Clinical Best Practices for Early Detection, Diagnosis, and Pharmaceutical and Non-Pharmaceutical Treatment of Persons With Alzheimer's Disease

TEXAS Department of State Health Services

As Alzheimer's disease research advances, it is recommended that new evidence-based therapies be incorporated into these guidelines.

Purpose and scope of this document

Today, an estimated 5.2 million Americans are living with Alzheimer's disease (AD), and 340,000 of those are Texans. One in nine older Americans has AD. It is the sixth-leading cause of death in the United States and the only cause of death among the top ten causes in the United States that cannot be prevented, cured, or even slowed. Nationally, Texas ranks third in the number of AD cases and second in the number of AD deaths. Moreover, Texas ranks second nationally in the amount of uncompensated care provided by caregivers. In 2012, the national direct and indirect costs of AD and other dementias were projected to exceed $200 billion. Alzheimer's disease exacts an enormous toll on individuals, families, the healthcare system, and American businesses. It is a serious problem affecting many aspects of our society. Until AD can be prevented or cured, the impact of this disease will only continue to intensify.

Currently there is no treatment available to slow or stop the deterioration of brain cells in individuals with AD. Five drugs are currently approved that temporarily slow symptom progression. Despite current lack of disease-modifying therapies, studies consistently show that active medical management of AD can significantly improve quality of life through all disease stages. Active management includes appropriate use of available treatment options, effective integration and treatment of coexisting conditions, and use of supportive services such as counseling, activity and support groups, and adult day care programs.

Most older adults, including those with AD, receive their medical care from primary care practitioners who may not have easy access to information and other resources

needed to treat this growing and demanding population. These guidelines were developed specifically for health care professionals who diagnose and treat individuals with AD for ease of reference to a vetted list of evidence based practices on appropriate medical management and treatment of AD. These guidelines are broad enough in scope that they can be used by physicians, nurse practitioners, physician assistants, social workers, nurses, and other professionals providing primary care to individuals with AD. Recommendations for management of associated neuropsychiatric symptoms and coexisting medical conditions often seen in persons with AD are included. Suggestions for easily administered and scored appraisal tools are incorporated when possible, as well as diagnostic and treatment pearls.

These guidelines also present best practices on the diagnosis and treatment of mild cognitive impairment (MCI), which can affect memory and other cognitive areas, while less severe than AD or other dementias. Information on the relationship between MCI and AD is also presented.

These guidelines were developed and peer-reviewed by a group of AD experts convened to address Disease Management objectives of the 2010-2015 Texas State Plan on Alzheimer's Disease. These groups include the Texas Council on Alzheimer's Disease and Related Disorders, the Alzheimer's Disease Program at the Texas Department of State Health Services, and many dedicated volunteers of the Texas Alzheimer's Disease Partnership.

Ultimately, it is our hope that these guidelines will help improve the quality of life for individuals living with this disease and those who provide care to them.

Clinical Best Practices for Early Detection, Diagnosis, and Pharmaceutical and Non-Pharmaceutical Treatment of Persons With Alzheimer's Disease

Early Detection

1. Individuals over the age of 55 should be routinely asked the following: Have you experienced any changes in memory and thinking?
    a. Progressive short-term memory loss recognized by an individual and/or friends and family is <u>not</u> a normal part of aging, and requires medical and neurological evaluation to determine its cause.
    b. The individual should be evaluated both for risk factors that may increase the likelihood of developing dementia later, as well as for the presence of Mild Cognitive Impairment (a clinical condition indicating high risk for advancing to Alzheimer's disease) or for a dementia.
2. Risk factors for the development of Alzheimer's disease (AD) and other dementias include: family history of degenerative dementia, genetic risk factors such as ApoE4 or SORL1, past severe head injury with loss of consciousness, hypertension, hyperglycemia, hypercholesterolemia, and hyperhomocysteinemia.

3. Alzheimer's disease is the most common cause of dementia in adults age 65 or older. However, an aggressive search for other disorders that affect cognition, such as one or more strokes, high or low thyroid hormone levels, vitamin B12 or folic acid deficiencies, kidney or liver failure, severe depression, sleep disorders, head trauma, side effects of common medications, and drug or alcohol abuse should be pursued. Rare disorders, such as autoimmune disease (e.g., Systemic Lupus Erythematosis with vasculitis) and infections (e.g., HIV, neurosyphillis) should be considered in high risk individuals. Other neurodegenerative dementias, such as Fronto-temporal dementia, and Creutzfeld-Jacob disease should be considered as well.

