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ASSESSMENT OF COGNITIVE IMPAIRMENT, ALZHEIMER'S DISEASE, AND OTHER FORMS OF DEMENTIA

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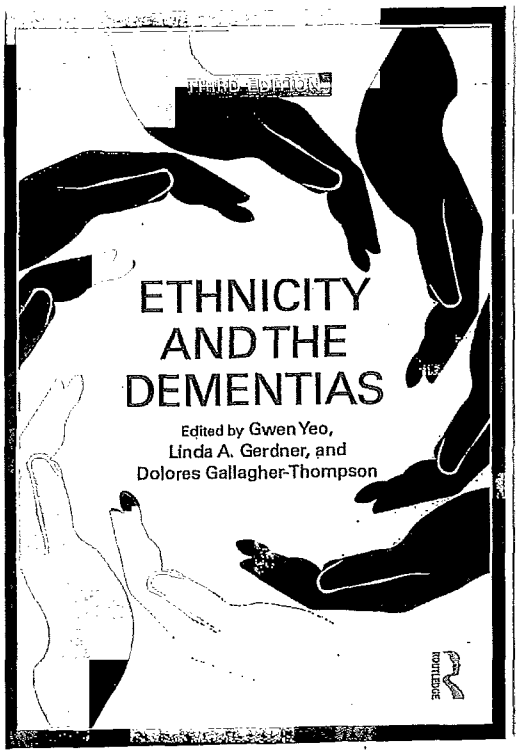

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This 3rd edition of *Ethnicity and the Dementias* includes the latest background, assessment, and ethnic-specific guidelines for working with culturally diverse elders with dementia and their family caregivers in the United States. Featuring contributions from leading clinicians and researchers, this text examines specific issues in dementia care in eleven ethnic/racial groups and the lesbian, gay, bisexual, and transgender population in the context of working with family. Recommended assessment of various types of dementia is followed by specific recommendations for assessing and caring for individuals for each cultural group. As an update to the first two editions, this third edition continues to be the only comprehensive resource on ethnicity and dementia. The book is ideal for practitioners, researchers, and policy makers in search of the most current ethnogeriatric findings and is widely used in gerontology courses.

Background

Alois Alzheimer was the first to describe the clinical course of dementia in an individual and associate it with specific pathological changes (Alzheimer, 1907). The initial case was a 51-year-old woman, whose symptoms began as a paranoid delusion regarding her husband. Memory deterioration and the development of other psychiatric symptoms, including general paranoia and social dysfunction, followed. There was a marked loss of the ability to encode information, with accompanying symptoms of aphasia, agnosia, and apraxia (loss of language, not knowing things, and how to do things). Yet neurologic reflexes were unremarkable. As the disease progressed, Alzheimer noted bewilderment, psychosis, screaming, and fluctuation of symptoms. After four years, the patient was bedfast, contracted, and incontinent, and soon died. At autopsy, her brain showed atrophy, arteriosclerotic changes, neurofibrillary changes, senile plaques, and gliosis. The description of this patient is typical of the clinical features manifested by patients with what we now call Alzheimer's disease (AD). The term "presenile dementia" (before age 65), which had been used for many years, was abandoned when neurofibrillary changes and senile plaques were found in older individuals, with neurofibrillary changes corresponding to dementia severity (Blessed, Tomlinson, & Roth, 1968; Nelson et al., 2007).

Since Alzheimer's first case, dementia is now considered a syndrome whose definition is complicated by the delineation of over 50 different causal or contributing conditions. In 2013, the American Psychiatric Association defined conditions related to the common term "mild cognitive impairment" as "Minor Neurocognitive Disorder" and dementia as "Major Neurocognitive Disorder" (Fifth Edition, DSM-5, 2013) (see Tables 3.1a and 3.1b).

Table 3.1a DSM-5 Specific Symptoms of "Minor Neurocognitive Disorder" (Similar to Mild Cognitive Impairment)

1 Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains, such as: complex attention, executive function, learning, memory, language, visual-spatial, complex motor movements, social cognition; preferably documented by standardized neuropsychological testing, or if neuropsychological testing isn't available, another type of qualified assessment.

2 Concern of the individual, a knowledgeable informant (such as a friend or family member), or the clinician that there's been a mild decline in cognitive function.

3 The cognitive deficits do not interfere with capacity for independence in everyday activities (e.g., complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required).

4 The cognitive deficits don't occur exclusively in the context of a delirium, and are not better explained by another mental disorder.

Table 3.1b DSM-5 Definition of "Major Neurocognitive Disorder" (Essentially the Same as "Dementia")

1	Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains: learning and memory, language, executive function, complex attention, perceptual-motor, social cognition.
2	The cognitive deficits interfere with independence in everyday activities. At a minimum, assistance should be required with complex instrumental activities of daily living, such as paying bills or managing medications.
3	The cognitive deficits do not occur exclusively in the context of a delirium.
4	The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

In developing greater scientific understanding of dementia, it is necessary to recognize that the brain has multiple complex functions (Ashford, Coburn, & Fuster, 1998). The challenge then is to categorize the multiple conditions which can adversely affect brain function thereby causing cognitive impairment and dementia. After the discovery of AD, clinicians learned that vascular disease and stroke, including cerebral hemorrhages and clots, could also disrupt mental function. Pathological observations of cerebral arteriosclerosis lead to the term "hardening of the arteries of the brain," which was used for many years. Head trauma associated with boxing became associated with the term "dementia pugilistica," now broadened to include any form of head trauma and termed "chronic traumatic encephalopathy." Over-use of alcoholic beverages and alcoholism was associated with an "alcoholic dementia." It is now understood that nearly any chronic medical or neurological condition can cause dementia, including vitamin or hormonal deficiency, cardio-pulmonary-vascular disease, and numerous organic conditions as well as many neurological conditions, including Parkinson's disease, fronto-temporal dementia, and Lewy body dementia.

This chapter updates reviews of methods and techniques used to assess cognitive impairment (Ashford, Schmitt, & Kumar, 1996, 1998) and focuses on the clinical evaluation of a patient whose cognitive dysfunction has risen to the level of concern. This chapter further addresses a wide range of issues, from the earliest self-reported memory concerns that have been reported as associated with AD neuropathology (Kryscio et al., 2014, 2016) to the clinical diagnosis of dementia, related medical comorbidities associated with dementia risk (Nelson et al., 2010; Zhang et al., 2017), and assessment of dementia progression.

Screening for Cognitive Impairment, Dementia, and Alzheimer's Disease

A major issue is screening to detect the first signs of cognitive impairment (Ashford, 2008; Ashford et al., 2007; Bayley et al., 2015; Borson et al., 2013; Morley et al., 2015). Memory and cognitive impairment screening is cost-effective beginning at age 65 years (Ashford et al., 2007). Individuals should consider a screening test especially if there is concern about memory or cognitive function, either by the individual, a family member, or someone else who knows the individual well. Specific risk factors for developing cognitive impairment include low education, history of diabetes mellitus, stroke, depression, or difficulty with managing usual affairs, such as appointments, checkbook, or medications. With a family history of cognitive problems, there is

an additional risk, and recently available genetic tests can help to determine that risk (Ashford, 2004; also see www.23andme.com).

Short cognitive tests that focus on "episodic memory" (recall or recognition of items after distraction) appear to distinguish very mild AD cases from the normal aging process and detect AD-related changes up to 10 years before it is possible to make a standard clinical diagnosis. Several brief cognitive tests have been recommended for screening purposes – for a review and assessment of the performance of cognitive screening tests, including the Mini-Mental State Exam, the Mini-Cog, the Memory Impairment Screen and the Brief Alzheimer Screen, see Ashford (2008), Bayley et al. (2015), and Cordell et al. (2013). The most carefully developed screening test which must be administered by a rater is the "Brief Alzheimer Screen" (BAS) (Ashford, 2008; Mendiondo, Ashford, Kryscio, & Schmitt, 2003), which takes about 3 minutes. At this time, many locations offer free screening tests (for example, www.alzfdn.org/memory-screening). Free memory tests are also available online which can be done in a private setting, take less than 2 minutes, and are indefinitely repeatable (for example, www.memtrax.com) (Ashford, Gere, & Bayley, 2011).

In the clinician's office, the Medicare Annual Wellness Visit, available annually for individuals over age 65 years old, is mandated to include a cognitive assessment to screen for developing problems. However, in routine clinical practice, specific focus on the patient's day-to-day functioning only begins after recognition of cognitive impairment. There are numerous other brief exams that can be used to further enhance the initial detection of dementia. However, all such tests must be used judiciously and are more meaningful when used with respect to values from confirmed normal individuals of similar backgrounds. For example, the number of animals the patient can name in 1 minute is a valuable index for discriminating between AD patients and normal individuals as part of a mental status examination, with most normal individuals able to name at least 15. Also, most normal individuals will know the name of the U.S. President and the immediate past U.S. President, though many mildly demented patients will claim that they do not keep track of such political issues. Abstractions – for example, similarities (oranges and bananas, cats and dogs, tables and chairs) – are often difficult for even very mildly impaired patients, but usually present no problem for even very elderly normal people (Ashford et al., 1992). Modifications of the Boston Naming Test can be used to identify the dysnomia associated with AD, although not all of the brief versions have equal sensitivity to the AD process (Katsumata et al., 2015). The Montreal Cognitive Assessment (MoCA) incorporates many of these items, only takes about 10 minutes, and is widely used test to screen for mild dementia (Borland et al., 2017; Ciesielska et al., 2016; Monsell et al., 2016; Nasreddine et al., 2005; Solomon et al., 2014). Another important factor in screening is daily function, which corresponds closely to cognitive impairment and general estimates of impairment (Ashford et al., 1992). With such additions, a clinician can make a clear determination that a patient has a clinically significant impairment and warrants further assessment.

