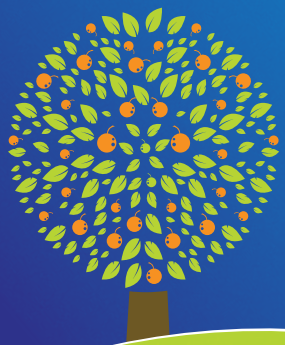
OCVBAP
Physician Guidelines



Orange County
Vital Brain Aging Program

hoag
Pickup Family
Neurosciences Institute

DISCLAIMER

These guidelines are intended to be informational only. These guidelines are not intended to be, and should not be considered, a substitute for medical or other professional advice and clinical experience. Medical procedures, treatments, and their outcomes are highly dependent on individual circumstances, and should always be considered in the context of appropriate medical or other professional advice and clinical experiences.

While information provided here is based on various published scientific studies and existing guidelines as of the time it was written, research on medical and health issues is constantly evolving, and dose schedules for medications are frequently revised to reflect the most up-to-date knowledge. Readers must therefore always check product information and procedure instructions with the most up-to-date, published, product information and data sheets, provided by the manufactures, and the most recent codes of conduct and safety regulations.

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About These Guidelines

As an initial step in developing this document, the Orange County Vital Brain Aging Program (**OCVBAP**) team reviewed published guidelines for managing dementia from the American Geriatrics Society, the American Academy of Family Physicians, and the College of Physicians. This provided a solid basis for guidance with demented patients.

Because managing cognitive health in a primary care setting requires early intervention against all conditions that impair cognition, these guidelines cover a broad spectrum of physician behavior and decision-making. All recommendations herein are founded on published research in the fields of patient education, risk factors that affect cognitive health, medical practice management and logistics, cognitive assessment tools and methods, diagnosing medical conditions that impair cognition, and treating medical conditions that impair cognition.

Best practices were gleaned from the medical literature and reviewed by the OCVBAP Expert Panel Physicians to finalize the guidelines.

OCVBAP Expert Panel Physicians

Valerie Acevedo, D.O. (Neurology)

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Guidelines on pharmacologic treatment of Alzheimer's disease are based on FDA approved "Prescribing Information." Certain portions of the prescribing information are appended with clinical expertise from the OCVBAP Expert Panel Physicians, to describe well-tested dosage and titration strategies.

Finally, the guidelines for treating Alzheimer's disease through psychosocial interventions are based on a thorough literature review by a key community partner in the OCVBA Program:

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Section 1 OCVBAP Clinical Path Overview

1. Educate Your Patients

Patients who are educated about the causes of memory loss, and who are aware of risk factors for cognitive decline, are more likely to proactively manage their cognitive health. This will help you intervene early when treatment can be most effective.

2. Select Appropriate Patients For Assessment

The current medical insurance environment requires physicians to establish "medical necessity" before conducting a reimbursable cognitive assessment. The criteria are clear and easily met. The OCVBAP guidelines will help you offer the highest standards of care within an economically viable model.

3. Select Appropriate Cognitive Assessment Method

There are 3 pathways for having your patients assessed for cognitive deficits. You may:

1. Perform an office-based assessment and earn reimbursement.
2. Refer to your usual channels for neuropsychological evaluation, or
3. Refer to the OCVBAP memory assessment service.