4. Subjective memory loss in the elderly, meaning a complaint of memory loss when none can be demonstrated on formal testing, is an independent risk factor for the later development of dementia. This complaint warrants a thorough baseline assessment for cognition, behavior, and function.

5. Failure to learn, or problems retaining new or recently acquired information, especially in conjunction with other cognitive changes (such as progressive difficulty in verbal expression, trouble with directions while driving, changes in personality and emotions, or altered reasoning, decision making and judgment), suggests dementia even if there are no problems with daily functioning.

6. Health care professionals evaluating individuals with memory loss should have a general understanding of normal memory functioning, disorders that can impair cognition, and familiarity with the tools used to identify cognitive changes. Alternatively, patients can be referred for neuropsychological testing when such changes are suspected.

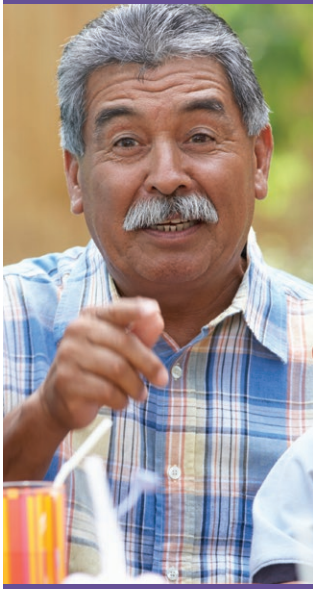
Medical Evaluation

1. Individuals who present with memory or other cognitive complaints should undergo a thorough medical and neurological evaluation that includes a comprehensive review of symptoms.
2. A family member or close friend should be encouraged to come with the patient to the medical evaluation to corroborate patient history and to provide additional information that the patient may be unaware of or unable to recall. If no one accompanies the patient, or the informant has inadequate information about the patient, the health care provider should contact a close

family member or friend, with the patient's permission. Inquiry should be made pertaining to the individual's cognitive function, emotional and behavioral function, activities of daily living, family history of dementia, current medications, and the presence of current and previous medical illnesses.

3. Estimate the onset and time course of memory loss with examples if possible.
4. Evaluate for the presence of cognitive changes, other than memory problems, such as disorientation to time and place, inattentiveness, impaired naming or other language difficulties like producing speech or comprehending verbal information, personality or emotional changes, impaired judgment or decision making, or disturbance in visual perception.
5. Note past history of conditions that increase Alzheimer's disease risk, such as hypertension, diabetes, high cholesterol, smoking, stroke, major head trauma, depression, family history of dementia, and overall poor emotional health.
6. Neuropsychiatric symptoms are not uncommon at any stage of Alzheimer's disease, and should be asked about. These can include apathy, anxiety, or depression in the early stages of the disease, followed by hallucinations, delusions, paranoia, and agitation as the disease progresses. These symptoms impair patient behavior and safety, and negatively influence the course of the disease.

7. The initial review of symptoms should include a standard battery of office cognitive testing. Suggested tests include the:
    a. Folstein Mini-Mental State Examination (MMSE);
    b. Mini-Cog;
    c. Kokmen Short Test of Mental Status; or the
    d. Montreal Cognitive Assessment Test (MoCA).
8. If none of these tests are available during the examination, or the results are inconclusive, the health care provider can try other simple techniques:
    a. Give the patient a street address to repeat and ask him/her to recall it after a 10 minute delay.
    b. Name three objects and place them in different areas of the room. In 15 minutes, ask the patient the name of the objects and where they are located.



c. Evaluate autobiographical memory by obtaining a list of important recent events in the patient's life over the last month from the accompanying caregiver before or after the exam, and then ask the patient about these events to evaluate their memory.

9. The Geriatric Depression Scale (GDS) is helpful for diagnosing depression, and recommended at the initial or follow-up visits, as time permits. It can be filled out by the patient or the accompanying caregiver on their behalf.

10. The assessment of Activities of Daily Living (ADLs), both complex and simple, is strongly recommended. The assessment forms should be given to the accompanying caregiver and be completed (if possible) at the time of visit. Verbally asking the patient and caregiver about ADLs can lead to patient and caregiver embarrassment and patient anger. A separate interview with family or friends is preferable, but is more time consuming in general practice.

    a. An example of a simple ADL survey is the FRSSD (Functional Rating Scale for Symptoms of Dementia) by J. Thomas Hutton.

    b. An example of a complex ADL survey is the Lawton & Brody Physical Self-Maintenance Scale (PSMS) and Instrumental Activities of Daily Living Scale (IADL).