Pathogenic Considerations in Dementia Assessment

In the assessment of cognitive impairment, the first consideration is the age of the patient. It is clear that dementia is by and large age-associated (see Chapter 2, on risk factors with age top of the list), although there are some conditions that cause significant cognitive impairment at

younger ages, such as Down syndrome, which usually presents by age 40 (Head et al., 2017; Salehi, Ashford, & Mufson, 2016) and Huntington's disease, which usually presents before age 50. With aging, a progressively larger number of conditions cause or contribute to dementia (Jansen et al., 2017). AD is the most common cause of dementia, with some AD pathology occurring in the majority of individuals by age 50 (Ohm, Muller, Braak, & Bohl, 1995), and estimates of the proportion of dementia patients worldwide having AD range from 60% to 75% (WHO Fact Sheet, No. 362). It is generally considered that one-third of dementia patients have "pure" AD, one-third have AD with at least one additional dementing condition, and one-third have no AD but have dementia due to one of the many other conditions commonly or uncommonly associated with dementia. These estimates of AD and other age-related dementias approximate reports of pathological findings (Abner et al., 2017; Nelson et al., 2007) discernible at autopsy when the brain can be comprehensively studied. Vascular dementia, spanning a spectrum from "small vessel ischemic disease" to multiple small strokes or infarcts to major strokes, accounts for 5% to 20% of all dementias (see Table 3.2a for estimates of proportion of dementia for non-reversible causes).

Recently, diffuse Lewy body disease, characterized by the buildup of alpha-synuclein protein in neurons and related to Parkinson's disease, has been recognized as occurring in up to 15% of cases. Fronto-temporal dementia resulting from the progressive degeneration of the temporal and frontal lobes of the brain may occur in about 5% of cases. Also, at autopsy, argyrophilic grain disease (argyrophilic grains and coiled bodies in brain tissue) can be found in over 10% of cases (Kovacs et al., 2008). Alcoholic dementia ranges from 5% to 15%, and has been more common in veterans. Other neurological and general medical conditions can cause dementia and need to be considered clinically. A major interest is the determination of conditions which can be treated in order to improve patient outcomes by maintaining daily functioning and quality of life. Table 3.2b lists conditions associated with dementia which are considered "treatable," in that there are accepted treatments which may reverse or slow the condition and potentially reverse of stop the decline of the cognitive impairment.

Clinical Diagnosis of Dementia

In the clinical setting, when the patient presents a cognitive problem and a diagnosis of dementia is under consideration, there is a well-accepted diagnostic regimen (Cummings, Isaacson, Schmitt, & Velting, 2015). Table 3.3 shows the various diagnostic tests and their underlying rationale.

Table 3.2a Untreatable and Irreversible Causes of Dementia

Condition	*Percentage of Total Cases*
Alzheimer's disease	60%–75%
Vascular disease	5%–20%
Diffuse Lewy body disease	Up to 15%
Alcoholism	5%–15%
Argyrophilic grain disease	Approximately 10%
Fronto-temporal dementia conditions	Approximately 5%
Hypoxic or anoxic encephalopathy (Anoxia can occur due to severe asthma, heart attack, carbon monoxide poisoning or other causes)	Not available
Traumatic brain injury	Not available
Rare neurological diseases	Not available
Infectious disease: herpes encephalopathy, meningitis, prion diseases (Creutzfeldt-Jakob, Mad Cow)	Not available
Immunologic conditions: Multiple sclerosis (treatable to some extent, before dementia occurs)	Not available
Idiopathic disorders	Not available

Table 3.2b Treatable Conditions Associated with Dementia and Impaired Cognition (Partial List)

Normal pressure hydrocephalus
Subdural hematoma
Brain tumor
Toxic conditions: drug side-effects (particularly anti-cholinergic medications and sedative-hypnotics), heavy metals, pesticides
Endocrine disorders: thyroid conditions, diabetes mellitus
Nutritional, vitamin deficiencies: thiamine, B12
Sensory disorders: visual impairment, hearing impairment
Metabolic, electrolyte imbalance: delirium
Sleep disorders: sleep apnea with hypoxic encephalopathy
Psychological conditions: depression, psychosis, dissociative disorder

Medical History and Physical Exam

The first step in the diagnostic regimen is to obtain a complete medical history. Because of the unreliability of the patient's memory, information from a third party is essential, typically a family member or close friend who is knowledgeable of the person's history and can give a more accurate timeline as to when symptoms began, what they consisted of, and how/when they worsened over time. The initial task is to determine the nature of the chief complaint. If memory dysfunction is present, it is important to determine whether this was the first symptom. Memory impairment is a presenting symptom about 50% of the time, but other psychiatric problems, such as depression, apathy, or suspiciousness, are present about 30% of the time. A different cognitive dysfunction or an impairment of day-to-day functions may also serve to precipitate the initial visit.

The next step in the evaluation is to determine whether any events or stresses were associated with the occurrence of the first symptom. Careful attention must be given to the course of the decline, including an estimation of the accuracy of the retrospective information, to determine if the disease course is progressive or characterized by abrupt changes, such as might be caused by vascular events, metabolic changes, or affective disorders. Clinically, a rapid course of decline, prominent behavioral or visuospatial changes, as well as symptoms of a movement disorder often serve as indicators of non-AD conditions.

A review of the patient's medical history should focus on illnesses that could have caused or contributed to the cognitive impairment. Of particular concern is the use of centrally active medications or toxins. Any medication with anticholinergic side effect could contribute to cognitive dysfunction, including anti-Parkinsonian agents (benztropine, trihexyphenidyl), tricyclic antidepressants (amitriptyline), older antipsychotics (thioridazine), antispasmodics (atropine, scopolamine, l-hyoscyamine, oxybutynin), or antihistamines (diphenhydramine, chlorpheniramine). Several medical conditions, such as head injury, post-traumatic stress disorder, and arthritis, and possibly hay fever or asthma and metal work, seem to influence the risk and age at the onset of dementia and AD.

A complete medical examination is a recommended component of the dementia evaluation. Not only can a variety of systemic conditions, including lung, liver, and kidney disorders, contribute to cognitive impairment, but a demented patient may not report medical difficulties adequately. After listening to the heart for murmurs and arrhythmias, the carotids and cranium should be auscultated carefully for bruits with follow-up EKG recommended with ultrasound if appropriate. Examination of the retinal fundi can provide an estimation of arterial, hypertensive, or diabetic disease, which may suggest a vascular component of the dementia. Retinal photographs can make this exam much easier and more reliable and contribute more to the diagnosis. In the near future, retinal photographs will be enhanced to show deposition of the beta-amyloid protein, which is more common in AD patients, and absence of this protein suggests that the cause of the dementia is not AD (Koronyo, Salumbides, Black, & Koronyo-Hamaoui, 2012).

Table 3.3 Standard Component Tests for Dementia Evaluation

Test	*Rationale*
Medical history	Many medical conditions can adversely affect cognitive function
Family history	Family history
Physical exam	Investigates non-neurological causes of dementia
Neurological exam	Evaluates neurological conditions associated with dementia (e.g., Parkinson's) and looks for characteristic changes in reflexes
Mental status exam	Assesses for the occurrence of mental problems and behavioral disorders, including depression and psychosis
Neurocognitive assessment	Determines presence or absence of cognitive deficits. Looks for factors that might exacerbate dementia symptoms in the elderly, e.g., temporary depressive episode over loss of close friend or relative
Complete blood count	Rules out infectious conditions, e.g., neuro-Lyme's disease
Estimated sedimentation rate	Checks for inflammatory processes suggestive of traumatic, infectious, or immunological origin
Blood chemistry panel (including liver and kidney function)	Liver or kidney failure can adversely affect brain function
Serum electrolytes (including magnesium and zinc)	Electrolyte imbalance can cause severe mental disturbance, e.g., Lasix overdose
Thyroid function tests	Dysfunctional thyroid can adversely impact affect and cognition
Vitamin B12/folic acid levels	Insufficient levels can adversely impact affect and cognition and cause peripheral neuropathy.
Chest x-ray	Screens for endocrine-secreting carcinomas; impaired ventilation or obstruction adversely affecting oxygenation
Serological test for syphilis	Late stage syphilis can cause severe psychological disturbance
HIV routine urinalysis	HIV infection can invade the brain
Electrocardiogram	Rhythm disturbances can lead to insufficient brain oxygenation
Brain scan (CT at minimum; MRI and SPECT/FDG-PET if available)	CT and MRI can detect structural defects, while SPECT/FDG-PET can detect blood-flow irregularities and glucose utilization

Table 3.4 Genetic Testing: Apolipoprotein-E (ApoE) Allele Combination and Risk of Alzheimer's Disease (Estimates for U.S. Caucasian Population; For Other Populations, see Corbo & Scacchi, 1999).

