary tract infection, hyperglycemia, restricted mobility, and age-related and pathological (e.g., prostatism, surgical injury) changes in sphincter anatomy, all of which are potentially treatable. Cognitive causes are inability to recognize when they need to go to the bathroom, forgetting where the bathroom is, delusions, and visuospatial impairments (agnosia, defective contrast discrimination). Drugs that are often effective for nondemented patients (anticholinergics, α-adrenegic antagonists, baclofen, dantrolene, opioid antagonists) are sometimes useful but frequently worsen memory or exacerbate behavioral problems. Donepezil can cause urinary incontinence (Hashimoto et al., 2000) but all ChEIs may precipitate or exacerbate this problem.

Nonpharmacological methods, while time consuming and labor intensive, are usually more effective, at least in early to mid-stage disease. These include prompted voiding and scheduled toileting, wearing incontinence pads, reducing evening fluid intake, and external collection devices when possible. The Alzheimer's Association website (www.alz.org/living_with_alzheimers_personal_care.asp#3) has additional useful suggestions.

Wandering and pacing Walking provides several health benefits for demented persons: preventing the consequences of deconditioning and muscle weakness; reducing the risk of urinary tract infections and pneumonia; and encouraging an experience of independence. Wandering refers to "aimless or purposeful motor activity that leads to getting lost, leaving a safe environment or intruding in inappropriate places" (Cummings & Benson, 1992). It occurs in about one-third of community-dwelling dementia patients and 10% of nursing home residents. Risks are traffic accidents, assault, exposure, and falling. Wandering implies casual or random walking. Pacing is a more driven, nearly constant walking and generally is a more intrusive and troublesome behavior.

As with other aberrant behaviors, specific causes and treatments are usually elusive, but precipitants nevertheless should be sought. Neuroleptic-induced akathisia, sedative hypnotics, some antibiotics, antidepressants, and anti-hypertensive agents are all possibilities. Reducing or discontinuing any drug not demonstrably necessary may be helpful. Anxiety, delusions, hallucinations, and sleep disturbances, on the other hand, are also important causes and are reasons for drug administration in the first place. Finding the correct balance between drug and non-drug treatment may require prolonged observation, therapeutic trial (and error) and, ultimately, lots of patience. Wandering behavior for those patients still at home can be diminished with the installation of complex door locks or in-house alarms or bells. Patient identification bracelets may help minimize the hazardous consequences of wandering (Yaari & Corey-Bloom, 2007). The Safe Return program is a nationwide service sponsored by the Alzheimer's Association to help police and private citizens identify, locate, and return people with dementia (www.alz.org/we_can_help_safe_return.asp).

In the 1970s, many nursing homes established special-care units that segregate demented residents from the mainstream residents. Ideally, residential units that specialize in the care of dementia patients should provide comfortable, less clinical environments, focused activities, and staffing patterns to promote the functional abilities of demented residents; environmental designs that allow residents to wander safely; and opportunities for the active involvement of family members. Nursing homes adopting a "sheltered freedom" approach (Cummings & Benson, 1992) provide indoor and outdoor structure that allows pacing, wandering, and exploration in a relatively uninhibited but safe environment.

Driving Restricting the driving privileges of patients with dementia deserves special mention because it is such an emotionally charged issue in many families. Regardless of what patients and their families may claim, as a group, persons with even mild dementia drive more poorly and have a greater risk of accidents than persons without dementia. Yet, in the very earliest stages of dementia, when memory problems are the only detectable deficits, many patients appear to drive safely on familiar streets, and the symbolic impact of reducing a patient's independence by preventing the patient from driving can be distressing and divisive within a family (Ott et al., 2008).

The decision to restrict or forbid driving on the basis of cognitive impairment is best made jointly by the family and the clinician since patients routinely resist surrendering this privilege, even when they are obviously too impaired to drive safely. The discussion should include:

- patient's capacity and competence
- patient's driving history;
- current driving patterns;
- potential alternative means for transportation.

There are no rules to help clinicians judge when to restrict patient driving and the neuropsychological heterogeneity of a disease like AD means that mildly impaired patients with visuospatial problems may be more dangerous on the road than patients with severe, but more straightforward, memory problems. A history of getting lost, misjudging distances, inappropriate speed, missing signs or signals, accidents or near misses should be documented. However, our clinical experience and some published literature suggest that problems are underreported by caregivers and that many mildly demented people are not safe drivers when directly observed. In questionable cases, a standardized driving evaluation may help determine some aspects of driver competence, although these assessments routinely cost hundreds of dollars and a substantial portion of mildly demented persons pass performance tests. Many rehabilitation hospitals offer formal driving evaluation programs that give a more sophisticated assessment of the patient's driving ability than the state motor vehicle department or commercial driving schools. But in progressive dementias, such a snapshot does not accurately reflect what the patient

will be like several months later, or even the next day, since there is such day-to-day fluctuation in concentration of impaired patients. Serial testing, at least every six months, essentially is mandatory. The AAN driving practice parameter offers specific suggestions based on the patient's cognitive status (Dubinsky et al., 2000), although these in part have been challenged as possibly too restrictive (Ott et al., 2008).

When the impairments are mild, the clinician can wean the patient from driving by encouraging the family to find alternatives and gradually begin using them well before driving must be terminated. When driving privileges must be restricted suddenly, a carefully worded statement implying that the loss of privilege will be temporary ("I'm afraid you will need to stop driving while we work on ways to help your memory problem") is not entirely honest but often softens the blow. The clinician can also relieve pressure within the family by accepting the blame for the restriction, since amnestic patients often quickly forget the conversation. These recommendations should also be applied to patients who operate heavy machinery or who possess guns or other potentially harmful equipment in the home (Green, 2005).

Elder abuse

Abuse and neglect of AD patients by family, friends, telemarketers, and professional caregivers is an unfortunate reality for which the health professional should be on the lookout (Lachs et al., 1997). Evidence includes malnutrition, decubitus ulcers, poor hygiene, and repetitive trauma. This is a very difficult issue, particularly since behavioral disturbances, if present, are clearly impediments to proper care. Counseling, family psychotherapy, respite, and alternative living arrangements, if possible, may be helpful but the physician needs to know the particular state's law on reporting of suspected elder abuse.

Placement/Hospice

Roughly 90% of AD victims are institutionalized before death (Smith et al., 2000). The threshold for custodial placement depends on patient (disruptive behaviors, incontinence) and caregiver (finances, his/her own medical problems) characteristics. When possible, planned nursing home care is preferable to unplanned admissions and clinicians should introduce the possibility of long-term care as a contingency well before it is necessary. Medicare does not pay for nursing home care. When money is an issue (as it is for most), the patient must qualify on the basis of financial need for enrollment in a Medicaid nursing home. Before choosing a long-term care facility, the family should access www.medicare.gov for reports of deficiencies in state inspections. Every family must individually negotiate the challenges of finding suitable placement and the traumas of moving the patient out of the home, sometimes in the face of bitter opposition and accusations.

A hospice may be an option for patients with life expectancy of less than six months. Hospice care must be prescribed by a physician for either home or institutional care.

Conclusion

AD is rapidly evolving as the predominant chronic illness of the new millennium. The past decade has brought unprecedented progress in understanding the genetics, pathophysiology, and natural history of AD. The clinical care of AD patients is still in relative infancy but is rapidly evolving, with important new advances in diagnosis and pharmacological and nonpharmocological management. We are at the dawn of more effective care and treatment of AD and related degenerative dementias. "The future looks bright" is something we'd all like to say to our next patient and his or her family. It is our expectation that this will be possible within the next decade.

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