11. Medical and neurological testing should include brain imaging. A non-contrast MRI of the brain with special attention to the medial temporal lobe and hippocampus region, looking for volume changes, is preferred. If unable to do a MRI, a non-contrast CT scan can be done. If structural lesions are known or suspected, the scans should be done with and without contrast. Unless recently performed, other tests to order include: chest x-ray, EKG, CBC, comprehensive metabolic and lipid profile, TSH, B12, folic acid, methylmalonic acid, VDRL, homocysteine, erythrocyte sedimentation rate, and serum protein electrophoresis. Additional testing for drug or alcohol abuse and antinuclear antibody (ANA) may be indicated.
    a. If there is a history of loss of consciousness, staring, or intermittent confusion with abrupt onset and resolution, an EEG should be performed to evaluate for a possible seizure disorder.

12. Lumbar puncture may be considered in cases of a rapidly progressive dementia, or the presence of abnormalities on physical or neurological exam with non-diagnostic or non-specific test results. Referral to a specialist may be indicated. Some conditions to consider are: chronic CNS infections (fungal meningitis), CNS vasculitis, carcinomatous meningitis, limbic encephalitis, or prion disease (Creutzfeldt-Jakob).

13. Formal neuropsychological testing should be considered if the cognitive exam and history suggest mild cognitive decline, or if office cognitive testing is normal, but collateral sources suggest cognitive impairment. Neuropsychological testing will identify and/or confirm which areas of cognitive function are normal or impaired and give important information about personality changes and depression. Referral to a specialist is recommended if the diagnosis is unclear.

Diagnosis

1. Alzheimer's disease should be suspected when:
    a. Onset of symptoms occurs gradually over months to years.
    b. Clinical evaluation and/or report from reliable informants reveals progressive worsening of cognition or impaired activities of daily living; however, impaired activities of daily living may not be apparent in the early stages of dementia.

c. There is no systemic illness or other brain disease that could account for the disorder, based on normal or non-specific testing results mentioned under the Medical Evaluation section.

2. Any atypical rate or rapid decline in any of the domains of cognitive function including behavior/and or psychotic features should prompt a thorough history, medical and neurological exam, and appropriate blood, urine and imaging tests to consider urinary tract or lung infection, liver, kidney or electrolyte imbalance, cerebral contusion, or subdural hematoma, among others.

3. There are two broad categories of Alzheimer's disease clinical presentation:

   a. Amnestic presentation: This is the most common type of presentation (over 90% of cases). It includes impairment in memory (learning and recall) of recently learned information. The diagnosis of Alzheimer's disease also requires

evidence of cognitive disturbance in at least one other domain:

i. Speech or language impairment: trouble with verbal expression or sentence completion, impaired writing, reading, or spelling.

ii. Personality change: including increased apathy or loss of drive, social withdrawal, loss of interest in previous activities, disinhibition, anxiety, depression, anger or aggressiveness.

iii. Visual perception: presence of adequate vision but with inability to recognize faces or common objects, trouble navigating in new or familiar places, and trouble getting properly dressed due to difficulty in orienting clothing to the body.

iv. Executive function: impaired reasoning and handling of complex tasks, impaired judgment, poor insight leading to inability to manage finances or plan complex activities, poor decision-making ability, or impaired social judgment.

b. Non-Amnestic presentation: Individuals with Alzheimer's disease may not have a prominent memory disturbance, at least initially.

This presentation is unusual and primarily affects functions other than memory in any one of the four cognitive domains. This presentation is seen more often in early-onset AD compared with sporadic or late-onset Alzheimer's disease. Patients with this presentation will eventually develop problems with learning and retaining new information.