Apolipoprotein Alleles	*Population Prevalence*	*Risk of Alzheimer's*	*Median Age at Onset (Years)*
ε2 allele	7 %		
ε2/ε2	Less than 1%	None known	
ε3 allele	80%		
ε3/ε3	65%	Comparison	88
ε3/ε2	11 %	About half of ε3/ε3	
ε4 allele	13%		
ε2/ ε4	2%	About same as ε3/ε3	
ε3/ε4	20%	3- to 5-fold x ε3/ε3	73
ε4/ε4	2%	12- to 20-fold x ε3/ε3	67

Note Numbers are approximated and calculated from references (Corder et al., 1993; Evans et al., 1997; Farrer et al., 1997). Risk of Alzheimer's is provided relative to ε3/ε3.

A genetic history has not yet become a standard, routine, or accepted part of the dementia evaluation. However, AD is strongly associated with a specific genetic factor, apolipoprotein-ε genotype with a significant contribution to the occurrence of AD beginning by age 60 (Ashford, 2004; Corder et al., 1993). This genetic factor even appears to contribute to memory changes in non-demented persons over the age of 70 (Jack et al., 2017). Table 3.4 shows the risk of AD as related to possession of the various combinations of the ε2, ε3, and ε4 alleles. Due to recent allowance by the FDA of "Direct to Consumer" genotyping services, many individuals are becoming aware of their APOE genotypes, and this genetic knowledge is becoming part of diagnostic considerations. Neurological Examination While the neurological examination of the AD patient is usually unremarkable and devoid of focal signs, there are several signs that are typical of AD patients, and others must be performed to rule out important differential issues. A cranial nerve exam should include testing for olfactory function (coffee, cinnamon, etc.). AD patients are noted for early loss of the ability to identify odors, later losing the capacity to detect smell sensation, though many normal adults have difficulty identifying scents as well. The patient's vision and hearing should be determined because impairment of either visual or auditory function can hamper cognitive performance.

A motor examination usually reveals normal strength and coordination in mild AD patients, but later there is difficulty following simple commands for testing motor performance along with incoordination. Extrapyramidal motor system signs such as rigidity and tremor can be indications of Parkinson's disease and suggestive of diffuse Lewy body disease, and they are associated with a more rapid course of dementia. Although AD patients may not have increased tone, they do have a tendency to not relax, and try to help with passive manipulation (a condition called Gegenhalten). Adventitious (spontaneously occurring) movements suggest consideration of Huntington's disease. Gait dysfunction may indicate a variety of problems, but should lead to consideration of normal pressure hydrocephalus, especially with the additional history of bladder control difficulties. Vascular comorbidities depend on the cerebral location of the lesion, but

usually affect watershed regions or small penetrating vessels in the basal ganglia and may cause gait or language difficulties. Gait problems related to Alzheimer pathology usually develop very late in the disease course. Reflexes in the AD patient tend to be mildly brisk, an indication of cortical dysfunction. Though the snout reflex (pursing of lips elicited by light tapping of the closed lips near the midline) is frequently present in the normal elderly individual, it is invariably found in the AD patient and becomes more severe as the disease progresses. Other pathological reflexes are not typically seen in the mild AD patient and may be more indicative of frontal (palmomental, grasp) or Parkinsonian (glabellar) pathology. A sensory exam should include testing for vibration. Impairment may indicate a peripheral neuropathy due to vitamin B12 deficiency or diabetes. The sensory exam is usually intact in the AD patient, and specific abnormalities should trigger an investigation of the cause. Focal neurological signs and symptoms should be noted carefully because of their potential relation to stroke and tumor, and they are not usually caused by Alzheimer pathology. Particular phenomena that indicate focality are visual field defects, hemiparesis, asymmetric deep-tendon reflexes, and an extensor plantar response. Myoclonus and rapid dementia progression suggest Creutzfeldt-Jakob disease.

Neuropsychiatric Assessment/Mental Status Examination

The evaluation of neuropsychiatric mental status is an important part of the dementia evaluation. Behavioral problems in early AD are associated with more rapid progression. These symptoms are frequently the most distressing to the family and caregivers and are the ones that lead most commonly to institutionalization, but are the most amenable to treatment. The psychiatric symptoms that occur most frequently in the dementia patient are depression, apathy, agitation, disorders of behavior, sleep disorders, and psychosis, including paranoia, hallucinations, and delusions (see Table 3.5; also see Ashford et al. [1998] for review). Neuropsychiatric symptoms occur as the initial observation in one-third of the patients, including both depression and psychosis. In original Alzheimer's cases, the initial symptom was a paranoid delusion. During the course of dementia development, many different psychiatric symptoms can occur, with the frequency of occurrence of different symptoms varying according to the severity of the dementia (see Table 3.6b, page 60). Significant depression is commonly reported in AD, though major affective disorder is much less common. Depression is important because depression might be a causative or risk factor in dementia, and the treatment of depression may produce modest improvement of cognitive function. As dementia becomes more severe, the mood is characterized more by apathy (Zeitzer et al., 2013).

Table 3.5 Domains of Aberrant Behavior in AD

Behavioral Domain	*Commonly Observed Symptoms*
Mood disorder	Depression, inactivity, apathy, indifference, lack of initiative, excess bodily concern, complaining, moaning, crying, tearfulness, manic behavior, elevated mood, irritable, anxious, nervous
Psychotic disorder	Distrustful, avoidant, paranoid delusions, suspiciousness, responding to hallucinations
Inappropriate behavior	Stealing, destroying property, spitting, inappropriate voiding, inappropriate robing, disrobing, verbal sexual advances, physical sexual advances
Aggression (nonphysical-verbal)	Uncooperative, argumentative, cursing, angry statements, demanding, verbal threats
Aggression (physical)	Grabbing, pushing, shoving, hitting, slapping, kicking, scratching, pinching, biting, throwing things, using weapons, combative, assaultive
Purposeless motor activity	Hand-wringing, fidgeting, overactive, rocking, restlessness, pacing, aimless wandering
Purposeless verbalizations	Repetitive questions, repetitive speech, sounds, yelling, screeching, screaming, moaning, crying
Sleep disorder	Excess daytime napping, excess nighttime wandering, shortened circadian rhythm, prolonged circadian rhythm
Mealtime problems	Refuses to eat, throws food, steals food, hoards, hides food, overeats, binges

Agitation is a common problem that encompasses a wide range of inappropriate behaviors, including aggression, purposeless activity, and verbal disruptiveness. Aggressive behaviors are more common in male patients and are associated with psychosis and underlying medical illness, as well as caregiver depression. Numerous psychotic symptoms occur in dementia patients, but frequent presentations are paranoid delusions and complex visual hallucinations (frequently just misinterpretations). Psychotic symptoms are associated with more rapid deterioration, but these symptoms are frequently responsive to therapeutic interventions. The recognition and treatment of agitation and psychosis is important because these symptoms are upsetting and disruptive to the caregivers and a major precipitant of placement in a long-term care setting. In long-term care settings, agitation places heavy demands on staff time, and aggressive behaviors frequently lead to injuries of staff and other patients. Disruption of the circadian rhythm is a problem which results in excessive daytime sleeping and nocturnal wandering. Nocturnal disruptiveness is particularly difficult for caregivers, and such behavior may be tolerated poorly in a nursing home if the patient is noisy or enters other patients' rooms. However, this symptom is among the most amenable to pharmacotherapy. The use of melatonin may even be able to keep the patient's cycle in synchrony with the environment. Neurocognitive Assessment/Neuropsychological Testing Neuropsychological assessment is an important component of the dementia evaluation. This component of the clinical examination gives the most explicit and objective description of the patient's difficulties and contributes directly to the differential diagnosis (Scott, Ostermeyer, &

Ahah, 2016). Neuropsychological measures reflect the loss of brain function caused by AD pathology and genetic risk (Caselli et al., 2014; Monsell et al., 2014). Neuropsychological deficits in AD reflect the effect of the AD pathological processes on memory structures and mechanisms (Ashford & Bayley, 2013). For any measure of dementia to be demonstrated to have reliability, it must correlate with the neuropsychological measures. A number of different tests can be employed using a detailed battery of tests to discriminate between normal function, AD, and other dementias (Weintraub, Wicklund, & Salmon, 2012). The Boston Naming Test can be used to identify the dysnomia associated with AD. To test visual spatial functions more completely, clock drawing and drawing a range of objects, such as a circle, a diamond, intersecting rectangles, and a cube, are also useful, though the critical issue for mild AD patients is whether they can draw these shapes from memory (Ellendt et al., 2017) or recognize complex visual images (Ashford, Gere, & Bayley, 2011).