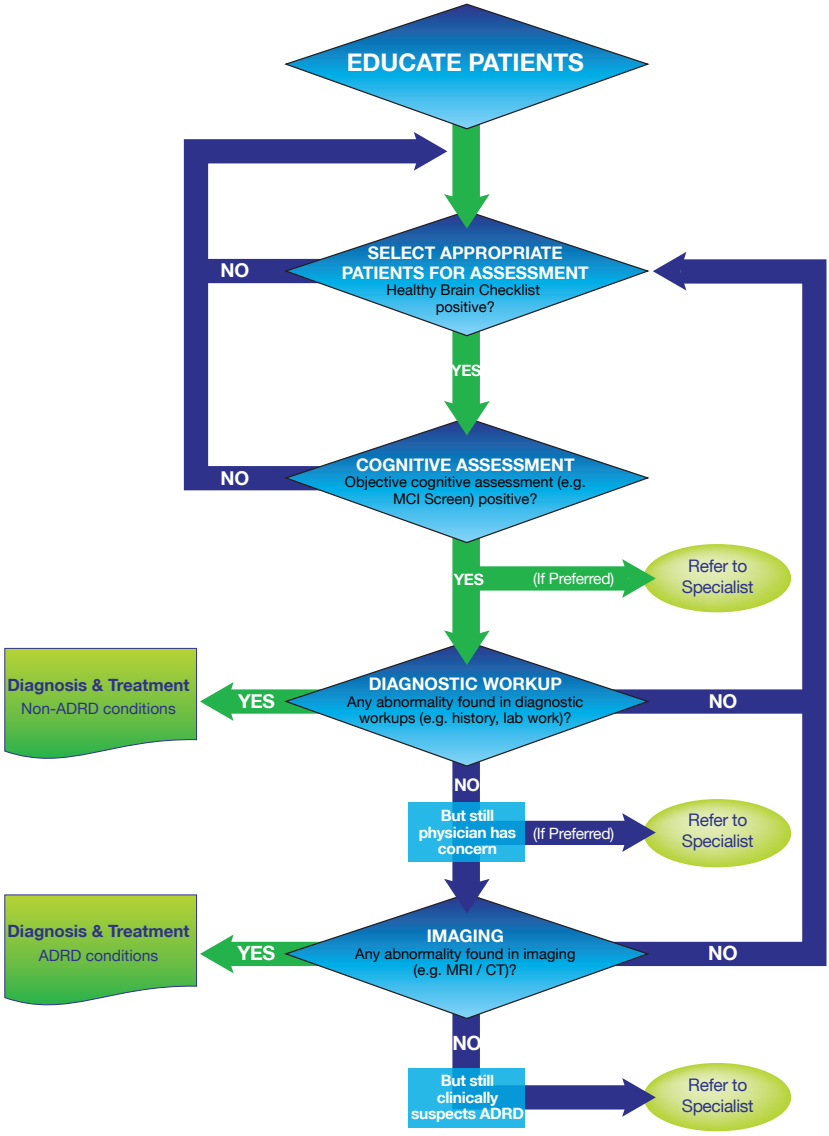
4. Diagnosis

Regardless of the assessment method chosen, your patients will likely remain in your care and need further management following the assessment. The nature of this clinical management will depend on whether or not any cognitive impairment was objectively identified in the assessment process.

Negative - No Cognitive Impairment Detected	Positive – Cognitive Impairment Detected
Reassure patient, educate them about risk factors they should manage, and plan to re-assess their memory in 12 months.	Pursue diagnosis of underlying cause in accordance with OCVBAP Guidelines and monitor cognition via quarterly memory assessment.

5. Treatment

It is important to treat all underlying medical conditions that are causing the cognitive impairment, including Alzheimer's disease. Generally, the earlier the treatment starts, the better the outcome will be.


EDUCATE PATIENTS
SELECT APPROPRIATE PATIENTS FOR ASSESSMENT
Healthy Brain Checklist positive?
NO
YES
COGNITIVE ASSESSMENT
Objective cognitive assessment (e.g. MCI Screen) positive?
NO
YES
(If Preferred)
Refer to Specialist
DIAGNOSTIC WORKUP
Any abnormality found in diagnostic workups (e.g. history, lab work)?
YES
Diagnosis & Treatment
Non-ADRD conditions
NO
NO
But still physician has concern
(If Preferred)
Refer to Specialist
IMAGING
Any abnormality found in imaging (e.g. MRI / CT)?
YES
Diagnosis & Treatment
ADRD conditions
NO
NO
But still clinically suspects ADRD
Refer to Specialist

Section 2 Educate Your Patients

Patients who are educated about the causes of memory loss, and who are aware of factors that impact the risk of cognitive decline, are more likely to raise timely concerns about their cognitive health. Therefore, well-educated patients are more likely to engage you constructively and to receive a high standard of care from your practice.

