A Handbook for the Rehabilitation Professional

Medical Aspects of Disability

FOURTH EDITION

Editors

Steven R. Flanagan

Herb Zaretsky

Alex Moroz

SPRINGER PUBLISHING COMPANY

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Alzheimer's Disease

Barry Reisberg, MD, Emile H. Franssen, MD, Liduïn E. M. Souren, RN, MSN, Sunnie Kenowsky, DVM, Imran A. Jamil, MD, Salman Anwar, MD, and Stefanie Auer, PhD

Evidence suggests that approximately 10–15% of community-residing persons in the United States, aged 65 and older, may be afflicted with Alzheimer's disease (AD) or closely related dementing illnesses of late life (Evans et al., 1989; Katzman, 1986). Presently, it is estimated that in the United States more than 5 million persons aged 65 and older and approximately 200,000 persons younger than 65 years have AD (Executive Summary, Alzheimer's Association, 2009). At the other end of the demographic spectrum, half of persons older than 85 years in the United States are believed to have AD. More specifically, in the United States, dementia, secondary to AD, in entirety or in part in the great majority of cases, affects about 30% of community-residing persons between 85 and 89 years of age and about 50% of those in the community between 90 and 94 years of age. For community-residing U.S. persons 95 years or older, nearly 75% are found to have dementia (Graves et al., 1996; Montine & Larson, 2009). Worldwide, it has been estimated that more than 24 million persons have AD (Ferri et al., 2005). The prevalence of AD approximately doubles every 5 years after the age of 65 in developed nations and every 7 years in developing nations (Larson & Langa, 2008; Lobo et al., 2000).

In the United States, AD is the fourth leading cause of death in the elderly, after heart disease, cancer, and stroke. AD is the single major cause of institutionalization of aged people in the United States and in many other industrialized nations in the world. Studies have indicated that a large majority of approximately 1.5 million residents in nursing homes in the United States manifest a dementia syndrome generally associated with AD (Chandler & Chandler, 1988; Rovner, Kafonek, Filipp, Lucas, & Folstein, 1986). In addition, the institutional or "semi-institutional" burden of AD, depending upon the precise definition of institutionalization, is truly much greater. Approximately 1 million persons in the United States reside in assisted living facilities, which are "depicted as residential settings for cognitively intact older people with functional limitations" (Kaplan, 2005). In a study of 22 such facilities in Maryland, approximately two thirds of these persons have been found to have dementia, and the great majority of these persons with dementia were found to have AD (Rosenblatt et al., 2004). These statistics may be applicable to the broader U.S. assisted living population. The dimensions of the institutional burden associated with AD are even more striking when it is noted that well under 1 million persons are in U.S. hospitals at any particular time.

Pre-AD conditions add further to the true burden of the disease. For example, approximately 15% of persons aged 65 and older in the United States have mild cognitive impairment (MCI)

(Executive Summary, Alzheimer's Association, 2009). This condition, which is a precursor of overt AD, is associated with a decrease in performance in complex occupational and social tasks (also referred to as executive activities), as well as a generalized decrement in cognitive performance and an increased susceptibility to delirium (Gauthier et al., 2006). MCI is also associated with a decrease in balance and coordination (Franssen, Souren, Torossian, & Reisberg, 1999). These MCI-related disabilities likely have considerable economic, social, and medical consequences, the dimensions of which are largely uncharted. In addition, a pre-MCI condition, termed subjective cognitive impairment (SCI), is now increasingly recognized as an early antecedent of eventual AD. Very subtle cognitive and functional changes appear to occur in this SCI stage of eventual AD, which have unknown consequences, apart from heralding an eventual decline to MCI and, ultimately, the dementia of AD (Reisberg, Shulman, Torossian, Leng, & Zhu, 2010). However, it is clear that large proportions of older persons take a variety of medications, nutriceuticals, vitamins, and other substances in an effort to mitigate their perceived symptoms, and the economic costs associated with this self-prescribing are very considerable (Reisberg, Franssen, Souren, Kenowsky, & Auer, 1998; Reisberg & Shulman, 2009).

The course of AD has been described in increasing detail over the past several years. The cognitive, functional, and behavioral concomitants at each stage of the illness can presently be described in detail (see Figure 3.1). The clinically observable symptomatology of AD dramatically changes in form from the earliest manifest deficits to the most severe stage; therefore, recognition and differentiation of the stages of this illness is imperative for proper diagnosis, prognosis, management, and treatment. Progressive cognitive changes that occur are manifest in concentration, recent memory, past memory, orientation, functioning and self-care, language, praxis ability, and calculation, among other areas (Reisberg, London, Ferris, et al., 1983; Reisberg, Schneck, Ferris, Schwartz, & de Leon, 1983). Characteristic behavioral symptoms are also a frequent component of AD (Finkel, 1996; Finkel & Burns, 2000; Kumar, Koss, Metzler, Moore, & Friedland, 1988; Lyketsos et al., 2000; Reisberg, Franssen, Sclan, Kluger, & Ferris, 1989; Rubin, Morris, Storandt, & Berg, 1987). These behavioral symptoms peak in occurrence at various points in the course of AD and subsequently recede in magnitude and frequency with the progression of the disease. A comprehensive view of the nature and progression of these cognitive, functional, and behavioral changes is critical for the optimization of residual capacity and the identification and management of excess disability in these patients.

An outline of global cognitive, functional, and behavioral changes in normal aging and progressive AD is provided in the Global Deterioration Scale (GDS) (Reisberg, Ferris, de Leon, & Crook, 1982), outlined in Table 3.1 and described in greater detail in the following sections.

GLOBAL DESCRIPTION OF NORMAL BRAIN AGING AND AD

Seven major, clinically distinguishable, global stages from normality to most severe AD have been described (Reisberg et al., 1982; Reisberg, Sclan, Franssen, et al., 2008). These stages and their implications are as follows:

Stage 1: No Cognitive Impairment—Diagnosis: Normal

No objective or subjective evidence of cognitive decrement is seen. A significant proportion, although possibly only a minority, of persons more than age 65, fall within this category (Blazer, Hays, Fillenbaum, & Gold, 1997; Brucki & Nitrini, 2008; Gagnon et al., 1994; Jonker, Geerlings, & Schmand, 2000; Reinikainen et al., 1990; Tobiansky, Blizard, Livingston, & Mann, 1995; Wang et al., 2000). The prognosis is excellent for continued adequate cognitive functioning (Geerlings, Jonker, Bouter, Ader, & Schmand, 1999; Kluger, Ferris, Golomb, Mittelman, & Reisberg, 1999; Reisberg, Shulman, Torossian, et al., 2010).

Stage 2: Subjective Cognitive Decline Only—Diagnosis: SCI

Many persons older than 65 years have subjective complaints of cognitive decrement such as a subjective perception of forgetting names of people they know well or of forgetting where they placed particular objects such as keys or jewelry. These subjective complaints may be elicited by comparing the person's perceived abilities with perceptions of their performance 5–10 years previously.

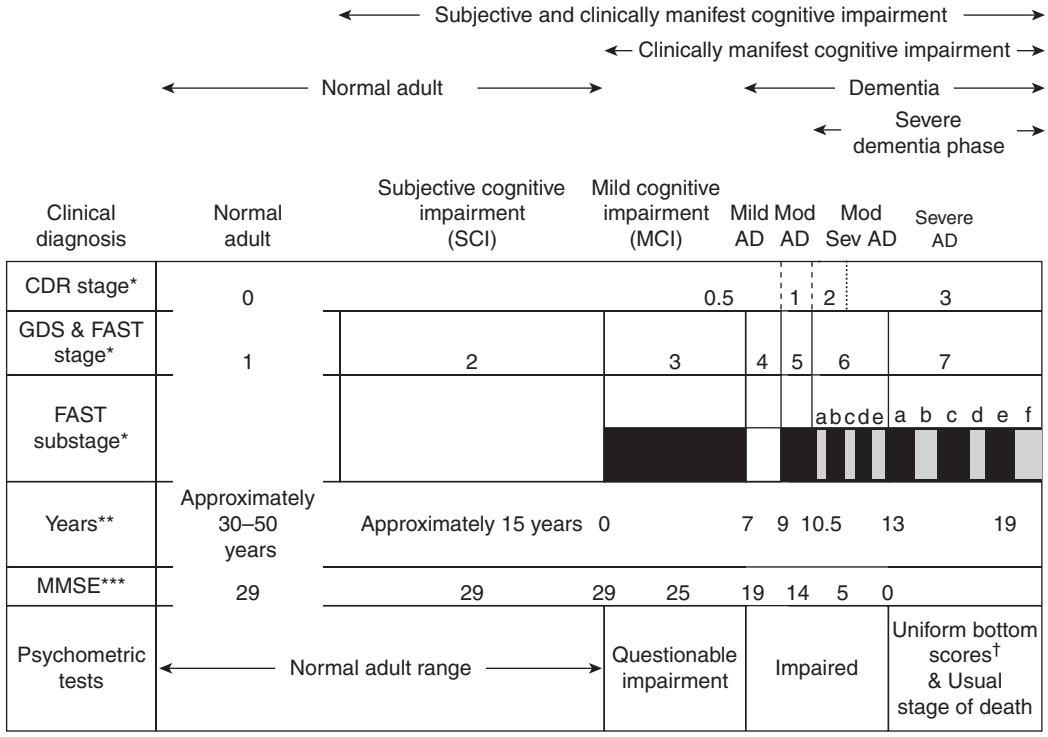


FIGURE 3.1 Typical time course of normal brain aging, mild cognitive impairment associated with Alzheimer's disease, and the dementia of Alzheimer's disease. AD - Alzheimer's disease; CDR - Clinical Dementia Rating (Hughes, Berg, Danziger, Coben, & Martin, 1982; Morris, 1993); FAST - Functional Assessment Staging (Reisberg, 1988; Sclan & Reisberg, 1992); GDS - Global Deterioration Scale (Reisberg et al., 1982; Reisberg et al., 1988); MMSE - Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975); Mod AD - Moderate Alzheimer's disease; Mod Sev AD - Moderately severe Alzheimer's disease. *Stage range comparisons shown between the CDR and GDS/FAST stages are based upon published functioning and self-care descriptors. **Numerical values represent time in years. For GDS and FAST stage 1, the temporal values are subsequent to the onset of adult life. For GDS and FAST stage 2, the temporal value is prior to onset of mild cognitive impairment symptoms. For GDS and FAST stage 3 and above, the values are subsequent to the onset of mild cognitive impairment symptoms. In all cases, the temporal values refer to the evolution of Alzheimer's disease pathology. All temporal estimates are based upon the GDS and FAST scales and were initially published based upon clinical observations in Reisberg (1986). These estimates have been supported by subsequent clinical and pathological cross-sectional and longitudinal investigations (e.g., Bobinski et al., 1995; Bobinski et al., 1997; Kluger et al., 1999; Prichep et al., 2006; Reisberg & Gauthier, 2008; Reisberg et al., 1996; Reisberg et al., 2010; Wegiel et al., 2008). The spacing in the figure is approximately proportional to the temporal duration of the respective stages and substages, with the exception of GDS and FAST stage 1, for which the broken lines signify abbreviated temporal duration spacing for this normal adult condition which lasts approximately 30–50 years. ***MMSE scores are approximate mean values from prior published studies. †For typical adult psychometric tests.