Neuropsychological assessment can often detect specific deficits even before family members have recognized related symptoms (see Schmitt & Sano [1994] for case examples). The Consortium to Establish a Registry in AD (CERAD; Morris et al., 1989) neurocognitive battery includes measures of verbal memory, verbal fluency, design copying, mental status, and other tests, and has been used widely. Recent reports on this brief battery show excellent discrimination between AD and non-AD cases as well as prediction of incident AD in primary care patients (Schmid, Ehrensperger, Berres, Beck, & Monsch, 2014; Wolfsgruber et al., 2014). A similar brief (one-hour) neuropsychological battery has been recommended for persons with suspected cerebrovascular disease and dementia (Hachinski et al., 2006). Recently, the standard neuropsychological battery (Uniform Data Set, UDS) of the Alzheimer's Disease Centers (ADCs), funded by the National Institute on Aging (NIA), was developed to assess "normal" cognitive abilities of elder adults, as well as dementia and its varying forms (Monsell et al., 2016). The UDS serves as a standardized data collection method across all ADCs. Medical history, medications, clinical diagnoses, imaging, biospecimen, and cognitive data from ADC volunteers is aggregated into a centralized database to support research into normal aging and dementia.

The neuropsychological battery includes the MoCA, Craft Story Recall, Benson Figure Copy, Trail Making Test, Verbal Fluency, and MINT tests (for details, see Appendix 3A). The clinical usefulness of a neurocognitive workup for AD and other neurodegenerative disorders involves differential diagnosis as well as disease detection when brief screening procedures are considered to be "normal," yet there is a clinical impression of cognitive change.

Laboratory Tests

A specific list of tests is commonly employed as part of the AD evaluation (see Table 3.3). However, this regimen should be adjusted for the individual. A cerebrospinal fluid (CSF) examination is usually done only in those cases where cancer or a cerebral infection is considered, particularly syphilis. Several recent studies of CSF have shown that AD patients

have significantly increased levels of the microtubule-associated protein tau (TAU) and diminished concentrations of beta-amyloid (Ashford, Salehi, et al., 2011). Although these two changes may not constitute a positive diagnosis of AD, they can give support to consideration of this disease in the differential diagnosis. Of specific relevance, the beta-amyloid changes are related to the APOE genotype and the risk for developing dementia, but not the presence of dementia, while the CSF levels of TAU are related to the presence of dementia (J. W. Ashford, Salehi et al., 2011). The combination of cognitive tests with in vivo biomarkers (CSF, amyloid PET, structural MRI) have been incorporated into new research criteria for the diagnosis of AD (Dubois et al., 2010; Morris et al., 2014).

Brain Imaging in Dementia Diagnosis

Indirect examination of the brain, from historical and now obsolete pneumoencephalograms (x-ray using replacement of CSF with air) and blood-flow-elucidating arteriograms to CT/MRI and PET/SPECT scans of the present, has long been advocated as part of the dementia evaluation. Brain imaging techniques have been improving rapidly for dementia and AD. There is general agreement in this field that a brain scan is a justifiable procedure to rule out a tumor, stroke, normal pressure hydrocephalus, or subdural hematoma, in a patient with mild or moderate cognitive dysfunction. This clinical objective can be accomplished with cerebral tomography (CT) without contrast. However, shrinkage in the medial temporal lobe also can be assessed with this technique to provide an accurate estimation of the atrophy associated with AD. The justification for a more extensive examination such as magnetic resonance imaging (MRI), photon emission computed tomography (SPECT), or positron emission tomography (PET) is a contested issue. However, techniques for brain and computer analysis are rapidly improving interpretation. MRI, particularly of the coronal sections in AD, shows atrophy of the hippocampus and temporal lobe, which can support the diagnosis of AD and give an estimation of the severity of the disease, but quantification using this technique is not standardized. PET, measuring metabolic activity, and SPECT, measuring cerebral blood flow, both show characteristic decreases of activity in the temporal and parietal regions of the brain (Ashford et al., 2000; Ashford, Salehi, et al., 2011). New PET techniques are able to provide estimates of the amount of beta-amyloid (approved by the FDA for clinical use) and TAU in the brain tissue. While these images may someday be accurate enough to provide an in vivo AD pathological determination, the images are still crude and are reimbursed by Medicare only for research purposes, not for routine evaluation. At this time, PET measurement of beta-amyloid is used in many research studies, with beta-amyloid presence considered an inclusion variable to support an AD diagnosis. However, though beta-amyloid PET changes are associated with clinic progression (Mormino et al., 2017), many individuals have positive beta-amyloid PET scans and do not have, and never get, dementia (Rentz et al., 2017). So, at this time, these scanning techniques are not considered clinically reliable, diagnostic, or worth their considerable cost.

Clinical Diagnosis of AD: Other Issues

The social dysfunction of dementia can be estimated effectively through a caregiver report, using the Instrumental and Basic Activities of Daily Living (ADL) scales (Ashford et al., 1992), or other structured interviews inventorying social function, such as the AD8, though such testing does not contribute further diagnostic information (Carpenter et al., 2011). The importance of such tools is their use in determining specific skills related to functional levels in such areas as shopping and management of finances or basic daily activities, such as grooming and toileting. In patients with AD, scores on rating scales and ADL scales correspond highly with each other, and the underlying brain deficit is reflected accurately by both types of measurement (Ashford et al., 1992).

Although AD accounts for at least half of the cases of dementia, the diagnostic criteria for dementia apply to a group of similar syndromes that can be caused by a multitude of conditions. The routine battery of examinations (Table 3.3) is a practical approach to investigating the possible causes of dementia other than AD. However, this battery frequently does not clarify the diagnosis because several dementing conditions may coexist (Ashford, Rosenblatt, Bekian, & Hayes, 1987). The principal justification for this battery of tests is the search for a reversible or treatable form of dementia (Table 3.3b). For example, a frequently discovered problem is the use of centrally active medications whose elimination improves the patient's cognitive function. In the clinical setting, there is a major urgency to discover potentially reversible causes of dementia, because several such conditions will become progressively more difficult to arrest or reverse. Of most concern are the diagnoses of subdural hematoma, normal pressure hydrocephalus, hypothyroidism, and vitamin B12 deficiency.

An important clinical feature of AD is the slow and insidious development of the symptoms, while traumatic head injury, surgery, stroke, or a specific hypoxic insult can result in a rapid onset of symptoms. Creutzfeldt-Jakob disease (CJD), brain tumor, and depression have gradual onset rates also, but these conditions usually progress faster than AD. However, the naturally slow development of other diseases (thyroid disorder, normal pressure hydrocephalus) may mimic the onset and course of AD. Further, a series of small strokes without focal neurological findings might induce a progressive loss of cognitive function that is difficult to distinguish from the AD symptom constellation even with neuropsychological testing and neuroimaging. Consequently, there are no definite clinical signs of AD that can definitively confirm the dementia diagnosis while the person is alive. For the benefit of the family, a clear diagnosis of dementia should be emphasized, while maintaining the consistent position that a definite diagnosis at this time requires autopsy confirmation; but the possibility or probability of AD can be estimated clinically based on the typicality of the presentation and the lack of other possible causes of dementia (McKhann et al., 2011).

Another aspect of the differential diagnosis of dementia is the variation of the neurocognitive presentation. For example, dementia associated with AD is characterized most typically as a disorder initially affecting the ability to store new information into episodic memory and a progressive loss of old memories, in a fashion reflecting the loss of function first of the hippocampus, then the posterior-temporal and inferior-parietal regions of the cortex, usually bilaterally. Unusual AD presentations can involve selective language dysfunction or visual

changes. Diffuse Lewy body dementia can be similar, but with hallucinations and behavioral problems, suggesting disruption of dopamine systems and the frontal lobes, which is analogically related to the motor dysfunctions seen in Parkinson's disease, a disorder of the specific dopamine neurons of the substantia nigra and more focal Lewy body pathology. Fronto-temporal dementia (affecting the more anterior portion of the temporal lobe) is characterized by less memory impairment and more loss of behavioral inhibitions. Similarly, Huntington's disease leads to a severe dementia with more frontal lobe types of behavioral pathology. Vascular dementia can precipitate many types of cognitive and behavioral dysfunctions depending on what regions are adversely affected by disruptions of cerebral blood flow. Also, chronic traumatic encephalopathy can lead to a wide array of behavioral disruptions depending on which brain regions were traumatized to the point of developing a chronic, progressive tauopathy.

As noted previously, an important diagnostic and management consideration is the co-occurrence of different types of medical problems in the older adults that could account for symptoms of dementia (Ashford et al., 1987; Eisdorfer, Sevush, Barry, Kumar, & Loewenstein, 1994). Although AD accounts for more than half of the cases of dementia at autopsy, there are a host of other common conditions that occur in dementia patients, including history of falls and of surgery, any of which also could account for all or even part of the patient's cognitive dysfunction. A history of head injury occurs five times more frequently in AD patients than the general population, leading to the speculation that certain injuries or stresses may initiate the Alzheimer process, most likely the TAU pathology, especially when they occur in elderly individuals. However, recent autopsy examinations of athletes with numerous concussions has suggested that the pathology related to traumatic brain injury is a specific type of tauopathy, now called chronic traumatic encephalopathy, which is anatomically distinct from AD (McKee, Alosco, & Huber, 2016). Multi-infarct disease, alcoholism, diffuse Lewy body, and Parkinson's disease also are commonly associated with dementia, and the prevalence of these conditions seems to vary according to geographic location (or at least to the institutions conducting the studies).