To address this opportunity, the OCVBA program offers two free educational brochures for your practice. We encourage you to order these OCVBAP brochures and make them available to your patient population.

About Memory Loss

This educational brochure explains the many common causes of memory loss and emphasizes the importance of early intervention to optimize treatment efficacy, regardless of the cause of the memory loss. The purpose of this brochure is to encourage those patients in your waiting room, who have a memory concern, to express that concern during their visit. You may order the brochure from the OCVBA Program.

Risk Factors for Memory Loss

This educational brochure explains the many risk factors for memory loss and other cognitive impairments. It also describes strategies for managing and reducing those risks. The purpose of this brochure is to help those patients who are in good cognitive health to manage their risk factors and remain so. Please request materials from the OCVBA Program.

Section 3 Select Appropriate Patients For Assessment

As described in more detail below, many patients should have their cognition assessed while many others need not. Following these basic guidelines will ensure that you offer your patient population the highest justifiable standards of care in an economically prudent manner.

Establishing Medical Necessity

Insurance companies, including Medicare, do not reimburse routine memory assessment without medical necessity. Any one or more of the following establishes medical necessity:

- a cognitive concern expressed by the patient.
- a cognitive concern expressed by the patient's family member or caregiver.
- a concern or observation by the physician or medical staff.

Office Visits for General (Non-Cognitive) Care

Regardless of the purpose of the patient's visit, it makes good sense to be vigilant about signs of memory loss in your "at-risk" or Medicare population, and to assess memory when medical necessity is met. The Healthy Brain Checklist is a short, check-box form that should be provided to patients at registration for each visit to your office. This is an excellent mechanism for proactively identifying early problems and for enabling patients to document medical necessity for further assessment. *Patients should have their memory assessed only if they meet medical necessity.*

Be Aware of the "High Risk" Group

Those patients aged 50 and older, with any one or more of the following risk profiles, warrant attention. They should have the opportunity to either complete the Healthy Brain Checklist, or be engaged in a direct discussion about their cognitive health:

- Personal history of stroke or head injuries
- Family history of AD or related disorders
- Cardiovascular risks, including high cholesterol, hypertension, obesity, and smoking
- Diabetes

All of these patients are at higher risk for cognitive problems, but do not meet medical necessity for further cognitive assessment based solely on their risk profile. These patients should be made aware of their increased risk and have their memory assessed only if they meet medical necessity (as outlined above).

Medicare Routine Physical Exams

Beginning in January 2011, CMS will honor two new reimbursement codes*, one for a "Welcome to Medicare Visit" that can be used within the first year of Medicare eligibility, and one for an annual "Medicare Wellness Visit". The guidelines for each of these visits stipulate that the physician assesses the patient for cognitive impairment. *All of these patients should complete the Healthy Brain Checklist.*

* Centers for Medicare Services established the two following codes taking effect on January 1, 2011:

- G0438 – Annual Wellness Visit; includes a personalized prevention plan of service (PPPS), first visit
- G0439 – Annual Wellness Visit; includes a personalized prevention plan of service (PPPS), subsequent visit

Any patient you see for an Annual Wellness Visit, who indicates a concern on the Healthy Brain Checklist, should be further evaluated. Guidelines for such further evaluation are summarized under "Select Appropriate Cognitive Assessment Method"

The Healthy Brain Checklist

This short, check-box form can be completed by patients at registration in less than two minutes.

Use it to identify early stage problems and to document medical necessity for an assessment.

Download at www.OCBrain.org/physician/index.seam
Email: info@ocvitalaging.org
Phone: 949-764-6288

Section 4 Select Appropriate Cognitive Assessment Method

There are three pathways from which you can choose how best to have your patients assessed for cognitive deficits. Each pathway is equally effective and physicians should choose the one that best fits within the scope and capabilities of their practice.