4. Other supporting evidence that may enhance the likelihood of a diagnosis of Alzheimer's disease includes:
    a. Changes in structural or functional brain imaging such as:
        i. General brain atrophy or atrophy of one or more medial temporal lobes, especially the hippocampus, basal and lateral temporal lobes and atrophy of the medial parietal cortex on volumetric MRI. Coronal images may be required to evaluate for this in addition to sagittal and axial images.

ii. Decreased blood flow in the parietal and/or temporal regions on single photon emission computerized tomography (SPECT) scan.

iii. Decreased glucose metabolism (FDG glucose) in the parietal and/or temporal regions on positron emission tomography (PET) scan.

iv. Increased PET imaging of amyloid, with a tracer such as [18F]AV45 or Amyvid,™ which was approved by the FDA in the United States in January 2011 to assess for abnormal accumulation of amyloid in the brain. A positive scan alone does not support a diagnosis of Alzheimer's disease when the clinical picture is not consistent. A negative scan does not rule out the diagnosis, as there is approximately a 15% false negative rate.

b. Spinal fluid analysis: Low CSF amyloid-beta 42, and/or elevated CSF total tau or phosphor-tau are strongly associated with Alzheimer's disease, yet these biomarkers lack the precision necessary for routine clinical use.

c. Genetics: Presence of an autonomic dominant gene mutation (APP, Presenilin 1, Presenilin 2).

5. The clinician or health care provider should discuss the diagnosis and treatment options with the patient and family in a manner consistent with their values, culture, educational level and abilities.

6. In the future, evidence supporting the diagnosis of Alzheimer's disease may include blood test markers and PET scans that may be able to identify the accumulation of brain tau.

Suggested Additional Resources

Alzheimer's Disease Guidelines, National Institutes of Health, National Institute on Aging: http://www.nia.nih.gov/research/dn/alzheimers-diagnostic-guidelines

Borson S., Scanlan J., Brush M., et al. (2000). The Mini-Cog: A cognitive 'vital signs' measure for dementia screening in multi-lingual elderly. *Int J Geriatr Psychiatry,* 15:1021–1027.

Fillit, H.M., Doody, R.S., Binaso, K., Crooks, G. M., Ferris, S.H., Farlow, M.R., Leifer, B., Mills, C., Minkoff, N., Orland, B., Reichman, W. E., & Salloway, S. (2006). Recommendations for best practices in the treatment of Alzheimer's disease in managed care. *The American Journal of Geriatric Pharmacotherapy*, 4(Supplement A), S9-S24.

Folstein, M.F., Folstein, S.W., & McHugh, P.R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12(3), 189-198.

Hutton, J.T., Dippel R.L., Loewenson, R.B., et al. (1985). Predictors of nursing home placement of patients with Alzheimer's disease. *Tex Med*, 81,40-43.

Klatka L.A., Schiffer R.B., Powers J.M., et al. (1996) Incorrect diagnosis of Alzheimer's disease, a clinicopathological study. *Arch Neurol,* 53, 35–42.

Kokmen E., Smith, G.E., Petersen, R.C., Tangalos, E., Ivnik, R.C. (1991). The short test of mental status. Correlations with standardized psychometric testing. *Arch Neurol* 48(7),725-8.

Lawton, M.P., & Brody, E.M. (1969). Assessment of older people: Self-maintaining and instrumental activities of daily living. *The Gerontologist*, 9(3), 179-186.

Montreal Cognitive Assessment Test (MoCA): www.mocatest.org

National Institute of Neurological and Communicative Disorders and Stroke: http://www.ninds.nih.gov/

Tools for Early Identification, Assessment, and Treatment for People with Alzheimer's Disease and Dementia: www.nccconline.org/pdf/CCN-AD_tools6-03.pdf

Yuan, Y., Gu, Z.-X., &, Wei, W.-S. (2009). Fluorodeoxyglucose- positron emission tomography, single-photon emission tomography, and structural MR imaging for prediction of rapid conversion to Alzheimer's Disease in patients with mild cognitive impairment: A meta-analysis. *American Journal of Neuroradiology, 33*(11), 404-410.

Mild Cognitive Impairment

1. Mild cognitive impairment (MCI) is a transitional stage of cognitive decline (confirmed by history and neuropsychological testing) distinct from normal cognitive aging and dementia.
2. Unlike in dementia, activities of daily living, such as paying bills, preparing meals, or shopping, are generally normal or very minimally impaired in MCI. Patients with symptoms of MCI make more errors, are less efficient, and take more time than previously.
3. MCI can occur in any cognitive domain. If memory is mainly impaired, it is called Amnestic MCI. If impairment occurs in any of the other cognitive domains, (speech/language, executive, visual perception, personality change) it is called Nonamnestic MCI.
4. MCI, especially the amnestic presentation (AMCI), is a risk factor for developing Alzheimer's disease. People with AMCI have been found to have a 10-15% risk per year of developing Alzheimer's disease compared to a 1-2% risk per year in healthy individuals with normal memory. MCI can also signal the beginning of other dementias including vascular, frontal temporal, Lewy body, and Parkinson's dementia. It can also occur in depression, brain trauma, vitamin deficiency, metabolic disorders, and/or sleep disorders.