Argyrophilic grain disease, Pick's disease, and other frontotemporal dementias can be distinguished from AD due to the initial personality changes and disinhibitions, but these distinctions are not reliable. While considering numerous other important conditions, including Huntington's disease, HIV infection, and Creutzfeldt-Jakob disease, it is important to keep the perspective that the existence of these other conditions does not rule out the independent co-occurrence of AD in a particular patient.

There are still other factors that commonly complicate the diagnosis of Alzheimer's disease, such as a history of alcohol abuse or exposure to other recreational or toxic substances. As discussed previously, dementia in the presence of the triad of incontinence, gait disturbance, and memory impairment, accompanied by a characteristic enlargement of the ventricles seen on brain scans, can be associated with normal pressure hydrocephalus, and is excluded by cisternography. Improvement after shunting can be demonstrated by brain scanning.

Importance of Vascular Changes

The distinction of AD and vascular dementia is the issue that most complicates the dementia differential diagnosis. This differentiation is a primary issue in the diagnostic accuracy of AD. The issue is critical because there are about 500,000 cases of stroke each year, 150,000 of these being fatal, whereas there are about 500,000 new cases of AD each year, with about 500,000 patients dying with AD each year after an average 10-year course (Ashford & Schmitt, 2001). Many AD prevention strategies are actually approaches to increasing cardiovascular health and decreasing the risk of cerebrovascular disease. Specific criteria have been proposed for identifying vascular dementias; however, these diagnostic approaches provide no specific criteria to define relative combinations of these two common entities. Arteriosclerotic pathology was even described in the original case reported by Alzheimer. Punctate white matter changes on MRI scans, suggestive of pathology in small arteries, are seen frequently in demented patients, even when the onset and progression have been reported as slow and progressive. White matter changes are associated with increasing age, hypertension, heart disease, and diabetes, but not considered to be part of Alzheimer diagnosis, though vascular pathology increases the severity of AD (Snowdon et al., 1997).

Assessment of AD Severity and Clinical Course

An important component of a dementia evaluation is the assessment of severity. Clinicians have developed a large number of tools to quantitate dementia severity. Many measures of dementia severity have been developed and studied extensively (Ashford, 2008). Certain measures, such as the Global Deterioration Scale (Reisberg, Sclan, Franssen, Kluger, & Ferris, 1994) and the Clinical Dementia Rating Scale (Hughes, Berg, Danziger, Coben, & Martin, 1982), provide quick clinical guidelines to define dementia severity. Further, systematic composites of other scales can substantially improve the precision and reliability of the severity estimate (Ashford et al., 1992; Papp, Rentz, Orlovsky, Sperling, & Mormino, 2017; Rattanabannakit et al., 2016; Wang et al., 2016), including estimates of where a patient lies on the temporal course of progression (Ashford, 2008; Ashford & Schmitt, 2001; Ashford, Shan, Butler, Rajasekar, & Schmitt, 1995; McCleary, Dick, Buckwalter, Henderson, & Shankle, 1996). Tables 3.6a and 3.6b provides an overview of the progression of Minor Neurocognitive Disorder through the latest phases of Major Neurocognitive Disorder. However, the complexity of dementia requires attention to the relationship between individual clinical characteristics and the disease course, as well as the capacity to discriminate among diverse clinical entities and biological factors contributing to the progress of the disease.

Table 3.6a Type of Impairment with Common Clinical Findings

Minor Neurocognitive Disorder, Mild Cognitive Impairment, Questionable Dementia: earliest symptoms can be recognized 10 years before the onset of dementia by the most sensitive tests (episodic memory); there is an average of 5 years from recognition of impairment to transition to clinical dementia
Memory: new learning impaired, slight forgetfulness
Language: occasional word loss, paraphasia
Visuospatial: problems with complex designs, unusual objects
Orientation: difficulty with exact date and time
ADLs: slight impairment at job, shopping, finances, hobbies
Subjective awareness: variable awareness of memory difficulties
Psychiatric: depressive symptoms in up to one-third of cases
CT, MRI: minimal cortical atrophy, some hippocampal atrophy (may not be noted);
PET/SPECT: mild temporoparietal hypometabolism/hypoperfusion (unilateral or bilateral)

Major Neurocognitive Disorder
Mild Dementia: typically lasts 2 years, range 1–10 years
Memory: moderate learning difficulty; defects in remote recall
Language: reticent, simple conversation, mild anomia
Visuospatial: mild difficulty identifying, using complex objects
Orientation: misses date, may become lost in unfamiliar places
ADLs: loss independent function, some prompting in personal care
Subjective awareness: unawareness of severity of memory difficulties
Psychiatric: sadness, may have delusions and/or hallucinations
CT/MRI: mild cortical atrophy, hippocampal thinning apparent
PET/SPECT: decrease of temporo-parietal metabolism/perfusion
Moderate Dementia: typically lasts 2 years, range 1–6 years
Memory: new information rapidly lost, personal history deficits

Note AD is a progressive disorder not manifesting discrete stages. However, epochs of this illness can be described conveniently using divisions delineated according to severity. Although illness duration is frequently estimated to last 7–8 years, the Time-Index carries the assessment to severe levels of dementia in AD that are associated with a high mortality.

Table 3.6b Cognitive Impairment Levels, Time-Index Estimates, Objective Measurements

DSM-5	*CDR-level*	*CDR*	*GDS-FAST*	*Time-Index*	*MoCA*	*MTX%corr*	*MTX-rt*
No Cognitive Disorder	Normal	0	0		30	98	0.730
		0	0	–18	29	97	0.789
		0	0	–15	28	95	0.848
		0	1	–13	27	94	0.908
		0	1	–11	26	93	0.967
		0	1	–9	25	91	1.026
Minor Neuro cognitive Disorder	Questionable Impairment	0.5	2	–8	24	90	1.085
		0.5	2	–6	23	89	1.145
		0.5	2	–5	22	87	1.204
		0.5	3	–2.9	21	86	1.263
		0.5	3	–1.4	20	85	1.323
		0.5	3	–0.6	19	83	1.382
Major Neurocognitive Disorder	Mild Dementia	1	4	0	18	82	1.441
		1	4	0.4	17	81	1.501
		1	4	0.9	16	79	1.560
		1	4	1.3	15	78	1.619
		1	4	1.7	14	76	1.678
		1	4	2.1	13	75	1.738
	Moderate Dementia	2	5	2.4	12	74	1.797
		2	5	2.6	11	72	1.856
		2	5	2.9	10	71	1.916
		2	5	3.1	9	70	1.975
		2	5	3.3	8	68	2.034
		2	5	3.4	7	67	2.094
		2	5	3.6	6	66	2.153
		2	5	3.7	5	64	2.212
		2	5	3.9	4	63	2.271
	Severe Dementia	3	6	4.0	3	62	2.331
		3	6	4.2	2	60	2.390
		3	6	4.4	1		
	Profound Dementia	4	7 a–c	7.7	0		
	Complete Dementia	5	7 d–f				

Notes Descriptions are based on typical progression associated with Alzheimer's disease (other dementia disorders may not follow this course). See for further discussion and development of Time-Index model: Ashford, Schmitt, and Kumar (1996, 1998); for references: Ashford and Schmitt (2001) and Ashford et al. (1995). CDR: Levels of dementia: questionable, mild, moderate, severe, adapted from the Clinical Dementia Rating Scale (CDR) (Hughes et al., 1982). CDR levels of profound, complete were imputed; GDS-FAST: General descriptions refer to Global Deterioration Scale-FAST (Reisberg et al., 1994); Time estimates for MoCA (Montreal Cognitive Assessment) derived from Monsell et al. (2016); MemTrax percent correct (MTX%corr) and recognition time (MTX-rt) available for no cost from: www.memtrax.com . Calculation of the relationship of these metrics to the MoCA based on preliminary data provided by Marjanne van der Hoek, Anne van der Heijden, Jaap Keijer; University of Wagingen, Netherlands (in preparation). Note that computerized testing has the capability of providing more objective and precise means to assess cognitive function.

Conclusions

The most careful application of clinical diagnostic criteria still results in uncertainty. The issues of diagnostic uncertainty lead to the question of how to determine the actual diagnosis. Autopsy is the only means available for establishing the type of dementia, especially given the possible presence of several etiologies (cf., Nelson et al., 2016). CSF analysis and the newly approved amyloid PET scans, and the developing TAU PET scans, as well as APOE genotyping, provide a greater degree of certainty about AD, but provide little confidence about the presence of other types of dementia. Diagnostic clarification by autopsy is important for the patient's family members, as well as for the advancement of research into the cause and treatment of AD and other dementias. Currently, there is no clinical justification for a biopsy in AD for diagnostic purposes. For research purposes, diagnostic certainty is important to support epidemiological, etiological, and prevention studies. Generally, the clinical diagnosis of AD has been considered to have an accuracy of about 90% in uncomplicated cases, and this rate compares favorably with many other medical diagnoses where definitive tests are not available. However, when dementia cases are more complex and the autopsy evaluations more stringent, diagnostic sensitivity can range from 70% to 90% and specificity from 45% to 70% (Beach, Monsell, Phillips, & Kukull, 2012).