TABLE 3.1 ***Global Deterioration Scale (GDS) for Age-Associated Cognitive Decline and Alzheimer's Disease (AD)***

GDS Stage	*Clinical Characteristics*	*Diagnosis*
1	No subjective complaints of memory deficit No memory deficit evident on clinical interview	Normal
2	Subjective complaints of memory deficit, most frequently in following areas: (a) forgetting where one has placed familiar objects (b) forgetting names one formerly knew well No objective evidence of memory deficit on clinical interview No objective deficit in employment or social situations Appropriate concern with respect to symptomatology	Subjective cognitive impairment
3	Earliest subtle deficits Manifestations in more than one of the following areas: (a) person may have gotten lost when traveling to an unfamiliar location (b) coworkers become aware of person's relatively poor performance (c) word and/or name-finding deficit become evident to intimates (d) person may read a passage or book and retain relatively little material (e) person may demonstrate decreased facility remembering names upon introduction to new people (f) person may have lost or misplaced an object of value (g) concentration deficit may be evident on clinical testing Objective evidence of memory deficit obtained only with an intensive interview Decreased performance in demanding employment and social settings Denial begins to become manifest in person Mild to moderate anxiety frequently accompanies symptoms	Mild cognitive impairment
4	Clear-cut deficit on careful clinical interview Deficit manifest in following areas: (a) decreased knowledge of current and recent events (b) may exhibit some deficit in memory of one's personal history (c) concentration deficit elicited on serial subtractions (d) decreased ability to travel, handle finances, etc. Frequently no deficit in following areas: (a) orientation to time and place (b) recognition of familiar persons and faces (c) ability to travel to familiar locations Inability to perform complex tasks Denial is dominant defense mechanism Flattening of affect and withdrawal from challenging situations occur	Mild AD

Continued

TABLE 3.1 ***Continued***

GDS Stage	*Clinical Characteristics*	*Diagnosis*
5	Patient can no longer survive without some assistance Patient is unable during interview to recall a major relevant aspect of their current life, e.g.: (a) their address or telephone number of many years (b) the names of close members of their family (such as grandchildren) (c) the name of the high school or college from which they graduated Frequently some disorientation to time (date, day of the week, season, etc.) or to place An educated person may have difficulty counting back from 20 by 2s Persons at this stage retain knowledge of many major facts regarding themselves and others They invariably know their own names and generally know their spouse's and children's names They require no assistance with toileting or eating, but may have difficulty choosing the proper clothing to wear	Moderate AD
6	May occasionally forget the name of the spouse upon whom they are entirely dependent for survival Will be largely unaware of all recent events and experiences in their lives Retain some knowledge of their surroundings; the year, the season, etc. May have difficulty counting by 1s from 10, both backward and sometimes forward Will require some assistance with activities of daily living: (a) may become incontinent (b) will require travel assistance but occasionally will be able to travel to familiar locations Diurnal rhythm frequently disturbed Almost always recall their own name Frequently continue to be able to distinguish familiar from unfamiliar persons in their environment Personality and emotional changes occur. These are quite variable and include: (a) delusional behavior, e.g., patients may accuse their spouse of being an imposter; may talk to imaginary figures in the environment, or to their own reflection in the mirror (b) obsessive symptoms, e.g., person may continually repeat simple cleaning activities (c) anxiety symptoms, agitation, and even previously nonexistent violent behavior may occur (d) cognitive abulia, e.g., loss of willpower because an individual cannot carry a thought long enough to determine a purposeful course of action	Moderately severe AD

Continued

TABLE 3.1 ***Continued***

GDS Stage	*Clinical Characteristics*	*Diagnosis*
7	All verbal abilities are lost over the course of this stage Early in this stage words and phrases are spoken but speech is very circumscribed Later there is no speech at all—only babbling Incontinent of urine and feces; requires assistance bathing, dressing, toileting, and feeding Basic psychomotor skills (e.g., ability to walk) are lost with the progression of this stage The brain appears to no longer be able to tell the body what to do Generalized and cortical neurological signs and symptoms are frequently present	Severe AD

Source: Reisberg, B., Ferris, S. H., de Leon, M. J., & Crook, T. (1982). The Global Deterioration Scale for assessment of primary degenerative dementia. *American Journal of Psychiatry, 139,* 1136–1139. Copyright © 1983 by Barry Reisberg, MD. All rights reserved.

Apart from the occurrence of complaints of cognitive impairment with, what appears to be seemingly "normal aging," these complaints may also occur with other, frequently more serious common conditions in the elderly, notably, MCI, dementia and depression. Persons with comparatively benign complaints associated with this stage can usually recall the names of two or more primary school teachers, classmates, or friends and are oriented to the time of day, date, day of week, month, season, and year (although, of course, occasional minor errors may occur). They also display normal recall when queried about recent events and normal concentration and calculation abilities, for example, when asked to perform serial subtractions of sevens from one hundred. The terminology "subjective cognitive impairment" has been suggested for this condition (Reisberg, Prichep, Mosconi, et al., 2008). The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*, refers to this condition under the more inclusive category of "age-related cognitive decline" (American Psychiatric Association, 1994). Clinical interview reveals no objective evidence of memory deficit, and there are no deficits in employment or social situations. However, physiological studies have shown clear, significant decrements in persons with these symptoms in comparison with age-matched subjects free of subjective complaints. For example, a recent study found an 18% decrement in cerebral metabolism in a particular brain region, the parahippocampal gyrus, as well as significant metabolic decrements in some other brain regions, in older persons with SCI in comparison with age-matched subjects who were healthy and free of SCI (Mosconi et al., 2008). Significant increases in urinary cortisol levels have also been reported in SCI subjects in comparison with age-matched control subjects (Wolf, Dziobek, McHugh, et al., 2005).

Current data from prospective longitudinal study indicates that these subjective impairments are in most cases a harbinger of subsequently manifest cognitive impairments after an average of about 7.5 years (Prichep et al., 2006; Reisberg & Gauthier, 2008). The total duration of this stage has been estimated to be an average of about 15 years prior to the onset of more overtly manifest impairments such as those associated with MCI (Reisberg, 1986; Reisberg & Gauthier, 2008). Although medications, nutriceuticals, and nostrums are frequently taken for these perceived deficits, largely in order to prevent further decline, there is no convincing evidence of their efficacy in treating the symptoms of this stage at the present time.

Stage 3: Mild Cognitive Decline—Diagnosis: MCI

This now widely recognized condition was first described, and subsequently named, in association with the GDS (Reisberg et al., 1988; Reisberg, Ferris, Kluger, et al., 2008). Various subsequent definitions of MCI have been proposed (e.g., Petersen et al., 1999; Petersen et al., 2001); however, current consensus definitions are consistent with the original GDS descriptions of the MCI entity (Gauthier et al., 2006; Winblad et al., 2004). MCI is a condition in which subtle deficits in cognition and cognition-associated functioning occur. Subtle evidence of objective decrement in complex occupational or social tasks may become evident in various ways. For example, the person may become confused or hopelessly lost when traveling to an unfamiliar location; relatively poorer performance may be noted by coworkers in a demanding occupation; persons may display overt word- and name-finding deficits; concentration deficits may be evident to family members and upon clinical testing; relatively little material may be retained after reading a passage from a book or newspaper; and/or an overt tendency to forget what has just been said and to repeat oneself may be manifest. A teacher who had routinely recalled the names of all of the students in his class by the end of a semester now may have difficulty recalling the names of any students. This same teacher may, for the first time, begin to miss important appointments. Similarly, a professional who had previously completed hundreds, perhaps thousands, of reports in the course of her lifetime now, for the first time, may be unable to accurately complete a single report. The person may lose or misplace objects of value. Mild to moderate anxiety is frequently observed and is an appropriate reaction to the awareness of impairment.

The prognosis associated with these subtle but objectively identifiable symptoms varies. In some cases, these symptoms are the result of brain insults, such as small strokes, which may not be evident from the clinical history, neurological examination, or neuroimaging findings. In other cases, symptoms are due to subtle and perhaps not clearly identifiable psychiatric, medical, and neurological disorders of diverse etiology. These symptoms are benign in many of the subjects who report them. However, in most cases, where other conditions have been ruled out in terms of etiology, these symptoms do represent the earliest symptoms of subsequently manifest AD. The mean true duration of this stage as a precursor of subsequently manifest mild AD has been estimated to be approximately 7 years (Reisberg, 1986). A review of 19 longitudinal studies found that the "overall conversion rate" (of MCI subjects per annum) was 10%, with large differences between studies (Bruscoli & Lovestone, 2004). They noted that self-selected clinic attendees had the highest conversion rates. In a rigorous 4-year prospective study of otherwise healthy subjects, fulfilling the exclusionary criteria for probable AD at baseline (except for the presence of dementia), MCI subjects declined at a rate of 17.8% per year to dementia, a rate quite similar to the 14.3% per annum change which would be anticipated from a stage which lasts approximately 7 years (Kluger, Ferris, Golomb, Mittelman, & Reisberg, 1999).

However, subjects commonly present with these symptoms well into this stage, and mild AD frequently becomes manifest after a much briefer period (Bowen et al., 1997; Daly et al., 2000; Devanand, Folz, Gorlyn, Moesller, & Stern, 1997; Flicker, Ferris, & Reisberg, 1991; Morris et al., 2001; Petersen et al., 1999; Tierney et al., 1996). Presently, no pharmacological agents have been approved for preventing further decline or in treating cognitive impairments in MCI.

Stage 4: Moderate Cognitive Decline—Diagnosis: Mild AD

Clinical interview at this stage reveals clearly manifest deficits in various areas, such as concentration, recent and past memory, orientation, calculation, and functional capacity. Concentration deficit may be of sufficient magnitude that patients may have difficulty subtracting serial 4s from 40. Recent memory may be affected to the degree that some major events of the previous week are not recalled, and there may be superficial or scanty knowledge of current events and activities. Detailed questioning may reveal that the spouse's knowledge of the patient's past is superior to the patient's own recall of his or her personal history, and the patient may confuse the chronology of past life events. The patient may mistake the date

by 10 days or more but generally knows the year and the season. The patient may manifest decreased ability to handle such routine activities as shopping or managing personal and household finances.

Psychiatric features that may be prominent in this stage include decreased interest in personal and social activities, accompanied by a flattening of affect and emotional withdrawal. These behavioral changes are related to the person's decreased cognitive abilities rather than to depressed mood. However, they are frequently mistaken for depression. True depressive symptoms may also be noted but are generally mild, requiring no specific treatment. In cases where depressive symptoms are of sufficient severity to warrant treatment, a low dose of an antidepressant is frequently effective in reducing affective symptoms. At this stage patients are still capable of independent community survival if assistance is provided with complex but essential activities such as bill paying and managing the patient's bank account. Denial is the dominant defense mechanism protecting the patient from the devastating consequences of awareness of dementing illness.

The diagnosis of probable AD can be arrived at with confidence in this stage. It is possible to follow patients through the course of this stage, whose mean duration has been estimated to be approximately 2 years (Reisberg, 1986; Reisberg, Ferris, Franssen, et al., 1996). The cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) have been approved for treating the symptoms of AD in this stage and appear to slow cognitive decline.

Stage 5: Moderately Severe Cognitive Decline—Diagnosis: Moderate AD

Cognitive and functional deficits are of sufficient magnitude that patients can no longer survive without assistance.

Patients at this stage can no longer recall major relevant aspects of their lives. They may not recall the name of the current president, their correct current address or telephone number, or the names of schools they attended. Patients at this stage frequently do not recall the current year and may be unsure of the weather or season. Concentration and calculation deficits are generally of sufficient magnitude as to create difficulty in subtracting serial 4s from 40 and possibly even serial 2s from 20. Patients at this stage retain knowledge of many major facts regarding themselves and others and generally require no assistance with toileting or eating, but they may have difficulty choosing the appropriate clothing to wear for the season or the occasion and may begin to forget to bathe regularly unless reminded.

Psychiatric symptoms in this stage of moderate AD are in many ways similar, although generally more overt, than those noted in mild AD. The patient's denial and flattening of affect tend to be more evident. True depressive symptoms, with mild to moderate mood dysphoria, may occur. Anger and other more overt behavioral symptoms of AD, such as anxieties, paranoia, and sleep disturbances, are frequently evident. Paranoid and delusional ideation peak in occurrence at this stage, with almost 75% of patients exhibiting one or more delusions. Such delusions as people stealing the patient's belongings or money, that one's house is not one's home, or that one's spouse is an impostor, are common. Aggressivity may include verbal outbursts, physical threats and violence, or general agitation. Depending on the nature and magnitude of the psychiatric symptomatology, treatment with an antidepressant or an antipsychotic medication may be indicated. When the latter is used, the dictum for the treatment of psychosis in the elderly applies: "Start low and go slow."

Patients who are living alone in the community at this stage require at least part-time assistance for continued community survival. When additional community assistance, such as day care or home health aides, is not feasible or available, institutionalization or a more protective environment such as an assisted-living facility may be required. Patients who are residing with a spouse frequently resist additional assistance at this stage as an invasion of their privacy and home. The duration of this stage is approximately a year and a half (Reisberg, 1986; Reisberg, Ferris, Franssen, et al., 1996). The cholinesterase inhibitor medications have been approved for the treatment of AD symptoms at this stage. Another class of pharmacological treatment, which has been shown to be efficacious in slowing the

course of AD in this stage, is glutamatergic antagonist treatment. Memantine, the first and only medication in this more recently developed class of agents, is believed to reduce the glutamate-induced excitotoxicity caused by presynaptic neuronal injury. Memantine reversibly blocks glutamate transmission postsynaptically at the *N*-methyl-D-aspartate receptor. A pivotal study has indicated that memantine slowed the progression of AD in this stage and the subsequent stage by about 50% in terms of cognitive and functional outcomes (Reisberg, Doody, Stöffler, et al., 2003). A subsequent study has indicated that the effects of memantine remain robust and may even be enhanced, when memantine is given in combination with the cholinesterase inhibitor, donepezil (Tariot et al., 2004).