5. MCI has also been shown to improve or not progress to dementia in some patients, although studies showing stability have been limited by their duration (i.e., subjects were only followed for a limited period of time).
6. Patients with MCI should be followed closely and reevaluated at least every six months or sooner if symptoms progress. Office cognitive testing and evaluation of activities of daily living done at these follow-ups should be compared to the initial diagnostic evaluation. Worsening cognitive function may necessitate repeat neuropsychological evaluation.
7. MCI is likely due to Alzheimer's in the presence of:
    a. CSF markers of neuronal injury:
        i. low beta amyloid, or
        ii. high tau or phosphorylated tau;
    b. positive amyloid PET scan;
    c. neuroimaging markers of neuronal injury:
        i. atrophy of hippocampal regions on MRI;
        ii. temporal/parietal hypometabilism on FDG-PET scan or hypoperfusion on SPECT scan.

8. People with subjective memory complaints despite a normal thorough cognitive evaluation have a higher incidence of developing future MCI than the normal population without memory complaints.

Suggested Additional Resources

Doody, R.S., Ferris, S.H., Salloway, S., Sun, Y., Goldman, R., Watkins, W.E., Xu, Y., & Murthy, A.K. (2009). Donepezil treatment of patients with MCI: A 48-week randomized, placebo-controlled trial. *Neurology,* 72(18), 1555-61.

Peterson, R. C., Thomas, R. G., Grundman, M., Bennet, D., Doody, R. Ferris, S., Galasko, D., Jin, S., Kaye, J., Levery, A., Pfeiffer, E., Sano, M., van Dyck, C. H., & Thal, L. J. (2005). Vitamin E and Donepezil for the treatment of mild cognitive impairment. *The New England Journal of Medicine,* 352(23), 2379-2388.

Lu, P.H., Edland, S.D., Teng, E., Tingus, K., Petersen, R.C., & Cummings, J.L. (2009). Donepezil delays progression to AD in MCI subjects with depressive symptoms. *Neurology,* 72(24), 2115-21.

Small, G.W. (2008). Beyond standard anti-dementia therapies: diet exercise, socialization, and supplements. *CNS Spectr*. 13(10 Suppl 16), 31-3.

Pharmacological Treatment

1. Cholinesterase inhibitors - donepezil (Aricept), rivistigmine (Exelon) and galantamine (Razadyne) - are FDA approved and effective in treating cognition, function and behavior in the mild to moderate stages of Alzheimer's disease.
2. Memantine (Namenda) is effective in moderate to severe stages of the disease.
3. Donepezil is also approved for the severe stage of the disease.
4. All of these medications may produce small improvements at the beginning of treatment, but more commonly stabilize abilities or temporarily slow disease progression.
5. Patients first diagnosed with mild Alzheimer's should be started on a cholinesterase inhibitor. Consideration can be given to starting a cholinesterase inhibitor (donepezil only, based on trials) when amnestic MCI has been diagnosed. This would represent off label use.
6. Memantine should be added when there are declines to moderate disease levels in the category of function or cognition. It may also be considered in patients who develop behavioral symptoms of irritability, agitation, aggressiveness, hallucinations, or delusions.

7. Memantine monotherapy should be reserved for patients who are intolerant of cholinesterase inhibitors.
8. Combination therapy (cholinesterase inhibitor and Namenda) provides greater benefit for patients who have moderate to severe stage disease compared with monotherapy (cholinesterase inhibitor alone). Combination therapy is appropriate for patients who decline on monotherapy.
9. If gastrointestinal side effects occur from any of the cholinesterase inhibitors, different options can be considered. One can try the same cholinesterase inhibitor with slow titration and encourage taking it on a full stomach. If this is not successful, then discontinue the cholinesterase inhibitor and begin another cholinesterase inhibitor. If unsuccessful, Memantine can be tried for a few months, followed by the addition of the cholinesterase inhibitor.
10. High dose donepezil therapy (23mg per day, FDA approved) may be a consideration for patients with moderately severe Alzheimer's disease who exhibit cognitive decline on the standard 10 mg dose.
11. When behavior and psychological symptoms, such as combativeness, hallucinations and delusions develop and do not respond to nonpharmacological treatments, it may be necessary to administer antidepressants and/or antipsychotic medications in the lowest possible dose to achieve improvement.