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Appendix 3A

ASSESSMENT MEASURES USED IN THE ALZHEIMER'S DISEASE CENTERS[1]

Nusha Askari

This section contains a detailed description of the process used by specialized Alzheimer's Disease Centers (ADCs) funded by the National Institute on Aging (NIA) across the country to determine if significant cognitive impairment is present and, if so, what is the likely subtype? The specific neuropsychological tests used to help assess a wide variety of cognitive functions are described, along with source data. While this detailed information may not be relevant to all our readers, we include it so that if you live in an area where such a Center exists you will better understand when and why to refer and what the patient will be asked to do when there. Hopefully this information also will promote greater understanding of testing results as they become available. To locate one of the Alzheimer's Research Centers near you, see www.nia.nih.gov/health/alzheimers-disease-research-centers.

As discussed in this chapter, "dementia" is an umbrella term used to describe a variety of neurological disorders of varying subtypes and symptomology that present unique neurocognitive profiles, the most common of which is loss of memory and cognitive skills such as decision making, judgment and problem solving that negatively impact daily life functions of the individual manifesting the disease. Etiology and duration can vary as well. The most commonly known subtypes are Alzheimer's disease (AD), also found to be the most prevalent, vascular dementia (VD), dementia with Lewy bodies (DLB), and fronto-temporal dementia (FTD).

Here we present the standard neuropsychological test battery (Uniform Data Set, UDS) of the ADCs, funded by the NIA, to assess "normal" cognitive abilities of elder adults, as well as dementia and its varying forms. The UDS was developed to provide a systematic and centralized method to assess both cognitively intact individuals and patients. It is used at all contributing ADCs. The 32 nationwide ADCs are currently using the third version of the UDS (UDS3). The tests in this battery measure attention, executive function, episodic memory, processing speed, and language. The battery includes MoCA, Craft Story Recall, Number span forward and

backward, Trail Making Test, Verbal Fluency, and MINT tests. Each will be briefly described below.

In addition to the neuropsychological testing battery, most individuals who participate in research at the ADCs receive a neurological exam/clinical and physical assessment, including the Geriatric Depression Scale (GDS), Clinical Dementia Rating Scale (CDRS), Neuropsychological Inventory Questionnaire (NPI-Q), and Functional Activities Questionnaire (FAQ). Typically, a health and family history is also taken, inclusive of all medications, imaging via MRI scans takes place, at least at the initial and potentially subsequent follow-up visits, and some biospecimens are collected, such as stool, blood, cerebrospinal fluid (CSF) via lumbar puncture, and skin specimen (though these can vary across Centers). It is important to note that while these tests, when evaluated for standardization with norms established across thousands of people, have fairly high accuracy (as much as about 90%–95%), they do not yield 100% accuracy in diagnosing any form of dementia. To date, only via post-mortem autopsy are we able to definitively diagnose Alzheimer's disease or other forms of dementia or neurodegenerative diseases such as Parkinson's disease.

The UDS collects information annually via a series of neuropsychological tests, on 918 variables, 20 of which are administrative, that are focused on the continuum of aging in cognitively "normal" control participants, to mild cognitive impairment (MCI), to early stage AD. The variables measured included demographics such as date of birth, sex, years of education, features of onset of dementia and course, concurrent medications, family history of dementia, and performance and behavioral measures from neurological and neuropsychological tests. Both the participant and their study partner (someone who is highly familiar with their daily habits and routines on a consistent basis, reporting subjectively on the participant's cognitive function, behavior, and level of functional ability in activities of daily living) are assessed by trained clinicians via structured interviews and objective test measures.

Recently, the ADCs moved to the new UDS3 to ensure ease of access to nonproprietary tests. Monsell et al. (2016) discuss the change from UDS2 to UDS3, preceded by Weintraub et al.'s (2009) analysis of the Alzheimer's Disease Centers' Uniform Data Set (UDS) Neuropsychological Test Battery. The UDS2 had some tests that were both proprietary and not easily accessible and there were some tests that were replaced. For example, the MMSE was replaced by the more sensitive MoCA – Montreal Cognitive Assessment test, which is also available in multiple languages. The WMS-R (Wechsler Memory Scale-Revised) Logical Memory Immediate and Delayed recall tests were replaced by the Craft Story 21 Recall (Immediate and Delayed). The WMS-R (Wechsler Memory Scale-Revised) Digit Span was replaced by the Number Span in the UDS3, as was the Boston Naming Test, replaced by the Multilingual Naming Test (MINT). All four new tests were found to have a good to strong correlation ($r = .68–.78$) with the previously used tests of cognitive ability (Monsell et al., 2016). As such, most, if not all, ADCs are now using the UDS3 in English, and there is likely to be a Spanish-language version of the UDS3 coming soon.

All information gathered via the UDS is submitted by each ADC funded by the NIA, on each participant, to the National Alzheimer's Coordinating Center (NACC) to support collaborative research in Alzheimer's disease and other neurodegenerative diseases among the various centers.

The original UDS was implemented in 2005, and the UDS3 in March 2015. According to NACC (www.alz.washington.edu),

> the UDS, which collects prospective and longitudinal clinical data, has grown in size to include over 35,000 subjects as of June 2017.
> The data are open to both ADC and non-ADC researchers and have resulted in more than 600 publications to date.

The NACC database has become one of the largest and most comprehensive databases of its type in the world, and also houses neuropathology data on over 4,000 people that have been followed on a longitudinal basis at the ADCs – and the database continues to grow.

Table 3A.1 provides a brief description of each test, what it measures, and source information. It includes both the tests in UDS3 and others that are used at the Stanford Alzheimer's Disease Center to distinguish/assess normal cognitive abilities, mild cognitive impairment and dementia. Some of these (WTAR, Selective Reminding Task, Verbal fluency [C], HVLT, Judgment of Line Orientation, Victoria Stroop Test, Digit Symbol, Clock Drawing Test, Letter–Number Sequencing, and Cookie Theft) are not part of the UDS3, but were added to ensure a comprehensive neuropsychological overview of the participant's cognitive abilities.

Premorbid Level of Functioning: WTAR (Holdnack, 2001)

The WTAR (Wechsler Test of Adult Reading ability) was designed to test English speakers between the ages of 16 and 89. The test relies on abilities thought to be unaffected by cognitive decline associated with neurological damage. Its norms are based on both the WAIS (Wechsler Adult Intelligence Scale) and the WMS (Wechsler Memory Scale). The individual is presented with irregularly spelled words ("tough") and is asked to pronounce each. Given the irregular grapheme to phoneme "match" (gh in tough, for "f" sound) basically tests for previously learned vocabulary, as the patient cannot really apply standard pronunciation rules to complete the task. The examiner is therefore able to estimate their premorbid IQ based on the established norms via their ability to pronounce irregularly spelled words. This test is not part of the UDS3 neuropsychological battery.

Table 3A.1 ADC Research Battery of Dementia Assessment Tests

Test	*Description*	*Source*
WTAR	This reading test estimates premorbid level functioning in adults. It takes less than 10 minutes to administer. Subjects read irregularly spelled words and are scored on their pronunciation. *Not* part of the UDS3.	Holdnack, H. A. (2001). *Wechsler Test of Adult Reading: WTAR*. San Antonio, TX: Psychological Corporation.
MoCA	This is a screening measure of global cognitive functioning level sensitive to detecting mild cognitive changes. It includes items across executive functioning, visuospatial, memory, attention, language, and orientation domains. Takes 10 minutes to administer. This test is part of the UDS3.	www.mocatest.org Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., et al. (2005). The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society, 53*(4), 695–699.
Free and Cued Selective Reminding Task (FCSRT) Immediate Recall	This is a controlled semantic learning and memory test consisting of 16 items. Participants are asked to study a card with 16 pictures and identify items to a category cue. Once the items are searched for and identified, the patient is tested to recall the four items. For items that are not recalled, the same category cues are provided and the card with pictures is shown again. This process is repeated until all 16 items have been identified and recalled. Learning takes about 12 minutes, 30-minute delay. *Not* part of the UDS3.	Grober, E., & Buschke, H. (1987). Genuine memory deficits in dementia. *Developmental Neuropsychology, 3*, 13–36. Ivnik, R. J., Smith, G. E., & Lucas, J. A. Free and cued selective reminding test: (1997). MOANS norms. *Journal of Clinical and Experimental Neuropsychology, 19*, 676–691.

Global Level of Functioning: MoCA (Nasreddine et al., 2005)

The MoCA, Montreal Cognitive Assessment, test was designed to test mild cognitive impairment and early stage Alzheimer's disease and has been validated and tested, indicating greater sensitivity than the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975). As a global rating scale, it measures a number of different cognitive domains: attention and concentration, executive functions, memory, language, visuospatial and constructional skills, conceptual thinking, calculations, and orientation. The cube and clock measure visuospatial, executive function, and constructional skills; naming (of animals) tests vocabulary/language, immediate and delayed recall of five words and sentence repetition measures memory. Verbal fluency is tested via naming of nouns that begin with a particular letter in 60 seconds. The alternate trail making measures visuospatial, attention, concentration and executive function domains. Attention is tested via the forward and backward digit span and finger tap tasks. Abstraction is tested by making similarity comparisons amongst different pairs, and orientation is tested via questions regarding date and location. A maximum score of 30 is a perfect score, with normal cognition cutoff at 26 or above. The test takes approximately 10 minutes to

administer for those with normal cognition. The MoCA has been translated into 55 different languages, including Spanish, Chinese, and Arabic.