Stage 6: Severe Cognitive Decline—Diagnosis: Moderately Severe AD

Cognitive and functional deficits are of sufficient magnitude as to require assistance with basic activities of daily living.

Recent and remote memories are increasingly affected. Patients at this stage frequently have no idea of the date and may occasionally forget the name of the spouse upon whom they are dependent for survival but usually continue to be able to distinguish familiar from unfamiliar persons in their environments. Patients know their own names but frequently do not know their correct address, although they may be able to recall some important aspects of their domicile, such as the street or town. Patients have generally forgotten the schools they attended but recall some aspect of their early lives, such as their birthplace, their former occupation, or one or both of their parents' names. Concentration and calculation deficits are of such magnitude that patients with moderately severe AD frequently have difficulty counting backward from 10 by ones and may even begin to count forward during this task.

Agitation and even violence frequently occur in this stage. Language ability declines progressively so that by the end of this stage speaking is impaired in obvious ways. At this point in the late sixth stage, stuttering and word repetition are common; patients who learned a second language in adulthood sometimes revert, to a varying degree, to their childhood language; other patients may use neologisms, or nonsense words, interspersed to a varying degree in the course of their speech.

In this stage, emotional and behavioral problems generally become most manifest and disturbing, with 90% of patients exhibiting one or more behavioral symptoms (Reisberg, Franssen, Sclan, et al., 1989). A fear of being left alone or abandoned is frequently exhibited. Agitation, anger, sleep disturbances, physical violence, and negativity are examples of symptoms that commonly require treatment at this point in the illness. Low doses of so-called atypical antipsychotics may be useful for many patients. Side effects can be avoided if the medication is titrated upward with intervals of weeks between dosage adjustments. Present efficacy data on the treatment of these symptoms are most compelling for the atypical antipsychotic risperidone (Brodaty et al., 2003; De Deyn et al., 1999; De Deyn et al., 2005; Katz et al., 1999).

However, the dosage of antipsychotic medications given by clinicians and the titration schedules used by clinicians are frequently much higher and many times more rapid than those which are recommended. For example, for risperidone, the recommendation for treatment is as follows:

> In terms of pharmacological treatment of behavioral and psychological symptoms of dementia (BPSD) symptomatology, the clinical adage "start low, go slow" applies. For risperidone treatment, this rule translates into an optimal starting dose of 0.25 mg daily. Although clinical circumstances dictate the schedule of dosage titration, an optimal clinical response is not achieved for many weeks on any particular dosage of medication. Also, extrapyramidal side effects may not peak until a patient has been on a particular dosage of medication for as long as 6 months (Stephen & Williamson, 1984). Therefore, ideally, the clinician should endeavor to leave a patient on a particular dosage of medication for many weeks before further dosage

> adjustments. The exigencies of particular situations, of course, will frequently not permit this time luxury in dose adjustments, and clinicians will frequently need to make rapid dosage adjustments. However, the clinician should also be prepared to adjust medication dosage downward as well as upward in response to particular patient needs and the emergence of side effects. After some months of treatment, a steady-state dosage of approximately 0.25–1 mg of risperidone daily is frequently effective in controlling BPSD symptoms. (Reisberg & Saeed, 2004)

In clinical trials of atypical antipsychotic medications in the treatment of BPSD in AD patients, dosages considerably greater than these recommended amounts titrated over a much more rapid time interval have been used. For example, in the study of Katz et al. (1999), dementia patients with BPSD were randomly assigned to treatment with placebo or 0.5, 1.0, or 2 mg/day of risperidone for 12 weeks. The mean age of the patients was 83 years, and 96% of the patients had moderately severe or severe AD as evidenced by Functional Assessment Staging (FAST) (Reisberg, 1988) scores of ≥6a and Mini-Mental State Examination (MMSE) (Folstein, Folstein & McHugh, 1975) mean scores of 6.6. When a meta-analysis was used to review the results of this and similar studies, an increased mortality associated with atypical antipsychotic medication used in dementia patients was found (Schneider, Dagerman, & Insel, 2005). This finding of Schneider et al. (2005) resulted in the U.S. Food and Drug Administration "black boxing" with a warning of "Increased Mortality in Elderly Patients with Dementia-Related Psychosis" antipsychotic medications used for the treatment of BPSD. This warning states in part that: "Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of … 1.6 to 1.7 times the risk in placebo-treated patients" (PDR Network, 2009, p. 2683). The warning also notes that the increased mortality is due to varied causes, of which most were related to cardiovascular (heart failure or sudden death) or infectious (such as pneumonia) factors. The Schneider et al., (2005) study and subsequent studies (eg., Wang et al., 2005) have also found an increased mortality associated with the treatment of BPSD (psychosis) in dementia patients with so-called "typical" antipsychotic medications (e.g., haloperidol). In general, the risk of mortality has been found to be greater for "typical" than so-called "atypical" (e.g., risperidone) antipsychotic medications, although one major study found no difference between the two classes of antipsychotic medication in terms of mortality (Kales et al., 2007).

Unfortunately, even more recently published studies of antipsychotic medications in dementia such as the CATIE-AD Study Group report (Schneider et al., 2006) continue to begin with higher dosages of medication than those suggested by Reisberg and Saeed (2004). For example, the Schneider et al. (2006) published study (which was embarked upon in April, 2001) used a starting dose of risperidone of 0.5 mg.

In summary, with respect to the treatment of BPSD symptoms in dementia patients (primarily persons with AD), current consenses have concluded that treatment with antipsychotic medications, approached judiciously, continues to be a necessary option. In the words of a 2008 consensus "there is insufficient evidence to suggest that psychotropics other than antipsychotics represent an overall effective and safe, let alone better, treatment choice for psychosis or agitation in dementia" (Jeste et al., 2008).

In the moderately severe AD stage, the magnitude of cognitive and functional decline, combined with disturbed behavior and affect, make caregiving especially burdensome to spouses or other family members. They literally must devote their lives to helping patients who often can no longer even recall their name, much less appreciate in all the ways which may be desired, the kindness and care being provided. The caregivers' burden may be alleviated, for example, through regular participation in a dementia caregivers' support group, utilization of day care and respite centers for patients, or utilization of home health aides, either part-time or full-time. Clinical experience suggests that if behavioral disturbances are not successfully managed, they become the primary reason for institutionalization, and successful management of the disturbances can postpone this need. The mean duration of this stage

is approximately two and a half years (Reisberg, 1986; Reisberg, Ferris, Franssen, et al., 1996). Memantine has been approved for treatment of AD in this stage and does appear to be useful in slowing the progression of cognitive and functional decline (Reisberg, Doody, Stöffler, et al., 2003; Tariot, et al., 2004; Winblad & Poritis, 1999). In 2006, donepezil became the first and still the only cholinesterase inhibitor approved for treating symptoms in this stage.

Stage 7: Very Severe Cognitive Decline—Diagnosis: Severe AD

A succession of functional losses in this stage results in the need for continuous assistance in all aspects of daily living. Verbal abilities are severely limited early in this stage, to approximately a half-dozen different intelligible words during the course of an average day, frequently interspersed with unintelligible babbling. Eventually, only a single word remains: commonly "yes," "no," or "OK." Subsequently, the ability to speak even this final single word is largely lost, although the patient may utter seemingly forgotten words and phrases in response to various circumstances for years after meaningful, volitional speech is lost. It is important to recognize that although the patient may no longer be capable of speaking, thinking capacity remains. Test measures originally developed for infants are able to demonstrate continuing thinking capacities of the patient (Auer, Sclan, Yaffee, & Reisberg, 1994). Although agitation can be a problem for some patients at this stage, psychotropic medication can generally be reduced as this stage progresses and ultimately discontinued.

Memantine has been approved for treating the symptoms (cognitive and functional) of AD patients in this stage. However, only one published memantine study has included these patients. That study (Winblad & Poritis, 1999) did investigate memantine's efficacy in institutionalized, primarily nursing home-residing patients. However, very few of the patients in the Winblad and Poritis study were in this final, severe AD stage. Therefore, there is very little current information regarding the role of memantine in this final stage of the disease.

Donepezil is the only cholinesterase inhibitor approved for the treatment of AD at this stage. The pivotal trial of Winblad et al. (2006) included 61 randomized and treated patients with a FAST stage of 7a or greater (25% of the study population). Hence, fully a quarter of the subjects in this pivotal trial had little or no remaining speech. In addition, 23 randomized and treated subjects were losing the ability to ambulate independently (FAST stage 7c). Hence, the most robust pivotal trial data for any medication in the treatment of persons in this final stage of AD at the present time is that available for donepezil treatment. However, even this trial had a requirement of a minimum MMSE score of 1 at entry. Since most stage-7 subjects, even in the early part of stage 7, have MMSE scores of zero (bottom), even this study of Winblad et al., (2006) included relatively cognitively less impaired final stage AD subjects (Reisberg, 2007).

Nursing homes or similar care facilities may be better equipped than spouses for the management of patients in this stage. If family members maintain the patient at home, round-the-clock health care assistance may be necessary to manage incontinence and basic activities of daily living such as bathing and feeding. Human contact continues to make a great difference in the quality of life of a patient, whether in the home or in an institution. A loving voice, attention, and gentle touch are important for the patient's emotional and physical well-being. As described subsequently, movement and physical activity are particularly important.

AD patients who survive until some point in the severe stage generally die from pneumonia, traumatic or decubital ulceration, or a less specific failure in the central regulation of vital functions. Although approximately half of all patients who reach this stage are dead within 2–3 years, patients may potentially survive for 7 years or longer in this final stage.

FUNCTIONAL CHANGES IN AD

Understanding the progression of AD from the standpoint of change and deterioration in functional abilities is of great importance to both clinicians and families. In terms of a primary diagnosis, as well as differential diagnosis, it is useful to determine whether the nature

of the dementia is consistent with uncomplicated senile dementia of the Alzheimer type, because dementing processes associated with other causes frequently proceed differently from AD in terms of functional progression. Knowledge of the functional progression of AD can assist in this differential diagnostic process and, additionally, in identifying possible remediable complications of the illness. Furthermore, even the most severe AD patients can be assessed in terms of a functional level when all traditional mental status and psychometric assessment measures produce uniform bottom (zero) scores (Reisberg, Franssen, Bobinski, et al., 1996; Reisberg, Wegiel, Franssen, et al., 2006b). Functional assessment is presently capable of producing a detailed, meaningful map of the entire course of AD and, from the standpoint of physical rehabilitation, is extremely important in describing the AD patient's level of incapacity and areas of residual capacity.

Requirements for the management of AD fall into two categories: those relating to the patient and those relating to the primary caregiver. It is essential for the benefit of both that management advice be appropriate to each stage of the illness.

Functional Description of AD

A practical diagnostic and assessment tool, the FAST of AD (Reisberg, 1988; Sclan & Reisberg, 1992) permits identification of the stages of characteristic decline in functional activities in AD and their estimated duration (outlined in Table 3.2). Because of their utility, these FAST stages of AD are mandated for usage for certain purposes by the Center for Medicare Services in the United States, as well as in certain international jurisdictions (Health Care Financing Administration, 1998). These stages of functional deterioration in AD correspond optimally with the GDS stages described above. Table 3.2 indicates the approximate corresponding mean MMSE scores for each of the FAST stages and substages (Folstein et al., 1975). Research has indicated strong relationships between progressive functional deterioration assessed on the FAST and progressive cognitive deterioration in AD (e.g., Pearson correlation coefficients of ~0.8 or greater between MMSE and FAST scores have been reported [Reisberg et al., 1984; Sclan & Reisberg, 1992]). Therefore, the relationships shown between FAST and MMSE scores are approximations of likely findings in individual patients, although there is variability. Functionally, the late stages of AD can be subdivided into stages 6a–e and stages 7a–f. Consequently, a total of 16 functioning stages can be recognized, that describe in detail the characteristic changes which occur with the progression of AD. In uncomplicated dementia of the Alzheimer's type, progression through each of the functional stages described below occurs in a generally ordinal (sequential) pattern (Sclan & Reisberg, 1992).

Stage 1: No Objective or Subjective Functional Decrement

The aged subject's objective and subjective functional abilities in occupational, social, and other settings remain intact, compared with prior performance. The prognosis is excellent for continued adequate cognitive functioning.

Stage 2: Subjective Functional Decrement but No Objective Evidence of Decreased Performance in Complex Occupational or Social Activities

The most common age-related functional complaints are forgetting names and locations of objects or decreased ability to recall appointments. Subjective decrements are generally not noted by acquaintances or coworkers, and complex occupational and social functioning is not compromised.