Pharmacological Resources

Atri, A., Shaughnessy, L. W., Locascio, J.J., & Growdon, J.H. Long-term course and effectiveness of combination therapy in Alzheimer Disease. *Alzheimer Dis Assoc Disord,* 22(3), 209-221.

Farlow, M.R., Salloway, S., Tariot, P.N., Yardley, J., Moline, M.L., Wang, Q., Brand-Schieber, E., Zou, H., Hsu, T., & Satlin, A. (2010). Effectiveness and tolerability of high-dose (23 mg/d) versus standard-dose (10mg/d) Donepezil in moderate to severe Alzheimer's Disease: A 24-week, randomized, double-blind study. *Clinical Therapeutics,* 32(7), 1234-1251.

Fillit, H.M., Doody, R.S., Binaso, K., Crooks, G. M., Ferris, S.H. Farlow, M.R., Leifer, B., Mills, C., Minkoff, N., Orland, B., Reichman, W. E., & Salloway, S. (2006). Recommendations for best practices in the treatment of Alzheimer's disease in managed care. *The American Journal of Geriatric Pharmacotherapy*, 4(Supplement A), S9-S24.

Lopez OL, Becker JT, Wahed AS, Saxton J, Sweet RA, Wolk DA, Klunk W, Dekosky ST. (2009). Long-term effects of the concomitant use of memantine with cholinesterase inhibition in Alzheimer disease. *J Neurol Neurosurg Psychiatry*. 80(6):600-7. doi: 10.1136/jnnp.2008.158964. Epub 2009 Feb 9. Erratum in: *J Neurol Neurosurg Psychiatry*. 2009 Sep 1;80(9):1056.

Rountree, S.D., Chan, W., Pavlik, V.N., Darby, E.j., Siddiqui, S., & Doody, R.S. (2009). Persistent treatment with Cholinesterase inhibitors and/or Memantime slows clinical progression of Alzheimer disease. *Alzheimer's Research & Therapy,* 1(2), 7.

Nonpharmacological Treatments

1. Treat medical co-morbidities and discontinue undesirable treatments (medications with sedative and anti-cholinergic properties) if feasible.
2. Memory and cognitive training with a trained professional can be helpful in mild to moderate stages of the disease.
3. Address and treat behavioral symptoms of dementia including psychosis, agitation, aggression, irritability, anxiety, depression, and sleep disturbances at each visit, and develop a baseline of cognition, function, and behavior to assess response to therapy.
4. Respite care allows the caregiver freedom and reduces burden. Patient neuropsychiatric symptoms may temporarily improve from activities such as music and pet therapy, board games, cards, puzzles, and movies, and have been shown to improve mood.
5. Encouraging regular physical activity, if possible, (i.e., 100-150 minutes per week of walking, pedaling a stationary bicycle, or swimming) may help slow cognitive decline and behavioral difficulties.

6. Discuss safety concerns with the patient and the caregiver (i.e., oven and stove safety, and door lock changes to prevent wandering), including necessary medication management and driving evaluation in all stages of Alzheimer's disease.

The local chapter of the Alzheimer's Association should be contacted by the family/caregiver to help identify resources and providers in the local community.

Late Stage/End Of Life

As the patient's dementia declines into the profound stage, the ability to understand and cooperate with treatments and participate in medical decision-making will decline. At this stage, care shifts to maintenance of any preserved areas of functioning and relief of discomfort. Further testing, hospitalization, and invasive procedures including artificial nutrition and hydration will depend on previously discussed care plans, conversations with the established durable power of attorney for health care, or the known wishes of the patient. Referral to hospice should be considered and discussed with the family/caregiver(s).

Suggested Additional Resources

California Workgroup on Guidelines for Alzheimer's Disease Management:
http://caalz.org/PDF_files/Guideline-OnePage-Natl.pdf

As Alzheimer's disease research advances,
it is recommended that new evidence-based therapies
be incorporated into these guidelines.

Alzheimer's Disease Program, Chronic Disease Branch
Division for Disease Control and Prevention Services
Texas Department of State Health Services
PO Box 149347 (MC 1945)
Austin, TX 78714-9347

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