This test is part of the UDS 3 battery.

Tests of Memory: SRT, Craft Story, Benson Figure Delay, HVLT

SRT (Buschke) Selective Reminding Test (Buschke, 1973)

This test was designed to test verbal memory through list learning on multiple trials. The participant is presented with a set of words, many of which can be grouped into different categories, such as sports or professions. Then the participant has to both recall and recognize words that were presented on a list after several repetitions and upon delay. This test is not part of the UDS3.

Craft Story 21 (Craft et al., 1996)

This is a test of memory. A brief story is read to the participant (about a paragraph) and they are asked to immediately recall as much as possible from the story (and then, after a 20-minute delay with intervening tasks, they are again asked to recall as much as they can from the story, testing their episodic memory). In the immediate recall, the verbatim recall can range from 0 to 44 items, and paraphrase (acceptable substitutes are provided with the scoring codebook) can range from 0 to 25 items.

HVLT (Form 5) (Hopkins Verbal Learning Test) (Brandt & Benedict, 2001)

The HVLT (Hopkins Verbal Learning Test) consists of three sets/trials of a 12-item list comprised of words from several semantic categories. In the first three trials, participants are read a set of 12 words (four words for each of three categories) and have to try to recall them. They are asked to listen carefully to the list and try to remember it, as they will be asked to repeat the list. They are read the list of words at about a rate of 2 seconds per word, and need to recall the same list in three sequential trials. This is followed by a recognition task, after the third trial, in which the participant is presented with a list of 24 words (12 of which are new, 12 of which are from the original list) and is asked to respond "yes" if the word had been part of the original list to recall and "no" if it is new/not part of the original list. Half of the new/distractor items are members of the same categories from the original list, though new words. Half of the distractors are unrelated to the semantic categories.

The HVLT typically takes no more than 10 minutes to administer and is well-tolerated in moderate to severe dementia patients. This test is not part of the UDS3 battery.

Tests of Language

Verbal Fluency – Phonemic Task (Hillis)

In this task, the participant is told a letter of the alphabet (F) and asked to state as many words as possible that begin with that letter within 60 seconds. After 60 seconds, this is repeated with a second letter (L). The primary measure of performance is the total number of correct F words and L words. Number of errors (non-F and non-L words are also tallied, and repetitions are not counted). (Note: Stanford ADRC also includes the letter C.) This test is part of the UDS3. For more information, see www.alz.washington.edu/NONMEMBER/NACCFormsAndDoc.html.

Category Fluency (Goodglass & Kaplan, 1983)

Participants are given 1 minute to first name as many animals as they can. This is followed by naming as many vegetables as they can in 1 minute. Number of correct responses and number of errors are coded accordingly. This test is part of the UDS3.

MINT (Multilingual Naming Test) (Ivanova, Salmon, & Gollan, 2013)

In this test, the participant is presented with 30 objects, hand-drawn in black and white, and is asked to name the object that appears in front of them. This test measures the ability of the participant to orally label (name) the objects. They are given both a semantic cue (type of category they would fall under), as well as a phonemic cue, and scoring is tallied for any that are correct with and without a cue accordingly. This test measures aphasia and object naming deficits. There is no time limit for this test, though it typically takes approximately 20–45 seconds per item, with 30 items (items 30 and 31 are in the same picture). This test is part of the UDS3.

Cookie Theft Picture (Goodglass, Kaplan, & Barresi, 2001)

This is a description task from the Boston Diagnostic Aphasia Examination meant to assess language ability (spontaneous discourse) and distinguish between different forms of aphasia. The participant is shown a black-and-white hand-drawn scene of a kitchen with several people in it, with the depiction of two children trying to "steal cookies from a cookie jar" while the mother's back is turned. It takes about 3 minutes to administer this test, but it takes a little longer (about 5 minutes) with Parkinson's patients. This is not part of UDS3.

Tests of Visuospatial Processing

Benson Figure Copy (Possin et al., 2011)

In this task, the participant is presented with a figure composed of geometric shapes and asked to reproduce the figure on the same page. The purpose of this test is to assess the participant's constructional and visual memory functions. The accuracy of each shape and its placement is recorded, and the number of parts being scored for correctness can range from 0 to 17, with higher scores reflecting greater accuracy. The Benson Figure Delay is also a test of memory.

JLO: Judgment Line Orientation (Form V) (Woodard et al., 1998)

This test evaluates visuospatial skills localized in the parietal lobe in the right hemisphere. It was originally designed by Arthur Benton to test spatial skills in people with right hemisphere lesions. A person is presented with 2 lines at various angles of orientation (these are numbered) and they need to select the corresponding numbers from a "matching template" of 11 numbered lines arranged in a semicircle, set apart at 18-degree angles. There is an original form of 30 items, and these have been normalized for ages 7–96; there is also a short form available.

Tests of Executive Functioning

Attention/Working Memory

Number Span (Kramer, 2013)

In the digit forward task, the participant is read number sequences of increasing length and asked to repeat them in the same order. The longest span forward length is the length of the highest digit sequence the participant is able to repeat correctly. The number of correct sequences range from 0 to 14, with the digits' length varying from as few as 3 to as many as 9. Thus, if the participant is presented with "8–4–9–7", they would need to repeat "8–4–9–7." Once the participant misses more than 2 sequential pairings, the task is discontinued. This is a widely used test of working memory (or attention). In the digit backward task, a similar sequence and process is followed, except that this time the participant has to recall the digits in reverse order. Thus, if the participant is presented with "3–6–8–2–9", they would need to repeat "9–2–8–6–3." For more information, see www.alz.washington.edu/NONMEMBER/NACCFormsAndDoc.html.

Letter–Number Sequencing (Wechsler, 2008)

This is a test of working memory and is included in the Wechsler Adult Intelligence Scale IV (WAIS-IV). The participant is read a series of numbers and letters. Their task is to recall (reorganize) the letters in alphabetical order and the numbers in ascending order. Thus, if one is given the following "J–7–Y–5–D–3–N–8–L–2," they need to repeat "2–3–5–7–8–D–J–L–N–Y." So, in this test, one needs to incorporate sequential processing, mental manipulation, memory span, and short-term auditory memory. It is especially challenging for patients with dementia, given its "cognitive load" of having to engage these multiple processes. This is not part of UDS3.

Digit Symbol Coding (Kaplan et al., 1991)

This test is taken from the original Wechsler Adult Intelligence Scale III and Revised (WAIS III and WAI-R). It is a test of sustained attention and psychomotor performance. Patients with cognitive deficits typically manifest a slowing in speed of processing, more so than average in normal aging. The participant is presented with empty squares, under which are corresponding numbers 1–7. There is a printed key above these squares that matches each number to an abstract symbol, e.g., "/\." The participant is told to complete each square as quickly as possible with the

correct symbol. The task is timed at 120 seconds to correctly complete the squares. This test is not part of the UDS3 battery.

Processing Speed

Trail Making Test (Armitage, 1945)

In Part A, the number of seconds spent in connecting 25 numbered circles in sequential order are tallied. The UDS variable reported is a maximum of 150 seconds. The number of correctly connected number circles is also tallied (25 maximum), as are the number of commission errors (range 0–25). In Part B, the same variables are tallied, for 300 seconds maximum time, but this time the task is to connect sequential number and letter pairings; in other words, for the numbers 1–13 and letters A–L, "1 is connected to A, which is immediately followed by and connected to 2 to B," for 13 pairings, without lifting the pencil or pen off the paper. This test is part of the UDS3.

Victoria Stroop Test (Regard, 1985)

The Stroop test was originally introduced by J. Ridley Stroop in the 1930s to test reading abilities of children. The test has participants read color names in different-colored ink, and is a test of divided attention and thus, executive function. The Victoria Stroop test has been found to be more appropriate for geriatric populations and patients with dementia, who are likely to fatigue from neuropsychological testing more quickly (Bayard, Erkes, & Moroni, 2011). The Victoria Stroop test has three sets of stimuli: the baseline test is a set of colored dots; a "control" test, which comprises color names printed in the matching ink color; and the divided attention test, being comprised of color names in non-matching ink colors. Participants are asked to name the colors of the dots from left to right in each successive row in the first list. For the second and third list, they are asked to name the color of the ink the word is written in, not read the word itself. Understandably, the third list poses greater challenge for people, given the "discrepancy" between the color name and the ink color. This test is not part of the UDS3 battery.