When affective disorders, anxiety states, or other remediable conditions have been excluded, the elderly person with these symptoms can be reassured with respect to the relatively benign prognosis for persons with these subjective symptoms.

TABLE 3.2 ***Functional Assessment Stages (FAST) and Time Course of Functional Loss in Normal Aging and Alzheimer's Disease (AD)***

FAST Stage	*Clinical Characteristics*	*Clinical Diagnosis*	*Estimated Duration in AD*[a]	*Mean MMSE*[b]
1	No decrement	Normal adult		29–30
2	Subjective deficit in word finding or recalling location of objects	Subjective cognitive impairment	15 years	29
3	Deficits noted in demanding employment settings	Mild cognitive impairment	7 years	24–27
4	Requires assistance in complex tasks, e.g., handling finances, planning dinner party	Mild AD	2 years	19–20
5	Requires assistance in choosing proper attire	Moderate AD	18 months	15
6a	Requires assistance in dressing	Moderately severe AD	5 months	9
b	Requires assistance in bathing properly		5 months	8
c	Requires assistance with mechanics of toileting (such as flushing, wiping)		5 months	5
d	Urinary incontinence		4 months	3
e	Fecal incontinence		10 months	1
7a	Speech ability limited to about a half-dozen words	Severe AD	12 months	0
b	Intelligible vocabulary limited to a single word		18 months	0
c	Ambulatory ability lost		12 months	0
d	Ability to sit up lost		12 months	0
e	Ability to smile lost		18 months	0
f	Ability to hold head up lost		12 months or longer	0

[a]In subjects without other complicating illnesses who survive and progress to the subsequent deterioration stage. [b]MMSE = Mini-Mental State Examination score (Folstein et al., 1975). Estimates based in part on published data summarized in Reisberg, Ferris, de Leon, et al. (1989) and obtained in Reisberg, Ferris, Torossian, et al. (1992).

Source: Adapted from Reisberg, B. (1986). Dementia: A systematic approach to identifying reversible causes. *Geriatrics, 41*(4), 30–46. Copyright © 1984 by Barry Reisberg, MD.

Stage 3: Objective Functional Decrement of Sufficient Severity to Interfere With Complex Occupational and Social Tasks

This is the stage at which persons may begin to forget important appointments, seemingly for the first time in their lives. Functional decrements may become manifest in complex psychomotor tasks, such as ability to travel to new locations. Persons at this stage have no difficulty with routine tasks such as shopping, handling finances, or traveling to familiar locations, but they may stop participating in demanding occupational and social settings. These symptoms, although subtle clinically, can considerably alter lifestyle. When psychiatric, neurological, and medical concomitants apart from AD have been excluded, the clinician may advise withdrawal from complex, anxiety-provoking situations. Because patients at this stage can still perform all basic activities of daily living satisfactorily, withdrawing from demanding activities may result in complete symptom amelioration for a period of years.

Stage 4: Deficient Performance in the Complex Tasks of Daily Life

Aspects of decreased functioning from former levels are apparent. At this stage, shopping for adequate or appropriate food and other items is noticeably impaired. The person may return with incorrect items or inappropriate amounts of a certain item. The individual may have difficulty preparing meals for family dinners and may display similar deficits in the ability to manage complex occupational and social tasks. Family members may note that the patient no longer is able to balance the checkbook, no longer remembers to pay bills properly, and may make significant financial errors. Persons who are still able to travel independently to and from work may not recall names of clients or details of their employment duties. Because choosing clothing, dressing, bathing, and traveling to familiar locations can be adequately performed at this stage, persons may still function independently in the community, although supervision is often useful.

Maximizing the patient's functioning at this stage is the goal of the family and health care professionals. Financial supervision and structured or supervised travel should be arranged. Identification bracelets, ID cards, or clothing labels with a name, address, and telephone number may be useful for unusually stressful situations where anxiety or other factors further impair the person's capacities.

Stage 5: Incipient Deficit in Performance in Basic Tasks of Daily Life

At this stage, persons with AD can no longer satisfactorily function independently in the community. The person not only requires assistance in managing financial affairs and marketing but also begins to require help in choosing the appropriate clothing for the season and the occasion. The person may wear obviously incongruous clothing combinations or wear the same clothing day after day unless supervision is provided.

At this stage, some patients develop anxieties and fears about bathing. Another functional deficit that frequently becomes manifest at this stage is difficulty in driving an automobile. The patient may slow down or speed up the vehicle inappropriately or may go through a stop sign or traffic light. Occasionally, the person may have a collision with another vehicle for the first time in many years. The person with moderate AD may be sufficiently alarmed by these deficits to voluntarily discontinue driving. Sometimes, however, intervention and coercion are necessary from family members or even from the patient's physician or licensing authorities. A useful strategy for the physician is to arrange for an automobile driving retest.

It is important that functional abilities be maximized. Persons at this stage are still capable of putting on their clothing with minimal guidance once it has been selected for them. They are also capable of bathing and washing themselves, even though they may have to be cajoled into performing these activities. A supportive environment that provides adequate stimulation, in addition to adequate protection, is desirable. It is important that the person continue to engage in and practice skills in which they remain capable.

Stage 6: Decreased Ability to Dress, Bathe, and Toilet Independently

Throughout the course of stage 6, which lasts for approximately two and a half years and encompasses five substages, increasing deficits in dressing and bathing occur. In addition to not being able to choose the proper clothing, early stage-6 patients develop difficulties in putting on their clothing properly (stage 6a). Other dressing difficulties include putting on street clothing over night clothing, putting clothing on backward or inside out, and putting on multiple and inappropriate layers of clothing. The patient may also have difficulty zippering or buttoning their clothing or tying their shoelaces. More overt dressing difficulties develop as this stage progresses and the patient requires increasing assistance in dressing.

A bathing difficulty that becomes apparent at this stage is a decreased ability to adjust the temperature of shower or bath water (substage 6b). Subsequently, taking a bath or shower without assistance becomes increasingly problematic, ultimately with difficulty getting into and out of the bath and washing properly. Fear of bathing may develop, combined with

resistance to bathing. This fear of bathing sometimes precedes actual difficulties in handling the mechanics of bathing.

Later in the course of this stage, patients begin to have difficulties with the mechanics of toileting: initially, they may forget to flush the toilet, dispose of toilet tissue improperly, and clean themselves inadequately (stage 6c).

Subsequently, urinary incontinence begins (stage 6d), followed by fecal incontinence (stage 6e), both of which appear to be the result of decreased cognitive capacity to respond appropriately to urinary or fecal urgency. Assisting the patient to use the toilet often helps to forestall and remediate incontinence. Anxieties regarding toileting are frequently noted in stage 6c prior to the actual development of incontinence. Patients may go to the toilet repeatedly even in the absence of a true need for elimination.

Motor capacity deficits also become notable during stage 6. Walking becomes more halting and steps generally become smaller and slower, but the ability to ambulate is still maintained. Because orientation in space is affected, patients may approach a chair and sit down with greater difficulty. Patients may also require assistance in walking up and down a staircase.

Full-time home health care is frequently useful at this time, and it may be appropriate or necessary to discuss nursing home placement with the caregiver and family members. Management strategies and supportive techniques must be developed to assist the patient in bathing, dressing, and toileting, as well as in minimizing the emotional stress of the caregiver.

Stage 7: Loss of Speech and Locomotion

This final stage of AD is marked by decreased vocabulary and speech abilities. Speech becomes increasingly limited from a vocabulary of a half-dozen different intelligible, purposeful, and meaningful words (stage 7a) to at most a single distinguishable purposeful word that may be uttered repeatedly (stage 7b). Eventually, speech becomes limited to babbling, unintelligible utterances, and occasional, intelligible, random utterances.

Prior to the loss of ambulatory ability, patients may exhibit a twisted gait, take progressively smaller and slower steps, or lean forward, backward, or sideways while walking. Eventually, the ability to walk unassisted is lost with the progression of AD (stage 7c). It should be noted that after the loss of speech ability, the ability to walk is invariably lost. However, AD patients, for various reasons, especially excess disability, are susceptible to the loss of ambulation from the beginning of the final 7th AD stage, as well as subsequently.

Approximately a year after ambulatory ability is lost, the ability to sit up without assistance (such as lateral chair rests) is also lost (stage 7d). Subsequently, the abilities to smile (stage 7e) and to hold up the head independently (stage 7f) are also lost. At this point, babbling and grasping may still be observed, and patients can still move their eyes, although familiar persons or objects are apparently no longer recognized. Approximately 3–4 years after the onset of stage 7, generally after the loss of ambulatory ability, many patients die. However, some patients survive in this stage for 7 years or longer. Pneumonia, which is often associated with aspiration, is a frequent cause of death.

Full-time assistance at home or in an institution is a necessity at this stage, and as AD patients are increasingly well cared for, it is likely that more will survive to these final substages of the illness.

FEEDING CONCOMITANTS OF AD

Progressive changes in the ability to prepare meals and in feeding skills have been observed in AD patients and enumerated in accordance with the corresponding GDS and FAST stages (Reisberg et al., 1990). These "Feeding Concomitants of Alzheimer's Disease" are outlined in Table 3.3. The progression of these disturbances in meal preparation and self-feeding,

TABLE 3.3 ***Feeding Concomitants of Alzheimer's Disease (AD)***

Stage[a]	*Clinical Characteristics*
1–2	No objective or subjective decrement in the ability to adequately prepare meals, order food and beverages in a restaurant setting, or in table etiquette
4	Decreased facility in preparing and/or serving relatively complex meals, and/or decreased facility in ordering food and beverages in restaurant setting
5	Decreased ability in preparing simple foods or beverages (e.g., coffee or tea); may occasionally make mistakes in eating food (e.g., improper use of seasoning or condiments)
6	(a) Occasional difficulty with proper manipulation or choice of eating utensils
	(b) Meat and similar foods must be cut up for the patient
	(c) No longer trusted to use a knife; may also eat foods that would have formerly been refused
	(d) No longer trusted to properly use a knife and decreased ability to use a fork, but can still properly use a spoon; may also display occasional misrecognition of dietary substances (pica)
	(e) Capable of going to the refrigerator or cupboard but has difficulty discerning and choosing food, may have difficulty chewing hard food
7	(a) Capable of picking up spoon or fork; will occasionally drop food or misutilize silverware (e.g., may attempt to drink soup or other liquids with a fork); capable of reaching for a cup when desirous of fluid
	(b) Must be assisted in actual feeding; generally, patients are not permitted to handle a knife or fork; may not be able to properly lift a cup
	(c) Can reach for and pick up food with hands; cannot properly pick up a fork or a spoon but can grasp a spoon or other utensil; must be spoon-fed, but can chew
	(d) Cannot distinguish foods from nondietary substances; will reach out for objects, including food

[a]Stages have been enumerated to be optimally concordant with the corresponding Global Deterioration Scale (GDS) and Functional Assessment Staging (FAST) stages in Alzheimer's disease.

Source: Reisberg, B., Pattschull-Furlan, A., Franssen, E., Sclan, S. G., Kluger, A., Dingcong, L., et al. (1990). Cognition related functional, praxis and feeding changes in CNS aging and Alzheimer's disease and their developmental analogies. In K. Beyreuther & G. Schettler (Eds.), *Molecular mechanisms of aging* (pp. 18–40). Berlin: Springer-Verlag. Copyright © 1988 by Barry Reisberg, MD.

as with the progression of deterioration in cognitive and functional abilities, appears to be characteristic of AD.

BALANCE AND COORDINATION

Although it is clear from the preceding description of functional losses in AD that balance and coordination are eventually lost with the progression of the illness process, these aspects are actually very early changes, coincident with the advent of MCI and mild AD. For example, a detailed study indicated that tandem walking, foot-tapping speed, hand pronation and supination speed, and finger-to-thumb apposition speed all decreased significantly in MCI subjects in comparison with normal elderly controls (Franssen et al., 1999). Additional decrements were noted in mild AD subjects.

Another study has demonstrated that complex motor and fine motor measures can be just as robust markers of MCI and mild AD as a cognitive psychometric battery (Kluger et al., 1997). These observations of motor and equilibrium changes in MCI and AD are consistent with neuropathological observations of robust clinicopathological correlations with cerebellar atrophy in AD (Wegiel et al., 1999).