Three Pathways to Assess Your Patients

1. You may perform an office-based assessment and earn reimbursement.
2. You may refer to your usual channels for neuropsychological evaluation.
3. You may refer to the OCVBAP memory assessment service.

1. Office-Based Assessment

Assessing memory in your office involves using a cognitive assessment instrument to objectively measure the patient's performance on a series of cognitive tasks, and then scoring their performance in accordance with established means for their demographic peer group. There are many instruments available and several are briefly described below.

Recommended:

- **MCI Screen –** This is the tool recommended, but not required, for participating physicians in the OCVBA program. It is a ten-minute, electronically scored test of short-term memory and has the highest sensitivity for detecting mild cognitive impairment among all tests in the published literature. It can be administered by office staff and is attractively reimbursed by Medicare and most private payers. It requires Internet connectivity at the point of care and a licensing fee. Instructions for establishing an account with a free trial are available at: www.mccare.com.

Alternative Approaches:

- **Mini-Mental State Exam (MMSE) –** This was the original standard for primary care assessment but is somewhat outdated and no longer reimbursed by Medicare and other payers. The primary advantage is that its 30-point scale is well known. The disadvantages are that it was designed to assess dementia (not mild cognitive impairment) and it is not sensitive for detecting subtle decline. Furthermore, it must be scored manually and there are no published norms to adjust for patient age and education level. It takes about ten minutes to administer. The testing materials and scoring instructions can be purchased through: www.parinc.com.

- **Clock Drawing Test** - This is another well-known standard for assessing severe impairment and dementia (not mild cognitive impairment). The scoring is somewhat more subjective than the MMSE and it has equally poor sensitivity for detecting subtle decline. It is not generally reimbursed but it is free to use and usually quick to administer, taking from 3 to 6 minutes. A key point of difference is that this tool tests visuo-spatial skills whereas most of the more common tools assess memory.
- **Montreal Cognitive Assessment (MoCA)** – This is a combination of many brief neuropsychological tests that have been assembled into a battery with a 30-point scale like that of the MMSE. It is a relatively new test with growing validation for detecting dementia but minimal data showing an ability to detect mild cognitive impairment. For use in a clinical setting, the MoCA requires the purchase of a licensing agreement. Instructions for administering and scoring the MoCA are available at: www.mocatest.org.

2. Refer to Usual Channels for Neuropsychological Evaluation

If you currently refer patients with memory complaints to a particular source for neuropsychological evaluation, there is no compelling reason to disrupt that established approach. However, you might consider using a simple, office-based assessment to determine which patients should be referred.

The most important aspect of these guidelines is that you are vigilant in identifying subtle complaints and ushering the patient forward along some constructive pathway toward a high standard of care.

3. Refer to OCVBAP Memory Assessment Service

You may wish to refer your patients to the OCVBAP Memory Assessment Service at Hoag Hospital. Through this pathway, your referred patients will be assessed with the MCI Screen and the test results will be provided to you so that you can decide appropriate next steps in accordance with those results. The OCVBAP has also assembled a panel of experts who can receive specialty referrals as needed.

For more information, please contact:
Education and Screening Coordinator
Phone: 949-764-6288

Section 5 Diagnosis

Regardless of the results of the memory assessment (normal or abnormal), it is important to follow the guidelines that promote ongoing cognitive vitality for your patients.

Normal Assessment Result

If the patient does not show objective evidence of memory or cognitive impairment, and that is clinically consistent with the physician's impression, then:

1. Reassure the patient and educate them about risk factors they should manage, and share the brochure "Risk Factors for Memory Loss."
2. Advise the patient to use the risk factor identification tool for Alzheimer's disease and related disorders (**ADRD**) at the OCVBAP website (www.OCBrain.org). This will make them aware of their risks, as well as how best to manage them, according to evidence-based medicine.
3. Schedule the patient for re-assessment in 12 months to assure that they remain cognitively healthy.