Note

1 To locate one of the Alzheimer's Research Centers near you, see www.nia.nih.gov/health/alzheimers-disease-research-centers

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Appendix 3B

PRACTICAL APPROACHES TO ASSESSMENT FOR HEALTH CARE PROVIDERS

Dolores Gallagher-Thompson

Our purpose here is to inform the reader of extensive resources on dementia assessment that are currently available (at no cost) on the main website of the national office of the Alzheimer's Association. Go to www.alz.org to begin. Once there, locate the "Professionals" tab and from the drop-down menu select "Health Care Professionals and Alzheimer's." At that point a screen will appear that contains specific information on several key topics with which all clinicians and researchers working in the dementia field should be very familiar. The first is current "Guidelines Index." This set of practice guidelines was developed by the Association in collaboration with the federal government and several professional organizations. By clicking on the embedded link, you are taken directly to the guidelines. Included there are such topics as detection of cognitive impairment in primary care and diagnostic criteria for MCI and for AD. There is also a place to register to receive regular updates, as recommendations may change over time. Being up-to-date on current practice guidelines should enhance clinical effectiveness and lead to better outcomes for patients and families.

A second topic on the home page is "Reliable Patient and Caregiver Resources" which can save time for busy clinicians, since that information is gathered in one place. Third, a CME course is offered on "Challenging Conversations about Dementia" that contains five modules on sensitive topics such as what needs to be addressed in the patient newly diagnosed with AD and discussing when it's time to stop driving. Next there is information about a free AD Pocketcard app (available at the App Store and Google play) that includes an online portal that can greatly simplify the assessment process, since all necessary information is in the app and thus at one's fingertips, available for immediate use. The "Pocketcard"/online portal feature a set of interactive tools – for example, the functional activities questionnaire, which comes up instantly on your screen, with scoring instructions and interpretation. Instructions for how to administer

another commonly used screening tool, the clock drawing test, are clear, and again scoring instructions, clearly explained, are included. There are currently 14 tools in this section. The next section contains an algorithm developed by the Association to help the clinician integrate test findings and come to a conclusion, following the "decision tree" provided. This is followed by sections on pharmacological management and dealing with behavior problems, as well as quick links to local Alzheimer's Association chapters in one's area. So, again, this well-organized and comprehensive set of tools is readily available and easy to use in clinical practice.

For those who prefer to download materials into their computer, and/or have paper copies available for use, there is a fully downloadable Cognitive Assessment Toolkit which contains essentially the same tests and tools as the app and online versions. This can be a tremendous time-saver for busy clinicians, who do not need to search out each test on their own and figure out how to use it. The Alzheimer's Association developed this toolkit to encourage early detection and diagnosis, with the belief that doing so will enable patients and families to more adequately cope with their changing situations and to get a headstart on planning for the future. Thus, the toolkit is being widely disseminated at this time. Improvements may occur in the future as new assessment tools become available, so this is part of the website to keep watching.

Unfortunately, at this time, no specific recommendations are made about which tests to use with persons of diverse cultural and linguistic backgrounds. Yet there is a fair amount of research indicating that not all cognitive tests are appropriate for those with low levels of formal education, for example, or those for whom English is not their first language. Hopefully this topic will receive more attention in the future and specific guidelines that take account of diversity issues will be developed. [For information on issues and assessment instruments to use with specific ethnic populations, see Chapters 4–7.]

Note that on the left side of the Health Care Professionals home page is a menu of nine topics that can be clicked on for more detailed coverage. These are: Cognitive Assessment, Dementia Diagnosis, Management, Care Planning, Guidelines Index, Clinical Trials, for Patients & Caregivers, Clinical Resources, and Conferences/CME. Clicking on each topic leads to extensive information in easily understandable form. For example, under "Cognitive Assessment" (which we have already discussed here in relation to the app and online portal) there is an overview, a section on who should be evaluated for cognitive impairment, and details of what kind of assessment is done as part of the Medicare Annual Wellness visit. The latter is a great resource to inform patients and caregivers about, since it is currently an under-utilized Medicare benefit that gives useful information on other issues such as depression, alcohol consumption, and social isolation, which are assessed in addition to cognitive function. Also included are recommended cognitive assessment tools to give to both patient and care partner – for example, the Mini-Cog, which is often used as a screen for impairment and is given to the patient, as well as a specific set of questions to ask the care partner about perceived cognitive decline in the patient. These tools themselves and scoring instructions are right there, thus simplifying the process for busy clinicians. There are also two instructional videos, so that it's clear what needs to be done and how best to do it. The goal is to foster standard administration of such tests so that scores can be considered reliable from one clinician to another.

Most clinicians who use this website report that the "Dementia Diagnosis" tab is particularly helpful. It contains four substantial subsections, each with information useful for a "deeper dive" into the complexities of diagnosis. First are the Alzheimer's Association diagnostic guidelines across the disease continuum from MCI through full-blown dementia. Criteria are clearly explained and illustrated. Second, the role of advanced imaging and biomarkers is discussed, including limitations of our present knowledge base. Next is a valuable section summarizing key points to be aware of in making a differential diagnosis of dementia sub-types. It includes a table showing some of the main clinical differences between the major dementias: AD, frontotemporal, dementia with Lewy bodies, Creutzfeldt-Jakob disease, and vascular dementia. This is followed by "Healthcare Professional Topic Sheets" on each of these disorders, explaining them in greater depth. Finally, within this subsection, there is a discussion on the relationship between Down syndrome and AD that includes a tool useful for identifying early signs and symptoms of dementia in adults with intellectual disabilities.

The last topic in this section addresses how to disclose a dementia diagnosis to the patient and family, and includes two instructional videos to guide the process. This sensitive subject is well handled and contains several helpful, concrete suggestions, such as: discuss the diagnosis at multiple office visits; do what can be done to treat comorbid conditions that may be exacerbating the problem (e.g., excessive stress, poor sleep habits, sleep apnea); and be familiar yourself with local and national resources, and provide information on these resources to the family so they realize they are not alone, there is hope for a cure and for effective treatment, and there are many supportive services available to help them adapt to their new status. The 24/7 helpline number is also provided and, although it is not specifically noted in this section, it is accurate to tell patients and families that interpreters are available. The line is answered in English, so a modicum of familiarity with English is required, but all other major languages can be accommodated (usually with a call back) once the issue is known and arrangements are made.

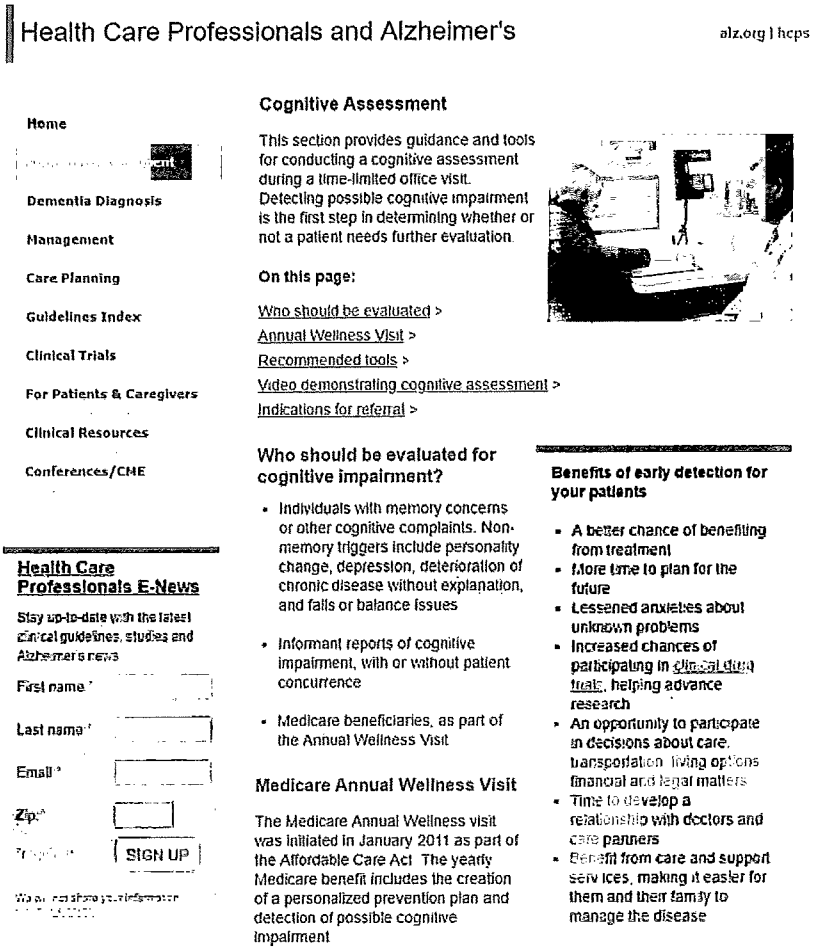

Figure 3B.1 Screenshot of Webpage from Alzheimer's Association Website

Of the nine topics covered in the "Health Care Professionals" section of this website, only the two discussed above pertain to assessment, so the other seven will not be described in detail here. The interested clinician or researcher should bookmark www.alz.org and return to it frequently for updated information, breaking news, and additional resources, which are added as available. Please be aware that the website is updated frequently, so the way it is described in this chapter may not be exactly the same in the future. It will, however, continue to contain similar valuable information for busy clinicians. It is well to keep in mind that there is a redundancy of information on this site: the same information appears in multiple sections, organized in slightly different ways, but always focused on meeting the everyday clinical practice needs of busy health care professionals. We hope that you will use these tools often in your work and (despite their limitations) will find them informative and helpful to you, your patients, and their caregivers.