RIGIDITY AND CONTRACTURES

In the latter stages of AD, rigidity becomes increasingly manifest (Franssen, Kluger, Torossian, & Reisberg, 1993; Franssen, Reisberg, Kluger, Sinaiko, & Boja, 1991). Initially, this rigidity is of a paratonic type, for example, elicited in response to an irregular motion of an extremity, such as an irregular movement of an elbow. Later, the rigidity becomes increasingly evident. Figure 3.2 depicts the emergence of paratonic rigidity in AD. Although infrequently manifest in patients with mild AD (i.e., GDS stage 4), approximately 50% of patients with moderate AD (GDS stage 5), 75% of patients with moderately severe AD (GDS stage 6), and virtually all patients with severe AD (GDS stage 7) manifest at least a mildly detectable form of paratonic rigidity. Figure 3.3 illustrates the methodology for the elicitation of this paratonic rigidity by the clinician.

One probable result of this increasing rigidity is the development of contractures (Figure 3.4). Contractures are irreversible deformities of joints, limiting range of motion. In a study by Souren, Franssen, & Reisberg (1995), a contracture was defined as a limitation of 50% or more of the passive range of motion of a joint, secondary to permanent muscle shortening, ankylosis, or both. Souren et al. found that contractures meeting this definition were present in 10% of moderately severe AD patients with incipient incontinence (i.e., AD patients at FAST stages 6d and 6e). In severe AD, contractures are very common. Forty percent of incipient averbal AD patients (FAST stages 7a and 7b) manifested contractures and 50% of incipient nonambulatory AD patients (FAST stage 7c) manifested these deformities. By late stage 7, that is, in immobile patients (FAST stages 7d–f), 95% of AD patients manifested these deformities. Furthermore, at all stages, when contractures occurred, they generally were present in more than one extremity. Specifically, the great majority of patients with contractures (69%) had contractures involving all four extremities. All but one of the 39 patients found to have contractures (97%) had at least two limbs affected. By limiting mobility, contractures predispose patients to further morbidity, such as decubital ulcerations. One third of the patients with contractures in the study of Souren et al. (1995) had decubital ulcerations, either noted by direct patient observation or in the patient's medical record.

There is evidence based upon patient observations that contractures may be prevented until very late in the course of AD by maintenance of patient activities, stretching, other movements, and, especially, specific range of motion exercises of all joints including the hands and fingers.

DIFFERENTIAL DIAGNOSTIC IMPLICATIONS OF THE CHARACTERISTIC FUNCTIONAL COURSE OF AD

Cognitive and functional deficits in patients with AD characteristically follow the progression outlined in the preceding sections. However, other disorders frequently associated with the presence of dementia do not necessarily follow this characteristic pattern. It has been observed that the characteristic pattern of functional loss in AD is useful in differential diagnosis (Reisberg, 1986; Reisberg, Ferris, & Franssen, 1985). Common functional presentations of non-AD dementing disorders are outlined in Table 3.4. For example, normal-pressure hydrocephalus (NPH) commonly presents with gait disturbance as the earliest symptom, antedating any overt cognitive disturbance. In NPH, this ambulatory disturbance is commonly followed by urinary incontinence. Only subsequently, after the advent of ambulatory disturbance and urinary incontinence in NPH, may cognitive disturbances become manifest. As summarized in Table 3.2, the sequence of functional loss in AD is very different. In AD, overt cognitive disturbance precedes urinary incontinence, which in turn precedes ambulatory loss.

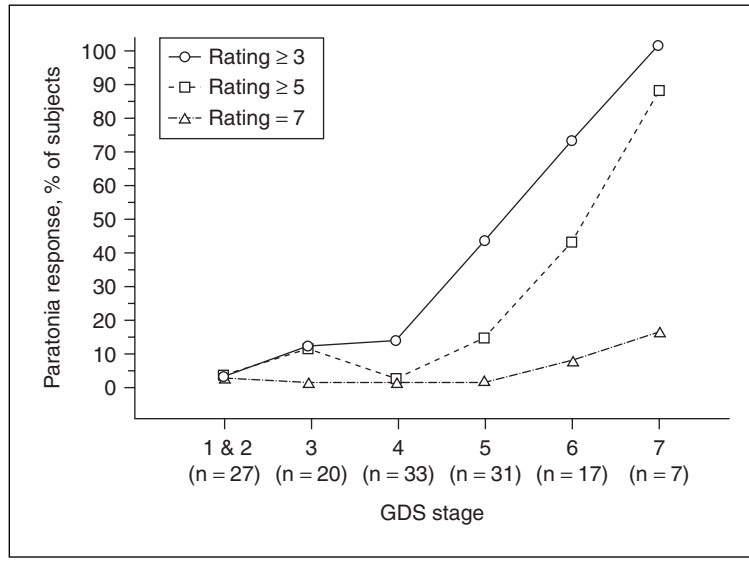


FIGURE 3.2 Percentage of subjects with increased paratonic rigidity in normal aging and Alzheimer's disease of progressively increasing severity. The graph depicts the percentage of subjects showing paratonia as a function of the Global Deterioration Scale (GDS) stage, using three different ratings of activity. Paratonic rigidity, defined as stiffening of a limb in response to contact with the examiner's hand and an involuntary resistance to passive changes in position and posture, was graded according to the amount of passive force necessary to elicit it. A rating of 1 denotes an absence of paratonic rigidity, whereas a rating of 7 indicates that minimal passive force is required for elicitation of the sequence. Further detail regarding the scoring procedure can be found in Franssen, E. (1993). Neurologic signs in aging and dementia. In A. Burns (Ed.), *Aging and Dementia: A Methodological Approach* (pp. 144–174). London: Edward Arnold. *Source:* Data and figure are from Franssen, E. H., Reisberg, B., Kluger, A., Sinaiko, E., & Boja, C. (1991). Cognition independent neurologic symptoms in normal aging and probable Alzheimer's disease. *Archives of Neurology, 48,* 148–154.

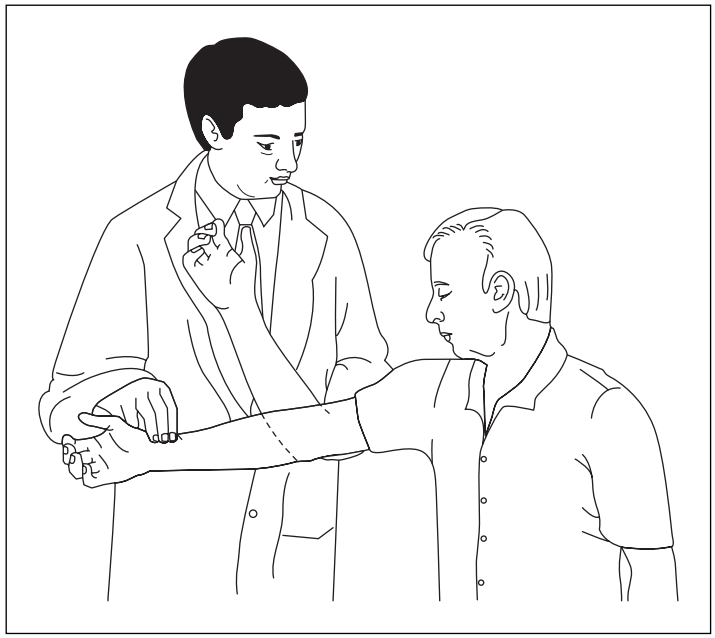


FIGURE 3.3 In the final stages of Alzheimer's disease, patients manifest increasing rigidity. Rigidity is evident to the examiner in the Global Deterioration Scale (GDS) stage 7 patient upon passive range of motion of major joints such as the elbow. Copyright © 1999 Barry Reisberg, MD.

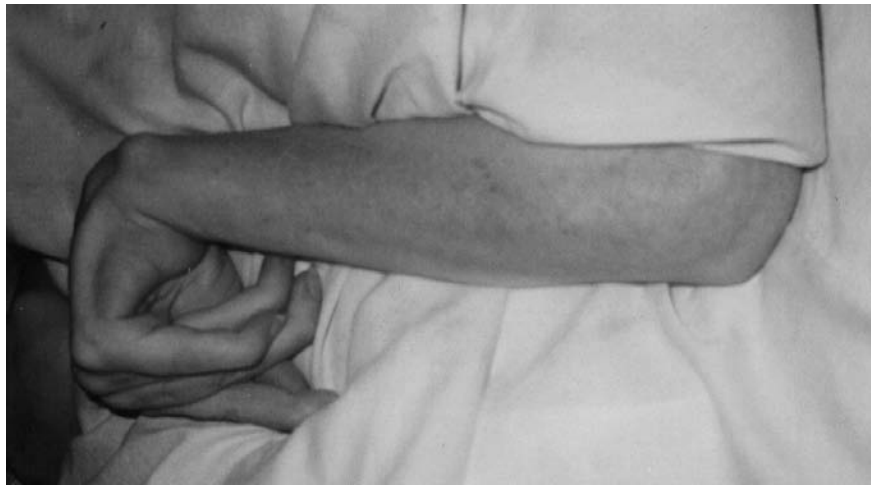


FIGURE 3.4 A stage 7 Alzheimer's disease patient with contractures of the left hand and fingers. Copyright © 1997 Liduïn Souren, RN, MSN.

Creutzfeldt-Jacob disease is a rare form of rapidly progressive dementia that presents with ambulatory disturbance as the earliest symptom in approximately one third of cases. In AD, the ambulatory disturbance is a much later event. The two conditions also may be distinguished temporally. The course of AD extends over many years, as outlined in Table 3.2, and is frequently much slower than the relatively rapid course of the acute and subacute forms of Creutzfeldt-Jacob disease.

Multi-infarct dementia, or dementia associated with an overt, large infarction, may produce speech disturbance as the only symptom. Alternatively, the infarction may produce urinary incontinence as the major overt manifestation. Commonly, ambulatory loss may be the major sequela of a stroke. Clearly, the evolution of functional losses in AD follows a very different and much more stereotyped pattern (as outlined in Table 3.2). As shown in Table 3.4, the evolution of functional disturbance in dementia associated with multiple infarctions may follow a very different course from that which is characteristic of AD.

Depression is a psychiatric disturbance associated with mood dysphoria and other symptoms. Among these other symptoms are negativity and subjective complaints of cognitive impairment. Occasionally, the depression produces a dementia-like syndrome that is potentially reversible when the underlying mood disturbance is treated. This potentially reversible dementia syndrome of depression, formerly called pseudodementia, does not necessarily follow the functional course outlined in Table 3.2. For example, as outlined in Table 3.4, depression may be accompanied by a refusal to dress and bathe as a result of the patient's negativity. However, the patient may be able to point to exactly the clothes he or she wishes to wear. In AD, the loss of ability to pick out clothing properly precedes the loss of ability to put on one's clothing properly.

As outlined in Table 3.4, dementia associated with hyponatremia or other electrolyte disturbances, CNS metastases, and other conditions all may follow a course markedly at variance with the course of AD as outlined in the FAST.

In a patient with AD, a variety of coexisting conditions may result in functional disturbances that may occur prematurely or nonordinally (i.e., out of sequence) in terms of the FAST predictions. Examples of conditions that may be associated with premature (i.e., nonordinal) functional losses in an AD patient are outlined in Table 3.5. For example, if an AD patient is at GDS stage 5 and FAST stage 5 and develops urinary incontinence, this incontinence may,

TABLE 3.4 ***Examples of the Order of Functional Loss in Non-Alzheimer Disorders Associated With Progressive or Gradual Onset of Dementia and Characteristic FAST Order of Functional Loss in AD***

Functional Loss in Non-Alzheimer Disorders			*FAST AD Distinctions*		
Disorder	*Pathology or Presumed Etiology*	*Example of the Order of Functional Loss in Non-AD Disorder*[a]	*Equivalent FAST Stage*	*Order of Functional Loss in AD per FAST*	*FAST Stages in AD*
Normal-pressure hydrocephalus	Dilated cerebral ventricles	1. Gait disturbance	7c	1. Loss of ability to perform complex tasks	4
		2. Urinary incontinence	6d	2. Urinary incontinence	6d
		3. Loss of ability to perform complex tasks	4	3. Ambulatory (gait) disturbance	7c
Creutzfeldt-Jakob disease	Prion	1. Gait disturbance	7c	1. Loss of ability to perform complex tasks	4
		2. Loss of ability to perform complex tasks	4	2. Gait (ambulatory) disturbance	7c
Multi-infarct dementia	Multiple cerebral infarctions	1. Loss of speech	7a–7b	1. Loss of ability to perform complex tasks	4
		2. Loss of urinary continence	6d	2. Loss of ability to pick out clothing properly	5
		3. Loss of ability to put on clothing	6a	3. Loss of ability to put on clothing without assistance	6a
		4. Loss of ability to bathe without assistance	6b	4. Loss of ability to bathe without assistance	6b
		5. Loss of ambulatory capacity	7c	5. Loss of urinary continence	6d
		6. Loss of ability to perform complex tasks	4	6. Loss of fecal continence	6e
		7. Loss of ability to pick out clothing	5	7. Loss of speech	7a–7b
		8. Fecal incontinence	6e	8. Loss of ambulatory capacity	7c
Dementia syndrome of depression ("pseudodementia")	Affective disorder associated with neurotransmitter imbalance	1. Loss of ability to perform complex tasks	4	1. Loss of ability to perform complex tasks	4
		2. Refusal to put on clothing (associated with negativity)	6a	2. Inability to pick out clothing properly	5

Continued

TABLE 3.4 ***Continued***

Functional Loss in Non-Alzheimer Disorders			*FAST AD Distinctions*		
Disorder	*Pathology or Presumed Etiology*	*Example of the Order of Functional Loss in Non-AD Disorder*[a]	*Equivalent FAST Stage*	*Order of Functional Loss in AD per FAST*	*FAST Stages in AD*
		3. Refusal to bathe (associated with negativity)	6b	3. Inability to put on clothing without assistance.	6a
		4. Loss of ability to pick out clothing properly	5	4. Inability to bathe without assistance	6b
Dementia associated with hyponatremia	Electrolyte disturbance	1. Loss of ability to perform complex tasks	4	1. Loss of ability to perform complex tasks	4
		2. Loss of ability to pick out clothing properly	5	2. Loss of ability to pick out clothing properly	5
		3. Loss of ability to dress, bathe and toilet independently	6a–6c	3. Loss of ability to dress, bathe, and toilet independently	6a–6c
		4. Loss of ambulation capacity	7c	4. Loss of urinary and fecal continence	6d–6e
		5. Loss of urinary and fecal continence	6d–6e	5. Loss of speech	7a–7b
		6. Loss of speech	7a–7b	6. Loss of ambulatory capacity	7c
Dementia associated with diffuse CNS metastasis	Neoplastic diffuse cerebral trauma	1. Loss of ability to perform complex tasks	4	1. Loss of ability to perform complex tasks	4
		2. Loss of ability to dress, bathe, and toilet independently	6a–6c	2. Loss of ability to dress, bathe, and toilet independently	6a–6c
		3. Loss of ambulation capacity	7c	3. Loss of urinary and fecal continence	6d–6e
		4. Loss of urinary and fecal continence	6d–6e	4. Loss of speech	7a–7b
		5. Loss of speech	7a–7b	5. Loss of ambulatory capacity	7c

[a]The sequences of functional loss shown are typical for normal-pressure hydrocephalus and Creutzfeldt-Jakob disease; the sequence for multi-infarct dementia is one of various common presentations; the sequences in the dementia syndrome of depression, dementia associated with hyponatremia, and dementia associated with diffuse CNS metastasis are previously observed examples of the presentation of these dementias. It should be noted that in some of the non-AD disorders, particularly multi-infarct dementia, the "sequence" described may appear abruptly, rather than over an extended time interval.
FAST = Functional Assessment Staging.
Source: Reisberg, B., Pattschull-Furlan, A., Franssen, E., Sclan, S. G., Kluger, A., Dingcong, L., et al. (1990). Cognition related functional, praxis and feeding changes in CNS aging and Alzheimer's disease and their developmental analogies. In K. Beyreuther & G. Schettler (Eds.), *Molecular mechanisms of aging* (pp. 18–40). Berlin: Springer-Verlag.

TABLE 3.5 ***Differential Diagnostic Considerations in Cases of Deviations From FAST***

Stage	*FAST Characteristics*	*Differential Diagnostic Considerations (Particularly if FAST Stage Occurs Prematurely in the Evolution of Dementia)*
1	No functional decrement, either subjectively or objectively, manifest	
2	Complains of forgetting location of objects; subjective work difficulties	Anxiety neurosis, depression
3	Decreased functioning in demanding employment settings evident to co-workers, difficulty in traveling to new locations	Depression, subtle manifestations of medical pathology
4	Decreased ability to perform complex tasks such as planning dinner for guests, handling finances, and marketing	Depression, psychosis, focal cerebral process (e.g., Gerstmann's syndrome)
5	Requires assistance in choosing proper clothing, may require coaxing to bathe properly	Depression
6	(a) Difficulty putting on clothing properly	(a) Arthritis, sensory deficit, stroke, depression
	(b) Requires assistance in bathing, may develop fear of bathing	(b) Arthritis, sensory deficit, stroke, depression
	(c) Inability to handle mechanics of toileting	(c) Arthritis, sensory deficit, stroke, depression
	(d) Urinary incontinence	(d) Urinary tract infection, other causes of urinary incontinence
	(e) Fecal incontinence	(e) Infection, malabsorption syndrome, other causes of fecal incontinence
7	(a) Ability to speak limited to one to five words	(a) Stroke, other dementing disorder (e.g., diffuse space-occupying lesions)
	(b) Intelligible vocabulary lost	(b) Stroke, other dementing disorder (e.g., diffuse space-occupying lesions)
	(c) Ambulatory ability lost	(c) Parkinsonism, neuroleptic-induced or other secondary extrapyramidal syndrome, Creutzfeldt-Jakob disease, normal-pressure hydrocephalus, hyponatremic dementia, stroke, hip fracture, arthritis, overmedication
	(d) Ability to sit up independently lost	(d) Arthritis, contractures
	(e) Ability to smile lost	(e) Stroke
	(f) Ability to hold up head lost	(f) Head trauma, metabolic abnormality, other medical abnormality, overmedication, encephalitis, other causes

FAST = Functional Assessment Staging.
Source: Reisberg, B. (1986). Dementia: A systematic approach to identifying reversible causes. *Geriatrics, 41*(4), 30–46. Copyright © 1984 by Barry Reisberg, MD.

at this early point in AD, be a remediable complication, perhaps secondary to a urinary tract infection.

Similarly, if a patient with AD at GDS stage 5 and FAST stage 5 develops loss of independent ambulation, this may be the result of a stroke or possibly of a variety of potentially treatable conditions common in the elderly, such as medication-induced parkinsonian symptoms, arthritis, fracture, and so on. Table 3.5 provides an extensive list of causes of premature functional losses in an AD patient, many of which are potentially remediable.

The relationship between the FAST and the GDS, or the FAST and the MMSE, is also useful in the identification of excess functional disability that may be remediable. Specifically, if an

AD patient is notably more impaired functionally, in comparison with the magnitude of the cognitive impairment (e.g., a GDS stage 5 patient who is at stage 6d on the FAST), this is an indication of the likely presence of excess functional disability. For example, the patient may have coexisting arthritis and AD. As a result of the combination of arthritis and dementia, in addition to not being able to handle finances and to pick out clothing without assistance (deficits that occur only because of the patient's AD), the patient may be unable to dress, bathe, and toilet without assistance, the latter resulting in occasional urinary incontinence. The arthritis may or may not be remediable. Similarly, the excess functional disability may or may not be remediable. Interestingly, when excess functional disability occurs in AD patients, it tends to occur "along the lines of the FAST." It appears that AD predisposes to functional losses outlined on the FAST. When an insult occurs, the closer the AD patient is to the inevitable point of loss of a functional ability on the FAST, the more predisposed the AD patient is to the premature loss of that capacity on the FAST. Not only illnesses but also psychological stressors may produce these premature losses. For example, if an AD patient at GDS stage 6 and FAST stage 6c is moved to an unfamiliar environment, the patient may develop urinary and fecal incontinence that remits when the patient is returned to familiar surroundings. Subsequently, these capacities will, tragically, be lost with the advance of AD.

Knowledge of the FAST progression of AD, in conjunction with the global concomitants, feeding concomitants, and other aspects, also provides invaluable information on the potential for treatment of disability, even in AD that is uncomplicated by the presence of additional pathology. For example, strategies for forestalling incontinence can be contemplated in FAST stage 6c. In FAST stage 6d or 6e, treatment of incontinence requires different strategies, such as frequent toileting. With the advance of deficits in FAST stage 7, strategies and goals for the management of incontinence need to be modified.

Other symptoms in AD, notably symptoms associated with the behavioral syndrome as outlined in Table 3.6, also require treatment. These symptoms are commonly treated with neuroleptics or other psychotropic medications. It should be noted that treatment of these symptoms may also be related to the treatment of functional disabilities. For example, it has been observed that AD patients with excess functional disability in relation to the magnitude of their cognitive disturbances may frequently have particularly marked behavioral disturbances. Conversely, marked behavioral disturbances may be associated with excess functional disability. This excess functional disability may be remediated in part by successful treatment of the behavioral symptoms.

OVERALL MANAGEMENT SCIENCE

As shown in Table 3.7, a very interesting and important aspect of the functional progression of AD is that the order of losses on the FAST is a precise reversal of the order of acquisition of the same functions in normal human development (Reisberg, 1986; Reisberg, Ferris, & Franssen, 1986). Subsequent work has indicated that AD also reverses normal development in terms of other functional parameters such as feeding abilities and figure drawings (Reisberg et al., 1990), as well as cognitively (Auer et al., 1994; Ouvrier, Goldsmith, Ouvrier, & Williams, 1993; Sclan, Foster, Reisberg, Franssen, & Welkowitz, 1990; Shimada et al., 2003).

For example, the MMSE is a well known and widely used cognitive assessment developed for the assessment of dementia patients (Folstein et al., 1975). The MMSE score has shown approximately as robust a relationship to the mental age of children, as it has shown to any noncognitive measure of dementia pathology. Initially, in a study of Australian children, a 0.83 Pearson correlation of the MMSE score to the mental age of children was found (Ouvrier et al., 1993). A subsequent study, in Spanish children, found a 0.76 Pearson correlation between childhood mental ages and MMSE scores, and a 0.80 correlation between MMSE scores and children's chronological ages (Rubial-Álvarez et al., 2007).

Conversely, a study was conducted in AD patients of a cognitive assessment measure specifically developed for infants and small children, the Ordinal Scales of Psychological

TABLE 3.6 ***Behavioral and Psychological Pathological Symptomatology in Alzheimer's Disease***

Paranoid and delusional ideation
The "people are stealing things" delusion
The "house is not one's home" delusion
The "spouse (or other caregiver) is an imposter" delusion
The "abandonment" delusion
The "infidelity" delusion
Other suspicions, paranoid ideation, or delusions
Hallucinations
Visual hallucinations
Auditory hallucinations
Activity disturbances
Wandering
Purposeless activity (cognitive abulia)
Inappropriate activities
Aggressivity
Verbal outbursts
Physical outbursts
Other agitation
Diurnal rhythm disturbance
Day/night disturbance
Affective disturbance
Tearfulness
Other depressive manifestations
Anxieties and phobias
Anxiety regarding upcoming events (Godot's syndrome)
Other anxieties
Fear of being left alone
Other phobias

Source: Reisberg, B., Borenstein, J., Franssen, E., Shulman, E., Steinberg, G., and Ferris, S. H. (1986). Potentially remediable behavioral symptomatology in Alzheimer's disease. *Hospital and Community Psychiatry, 37,* 1199–1201. Also adapted from "Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD)." Copyright © 1986 by Barry Reisberg, MD. All rights reserved. Published in: Reisberg, B., Borenstein, J., Salob, S. P., Ferris, S. H., Franssen, E., and Georgotas, A. (1987). Behavioral symptoms in Alzheimer's disease: Phenomenology and treatment. *Journal of Clinical Psychiatry*, *48*(5, Suppl.), 9–15.

Development (OSPD) assessment (Uzgiris & Hunt, 1975). This OSPD test was slightly modified for use in severe dementia patients. The resulting modified-OSPD measurement of cognition (the M-OSPD) showed approximately the same relationship to the FAST stage in stage 6 and stage 7 AD patients (a 0.8 correlation) as is seen between the FAST functional stage and MMSE cognitive assessment in somewhat less severe AD patients who are testable with the MMSE (Auer et al., 1994; Reisberg, Ferris, Torossian, Kluger, & Monteiro, 1992).

Similarly, a widely used intelligence test measure for children, the Binet scale, has been applied to AD patients in FAST stages 5, 6, and 7. A Spearman correlation of −0.85, between the Binet test measure basic age value and the FAST stage, was found (Shimada et al., 2003). This is at least as robust as the relationship between the MMSE and the FAST assessment in dementia patients in the corresponding FAST range (Reisberg et al., 1992).

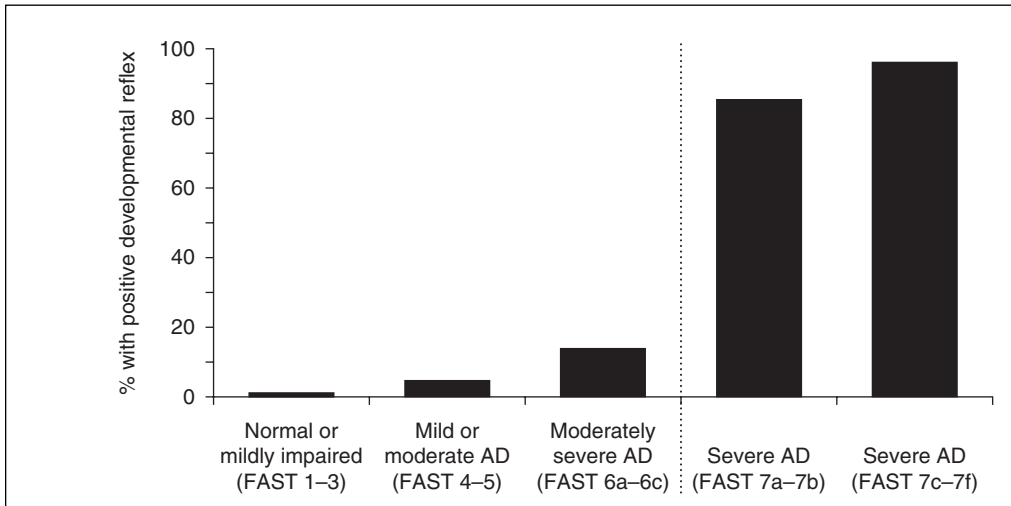
Table 3.7 illustrates that the FAST stages of AD can be expressed in terms of developmental ages (DAs). Remarkably, so-called developmental infantile reflexes appear to be equally good markers of the emergence of the stage of severe AD, corresponding to a DA of infancy, as the same reflexes are in marking the emergence from infancy in normal development (Franssen, Souren, Torossian, & Reisberg, 1997) (see Figure 3.5). Similar to the findings

TABLE 3.7 ***Functional Landmarks in Normal Human Development and Alzheimer's Disease (AD)***

Alzheimer's Degeneration
Approximate Total Duration: 20 Years

Normal Development
Approximate Total Duration: 20 Years

Approximate Age		*Approximate Duration in Development*	*Acquired Abilities*	*Lost Abilities*	*Alzheimer Stage*	*Approximate Duration in AD*	*Developmental Age of AD*
Adolescence	13–19 years	7 years	Hold a job	Hold a job	3—Incipient	7 years	19–13 years: Adolescence
Late childhood	8–12 years	5 years	Handle simple finances	Handle simple finances	4—Mild	2 years	12–8 years: Late childhood
Middle childhood	5–7 years	2.5 years	Select proper clothing	Select proper clothing	5—Moderate	1.5 years	7–5 years: Middle childhood
Early childhood	5 years	4 years	Put on clothes unaided	Put on clothes unaided	6a—Moderately severe	2.5 years	5–2 years: Early childhood
	4 years		Shower unaided	Shower unaided	b		
	4 years		Toilet unaided	Toilet unaided	c		
	3–4.5 years		Control urine	Control urine	d		
	2–3 years		Control bowels	Control bowels	e		
Infancy	15 months	1.5 years	Speak 5–6 words	Speak 5–6 words	7a—Severe	7 years or longer	15 months to birth: Infancy
	1 year		Speak 1 word	Speak 1 word	b		
	1 year		Walk	Walk	c		
	6–10 months		Sit up	Sit up	d		
	2–4 months		Smile	Smile	e		
	1–3 months		Hold up head	Hold up head	f		



Functional capacity	Independent	Deficient IADLs & incipient ADL deficit	Deficient ADLs	Incipient nonverbal	Incipient nonambulatory & immobile
Developmental age	Adult or adolescent	12 years to 5 years	5 years to 4 years	15 months to 12 months	12 months to newborn

FIGURE 3.5 Neurologic retrogenesis. Percentages of patients with one or more of the following developmental reflexes (also known as primitive reflexes or frontal release signs) are shown: the tactile sucking reflex, the palmar grasp (hand grasp) reflex, the plantar grasp (foot grasp) reflex, and the plantar extensor (Babinski) reflex. All reflexes were elicited according to standard procedures and were assessed as being present when they were prominent and persistent, defined by a rating of ≥5 on the scale of Franssen (Franssen, 2003; Franssen et al., 1991, 1993). For the three reflexes which were assessed bilaterally, specifically, the palmar grasp reflex, the plantar grasp reflex, and the plantar extensor reflex, a positive response on either side was assessed as positive. Subject samples were as follows: Deficient ADLs (FAST stages 6a to 6c), n = 113; Incipient nonverbal (FAST stages 7a to 7b), n = 29; Incipient nonambulatory and immobile (FAST stages 7c to 7f), n = 32. IADLs are instrumental (complex) activities of daily life; ADLs are basic activities of daily life. *Source:* Data and figure are adapted from Franssen, E. H., Souren, L. E. M., Torossian, C. L., & Reisberg, B. (1997). Utility of developmental reflexes in the differential diagnosis and prognosis of incontinence in Alzheimer's disease. *Journal of Geriatric Psychiatry and Neurology, 10,* 22–28.

with neurological reflexes, a leading investigator in neurometabolism, Michael Phelps, has reported remarkable similarities between the pattern of brain metabolic activity in the late-stage AD patient and that in the normal infant brain (Phelps, 2000). These findings, obtained using positron emission tomography (PET) techniques, are very different from the metabolic patterns observed in the normal adult brain.

Neuroanatomic brain changes in AD have also been observed to mirror in various ways, the brain changes in normal human development. In early studies of the neuropathology of AD, Brun and Gustafson (1976) noted that "maximal cortical degeneration occurred in the medial temporal (limbic) area and in the lateral hemisphere" and that other brain regions were notably spared. These brain regions, which were observed to be relatively free of AD-related pathology, were observed to be "mainly the anterior cingulate gyrus and the calcarine and

cortical motor areas (primary projection areas)." The investigators concluded that, "the pattern described may be related to ontogenic [developmental] features" (Brun & Gustafson, 1976). Subsequently, McGeer et al. (1990), noting the patterns of neuronal loss described by Brun and Englund (1981), and their own PET studies of neurometabolic changes in AD, concluded that the AD neurodegenerative process appears to relate to the pattern and process of brain myelination in normal development (McGeer et al., 1990). They observed that the areas of the brain, which are the last to be myelinated in normal development (and which are therefore the most thinly myelinated) (Flechsig, 1920), appear to be the areas that are the most vulnerable to the pathology of AD in terms of neuronal losses and decrements in cerebral metabolism (reviewed in Reisberg, Franssen, Hasan, et al., 1999). The pattern of neurofibrillary pathology in AD has also been related to the developmental pattern of myelinization of the brain in reverse (Braak & Braak, 1991, 1996). Raz (1999) has provided a numerical value for these anatomic relationships between myelinization in normal human development and myelin loss in the AD pathological process as seen with neuroimaging. He noted that, "The gradient of vulnerability seems to follow the rules of last (….ontogenetically) in—first out… the later a region completes its myelination, the greater age-related difference in volume it exhibits, $r = .60$, $p < 0.05$" (Raz, 1999). This process by which the degenerative changes in AD, and to some extent other dementias, reverse the order of acquisition of capacities and processes in normal development has been termed retrogenesis (Reisberg, Franssen, Hasan, et al., 1999). The process of myelin loss, which is associated with the retrogenic process occurring in AD, has been termed "arboreal entropy" (Reisberg et al., 2002). "Just as the bark of a tree protects it from… injury and, to some extent, the thicker the bark, the greater the protection, the myelin protects the axon and its neuron. Hence, to some extent,… the thicker the myelin, [and the earlier in development the neuron is myelinated] the greater the protection" (Reisberg et al., 2002).

Interestingly, the retrogenesis process can explain many of the other symptoms and findings in AD, such as the nature of patient behavioral disturbances (Reisberg, Auer, Monteiro, Franssen, & Kenowsky, 1998), and the kind of symptoms that are progressively and invariably lost, such as speaking and walking, in comparison with the kind of symptoms that are more variable, such as the behavioral disturbances (Reisberg, Franssen, Souren, Auer, & Kenowsky, 1998). Most importantly, the retrogenic process provides a rapid appreciation of the general care and management needs of the AD patient at each stage of the disease (Reisberg, Kenowsky, Franssen, Auer, & Souren, 1999) (Table 3.8).

An understanding of the retrogenic process in AD also provides the basis for a detailed management science (Reisberg et al., 2002). This science includes care axioms, care postulates, and care caveats. The care axioms apply to all human beings and to AD patients at all stages (Table 3.9). The postulates are testable hypotheses of AD patient care based on the DA retrogenesis model (Table 3.10). Finally, the caveats are based on acknowledged differences between AD patients and their DA peers (Table 3.11). The combination of these care axioms, postulates, and caveats forms the nascent science of AD management.

RELATIONSHIP BETWEEN AD'S CLINICAL COURSE AND MANAGEMENT AND ITS OBSERVED PATHOLOGICAL AND BIOMOLECULAR FEATURES

The classical observed pathology accompanying the dementia of AD, as viewed upon microscopic examination of the brain, is extracellular plaques containing a substance called amyloid and intraneuronal neurofibrillary tangles. The amyloid plaques are primarily composed of a protein called β-amyloid. The intracellular neurofibrillary tangles are derived from neuronal microtubules. These microtubules are the "tubes" that are used to transport nutrients and other essential substances through the axonal fibers. The axons can be very long, and the axons degenerate in the absence of this essential neurotubular transport.

As noted earlier, the amyloid protein in the amyloid plaques is mainly composed of β-amyloid protein. This β-amyloid protein, like all proteins, is made up of amino acids. There

TABLE 3.8 ***Stages of Aging and Alzheimer's Disease (AD) and Corresponding Developmental Ages (DAs): Care Needs and Care Recommendations***

GDS Stage	*Diagnosis*	*Developmental Age (DA)*	*Care Needs*	*Care Recommendations*
1	Normal	Adult	None	None
2	Subjective cognitive impairment	Aged adult	None	Reassurance with respect to relatively benign prognosis
3	Mild cognitive impairment	Adolescence	None	"Tactical" withdrawal from situations that have become, by virtue of their complexity, anxiety provoking
4	Mild AD	Late childhood	Independent survival still attainable	Assistance towards goal of maximum independence with financial supervision; structured or supervised travel; identification bracelets and labels may be useful
5	Moderate AD	Middle childhood	Patient can no longer survive in the community without assistance; needs supervision with respect to travel and social behavior	Part-time home health care assistance can be very useful in assisting the patient's caregiver. Driving becomes hazardous and should be discontinued at some point over the course of this stage. Family may require guidance in handling patient's emotional outbursts
6	Moderately severe AD	Early childhood	Patient requires assistance with basic activities of daily life. Early in this stage, assistance with dressing and bathing is required. Subsequently, assistance with continence becomes necessary as well	Full-time home health care assistance is frequently very useful in assisting the patient's caregiver. Strategies for assistance with bathing, toileting, and in the management of incontinence should be discussed with the family. Emotional stress in the caregiver should be minimized with supportive techniques
7	Severe AD	Infancy	Early in this stage assistance with feeding as well as dressing, bathing, and toileting is required. Subsequently, assistance with ambulation and	Full-time assistance in the community home residence or institutional setting is a necessity. Strategies for maintaining locomotion should be

Continued

TABLE 3.8 ***Continued***

GDS Stage	*Diagnosis*	*Developmental Age (DA)*	*Care Needs*	*Care Recommendations*
			purposeful movement becomes necessary. Prevention of aspiration, contractures, and decubiti is a major issue in care	explored. The need for psychopharmacological intervention for behavioral disturbances decreases. Soft food or liquid diet is generally tolerated. Patients must be fed and instructed and encouraged to maintain chewing and basic eating skills

are generally 40–42 amino acids in the β-amyloid protein. This β-amyloid protein is itself derived from a much larger protein, the amyloid protein precursor (APP) protein, which is 365–770 amino acids long. The APP protein is known as a transmembrane protein, because it crosses the cell membrane of the neuron. Part of the APP is outside the neuronal cell membrane, part is inside the neuronal cell membrane, and part of this protein is inside the cell, in the cytosol, the neuronal cell substance. The APP protein is normally cleaved by an enzyme known as α-secretase, which cleaves the APP outside the cell membrane. When α-secretase cleavage occurs, there is no amyloid β (Aβ) produced. Alternatively, the APP is cleaved by another enzyme, the β-secretase enzyme, which is, like the α-secretase, located outside the cell membrane. β-Secretase cleavage is followed by cleavage within the cell membrane by an enzyme known as γ-secretase. The result of this β- and γ-secretase cleavage is the Aβ protein, which is in the plaques in AD. Both aging and AD are associated with increased Aβ protein in the brain (Näslund et al., 2000; Seubert et al., 1992).

TABLE 3.9 ***Alzheimer's Disease (AD) Care Axioms***

Axiom I	All human beings avoid trauma and humiliation
Axiom II	All human beings seek a sense of accomplishment
Axiom III	All human beings seek a sense of dignity and self-worth
Axiom IV	All human beings are social organisms
Axiom V	All human beings seek praise and acceptance
Axiom VI	All human beings have the capacity to learn
Axiom VII	All human beings require love
Axiom VIII	All human beings have the capacity for happiness if basic needs are fulfilled
Axiom IX	All human beings have the need for physical movement
Axiom X	All human beings have the capacity to remember
Axiom XI	All human beings have the capacity to think
Axiom XII	All human beings seek to influence their environment
Axiom XIII	All human beings have a sense of "taste," i.e., likes and dislikes

TABLE 3.10 ***Alzheimer's Disease (AD) Care Postulates***

Postulate I	The magnitude of care and supervision required by an AD patient, at a developmental age (DA), is mirrored by the amount of care and supervision required by a child or infant at the corresponding DA
Postulate II	The kinds of activities enjoyed by an AD patient, at a particular DA, are mirrored by the kinds of activities enjoyed by children at a corresponding DA
Postulate III	The capacity of an AD patient to perform in an area of residual expertise is dependent on the patient's DA
Postulate IV	Previous experiences may determine the kinds of activities enjoyed by an AD patient
Postulate V	The emotional level of the AD patient is dependent on the DA
Postulate VI	Life experiences appropriate to the DA become most relevant for AD patients at any particular stage
Postulate VII	Socialization of the AD patient is dependent on the DA
Postulate VIII	Diversity in children's and infants' activities and interests is mirrored in diversity in AD patient's interests and activities at a corresponding DA
Postulate IX	The emotional changes that occur in AD at a DA are mirrored by the emotional changes observed in children at a corresponding DA
Postulate X	Care settings appropriate to AD patients at a DA are mirrored by care settings appropriate to children at the corresponding DA
Postulate XI	Vulnerability (emotional, physical, and cognitive) of the AD patient at a DA is mirrored by the vulnerability of children at the corresponding DA
Postulate XII	The need of an AD patient for physical movement is mirrored by the corresponding DA
Postulate XIII	Just as one judges development in an infant or child by what the infant or child can do and has achieved, not by what the infant or child cannot do, the AD patient at any particular DA should be assessed in terms of his or her residual skills and accomplishments, what they have learned and relearned, not by what they cannot do
Postulate XIV	The developmental analogy is sufficiently strong to trigger DA-appropriate childhood memories, beliefs, and anxieties in the AD patient
Postulate XV	The language changes of the AD patient are mirrored by the DA

DA = Developmental ages.

TABLE 3.11 ***Alzheimer's Disease (AD) Care Caveats***

Caveat I	Development in infants and children is accompanied by increasing expectations, whereas AD at all stages is accompanied by progressively diminished expectations
Caveat II	AD patients experience developmentally analogous brain changes; however, they do not undergo developmentally analogous physical changes
Caveat III	AD patients can, to some extent, draw upon previously mastered skills, whereas infants and children may not have access to these skills
Caveat IV	AD patients can, to some extent, draw upon previously mastered knowledge, whereas infants and children may not have access to this knowledge
Caveat V	AD patients are older than their DA peers, and old age predisposes to various physical disabilities that influence the life and experience of an AD patient
Caveat VI	AD patients appear to be more prone to rigidity than their DA peers
Caveat VII	AD patients can potentially concentrate on a task longer than infants or children at a corresponding DA
Caveat VIII	AD patients appear to be less fascinated by the world and less inquisitive than infants and children at a corresponding DA

DA = Developmental ages.

The neurofibrillary tangles in AD, seen inside the neuron, are composed of paired helical filaments (Kidd, 1963). The major constituent of these paired helical filaments is a protein known as "tau" (Kondo et al., 1988; Wischik, Novak, Edwards, et al., 1988; Wischik, Novak, Thøgersen, et al., 1988). Tau is believed to be a scaffolding molecule, which maintains the structural integrity of the microtubules in the neurons.

The relationship between the clinically observed "plaques and tangles" of AD (including the more recently discovered biomolecular constituents of the plaques and tangles) and the observed behavioral course of AD, described in the preceding sections of this chapter, can presently be elucidated.

As described in the prior sections, remarkably similar patterns between the neurometabolic activity of a late-stage AD patient and those of the infant brain have been noted (Phelps, 2000). In 2002, Reisberg et al., hypothesized that these patterns could be explained if "the most metabolically active regions of the brain in AD … are the regions which are the most vulnerable in AD" (Reisberg et al., 2002). In 2005, it was found by Buckner et al. that, in fact, the pattern of deposition of amyloid plaques in the brain of AD patients appeared to occur in the regions of the brain that are the most active during the resting, so-called, default state, when the brain is not focused upon any particular activity (Buckner et al., 2005). Hence, there appears to be a direct relationship between the metabolic activity of the brain and a major form of microscopically evident AD pathology, the amyloid plaques, containing β-amyloid.

In 1980, Ferris and associates reported, using the then new PET scanning techniques, that there is a continuous decrease in metabolism in many brain regions, with the advance of the behaviorally evident AD process (Ferris et al., 1980). These findings have been replicated and supported in numerous subsequent studies. This process of continuing neurometabolic loss in AD has been termed "neurometabolic entropy" (Reisberg, Wegiel, Franssen, et al., 2006a). The continuing neurometabolic entropy, affecting first, the most metabolically active brain regions, appears to provide an explanation for the observed neurometabolic retrogenesis seen in AD.

Recent studies have provided an understanding of the mechanisms underlying these metabolic changes in AD. The insulin receptor and the insulin-like growth factor (IGF) receptor signaling pathway play a major role in controlling maximum lifespan and age-associated diseases in all species of multicellular organisms that have been studied, including yeast, worms, flies, and mammals (Puglielli, 2008). Interestingly, a decrease in IGF-1 blood levels occurs with normal aging in a retrogenic-like pattern. Specifically, there is a continuing increase in IGF-1 blood levels from infancy to about 15 years of age and this is followed by a continuing decrease in levels of IGF-1 in the blood, reaching an infant and early childhood level by about age 80–85 (Laboratory Corporation of America, accessed 2003; Reisberg, Wegiel, Franssen, et al., 2006a). These circulating blood changes in IGF-1 levels may be related to currently observed changes in the IGF-1 insulin receptor in aging and AD. A decreased number of neurons are now being reported to express the IGF-1 receptor in AD (Moloney et al., 2010). Also, Moloney et al. are reporting that the IGF-1 receptor is aberrantly distributed in AD, particularly in neurons affected by neurofibrillary tangles, in that it is concentrated intracellularly rather than at the neuronal cell membrane. Related to this, Moloney et al. are reporting decreased insulin receptor substrate levels in AD neurons, and these decrements are localized with the neurofibrillary tangles. Interestingly, in terms of the other major microscopically observed pathology in AD, the β-amyloid, formed in part by γ-secretase cleavage, the same enzyme, γ-secretase, is also being related to the IGF-1 receptor. Specifically, γ-secretase has now been reported to be involved in the proteolysis (breakdown) of the IGF-1 receptor (McElroy, Powell, & McCarthy, 2007).

In addition to direct relationships between the IGF-1 receptor and AD pathology, the insulin receptor is also being directly related to AD pathology. Soluble, Aβ (Townsend, Mehta, & Selkoe, 2007), as well as Aβ oligomers (Zhao, DeFelice, Fernandez, et al., 2008) have been shown to impair insulin receptor function.

The net result of these changes in the IGF-1 receptor and in insulin receptor signaling is that the neurons which degenerate in AD may be more resistant to these signals (Moloney et al., 2010). This resistance is being widely observed, and AD is now frequently referred to as type 3 diabetes (Hoyer, 1998; Steen et al., 2005). As with many changes in biology, the arrows, in terms of etiopathogenesis of metabolic deficits in the brain in AD, appear to point in both directions. The decrease in oxidative metabolism, which occurs in the brain in AD, has been observed to be associated with amyloid accumulation in several studies (Pluta, 2002; Popa-Wagner, Schröder, Walker, & Kessler, 1998; Sinigaglia-Coimbra, Cavalheiro, & Coimbra, 2002).

To fully understand the nature of the pathology in AD, together with associated pathogenic mechanisms, and their relationship to the clinical manifestations of AD, an additional principle must be recognized and addressed. This is that there is a homeostatic, regenerative, developmental, physiological response to the progressive pathology of AD. This regenerative physiological response in AD has many elements, which notably include: (1) there is a reactivation of the cell cycle enzymes in terminally differentiated neurons in AD (reviewed in Reisberg et al., 2002); (2) there is an activation of neurogenesis (new neuron production) in a region of the hippocampus (the dentate gyrus) in AD; (3) the activation of the β-secretase enzyme appears to be associated with a myelin regeneration effect; (4) the activation of γ-secretase may also be associated with a regenerative effect; (5) the production of Aβ may be associated with injury repair in the brain; and (6) the reduction in IGF-1 signaling appears to delay age-associated protein-related toxicity (e.g., from toxic soluble and oligomeric forms of Aβ).

For example, to the extent that the function of the β-secretase enzyme is known, apart from its role in the generation of amyloid β, it plays an important role in cleavage associated with the production of myelin (Glabe, 2006; Willem et al., 2006). Interestingly, IGF-1 also plays a role in myelin production, causing the oligodendrocytes, the myelin producing brain cells, to produce more myelin (Carson, Behringer, Brinster, & McMorris, 1993; Flores et al., 2008). β-Secretase knock-out mice show decreased myelin production and decreased IGF-1 signaling (Hu et al., 2006). Therefore, the β-secretase response in AD appears to be a homeostatic compensation for the decrease IGF-1 activity with aging and AD. Nevertheless, as described above, there are continuing IGF-1 signaling abnormalities in AD, and these can account for the observed myelin arboreal atrophy and myelin retrogenesis seen in AD.

Activation of γ-secretase also appears to be a developmental response to the pathology in AD, in addition to its role in the production of β-amyloid and in the protein breakdown of the IGF-1 receptor. For example, notch, an element of the γ-secretase complex, is involved in signaling, which is "crucial for long-term memory" (Costa, Drew, & Silva, 2005). Also, "the notch pathway has been shown to regulate neurite growth and adult neurogenesis" (Breunig, Silbereis, Vaccarino, Sestan, & Rakic, 2007; Costa et al., 2005).

Aβ itself appears to be involved in brain injury repair. Brody et al. (2008) have shown that there is an increase in Aβ in the brain interstitial fluid in the 72-hour period after a brain trauma associated with coma, in the persons who show signs of recovering from a coma. However, this increase in Aβ in the brain interstitial fluid is not seen in the persons with poor signs of coma recovery.

Additionally, the reduced insulin and IGF-1 signaling in AD appears to be, in part, a physiological homeostatic response to toxic proteins produced by the AD process. For example, a recent study showed that reduction in IGF signaling in an Alzheimer mouse model decreased behavioral impairment, neuroinflammation, and neuronal loss (Cohen et al., 2009).

Hence, there is a complex homeostatic, physiological response to the behavioral and biomolecular changes associated with AD. This response can presently provide a good understanding of the nature of the changes seen in AD, including the retrogenic physiological process and the consequent management needs in AD.

CONCLUSIONS

AD is a very common condition in elderly persons, marked by a characteristic cognitive and functional course of disability. Knowledge of this characteristic course is essential for the identification and treatment of excess functional disability and for many other aspects of patient management and care. Proper management and care can alleviate, indeed, even eliminate suffering in the patient and reduce burden in the caregivers of AD victims.

ACKNOWLEDGMENT

This work was supported in part by U.S. Department of Health and Human Services (DHHS) grants AG03051, AG08051, AG09127, and AG11505 from the National Institute on Aging of the U.S. National Institutes of Health; by grants 90AZ2791, 90AM2552, and 90AR2160 from the U.S. DHHS Administration on Aging; by grant NCRRM01 RR00096 from the General Clinical Research Center Program and by Clinical and Translational Science Institute grant 1UL1RR029893 from the National Center for Research Resources of the U.S. National Institutes of Health; by the Fisher Center for Alzheimer's Disease Research Foundation; by a grant from Mr. William Silberstein; by the Leonard Litwin Fund for Alzheimer's Disease Research; by the Woodbourne Foundation; and by the Hagedorn Fund.

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