Abnormal Assessment Result

If the patient shows objective evidence of memory or other cognitive impairment, then the cause of the problem should be diagnosed and treated by using one of the following two options:

1. Order ADRD Diagnostic Work-Up

Following the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (**NINCDS-ADRDA**) diagnostic guideline for ADRD will generate an accurate diagnosis in more then 90% of cases.

These diagnostic guidelines are summarized in the following pages:

- ADRD Diagnostic Work-Up Guidelines (Section 5.1)
- Other Diagnostic Work-Up Guidelines (Section 5.2)

2. Refer to an ADRD Specialist

OCVBAP maintains a list of specialists who can accept referrals as needed. To obtain the list, please contact the program Education and Screening Coordinator.

Delivering an Alzheimer's Diagnosis

In recognition of the growing importance of Alzheimer's disease, the National Alzheimer's Association held four regional town hall meetings with more than 800 participants, including 300 people living with the disease. The outcome of the meetings, summarized as *The 2008 Report: Voices of Alzheimer's Disease*, identified diagnostic challenges and dissatisfying interactions with the medical community as key challenges to address.

Several specific insights were voiced by the meeting participants and published by the Alzheimer's Association as *Principles for a Dignified Diagnosis*. These insights from families and patients with Alzheimer's disease provide suggestions on how to improve the diagnostic challenges and process that both patients and physicians face. These insights include:

- Talk to me (a patient) directly, the person with dementia.
- Tell the truth.
- Test early.
- Take my concerns seriously, regardless of my age.
- Deliver the news in plain but sensitive language.
- Coordinate with other care providers.
- Explain the purpose of different tests and what you hope to learn.
- Give me tools for living with this disease.
- Work with me on a plan for healthy living.
- Recognize that I am an individual and the way I experience this disease is unique.
- Alzheimer's is a journey, not a destination.

As a healthcare professional who touches patients' lives, you might be interested in reading the short document Principles for a Dignified Diagnosis.

You may download the *Principles for a Dignified Diagnosis* document at *www.OCBrain.org/physician/index.seam*.

5.1 Differential Diagnostic Work-up for Alzheimer's Disease and Related Disorders (ADRD)

Routine ADRD diagnostic tests include:

a. Blood tests to exclude potentially contributing causes of cognitive impairment, including:

- Chemistry panel: hyponatremia, hypocalcemia, hypercalcemia, hypokalemia, renal dysfunction, hepatic dysfunction, hyperglycemia, hypoglycemia, protein wasting.
- CBC with differential: anemia, leukopenia, leukemia, thrombocytosis, thrombocytopenia, megaloblastosis, lymphocytopenia, lymphocytosis, monocytosis, acute infection.
- Fasting lipid panel: low HDL (<45), high LDL (>100).
- Vitamin D-1,25(OH)2, B12, folate: vitamin deficiencies.
- Homocysteine: homocysteinemia (>14).
- TSH, free T4: hypothyroidism, hyperthyroidism.

b. Urinalysis: proteinuria, glucosuria, ketonuria, hematuria, bacteruria.

c. Non-contrast MRI with volumetric assessment of hippocampus (CT if MRI not possible). Radiologic interpretations consistent with a diagnosis of:

Alzheimer's Disease

- Relatively greater atrophy in the hippocampus, medial temporal or temporal lobe.
- Amount of ischemic vascular disease does not explain any observed atrophy.
- Absence of hydrocephalus, masses, or hemorrhages.
- Subtle amounts of atrophy may be missed. Therefore a negative CT or MRI report (e.g., normal, age-related changes, mild generalized atrophy) does not exclude Alzheimer's disease if there is objective cognitive impairment.

Cerebrovascular Etiology

- Extensive ischemic white matter disease.
- *Well-placed* lacunar infarcts or hemorrhages in the hippocampus or thalamus.

- Large infarct of the anterior, middle or posterior cerebral artery.
- Medium to large cerebral hemorrhages, or residua thereof.

Traumatic Brain Injury

- Focal or asymmetric patterns of atrophy, especially in inferior frontal or anterior temporal lobes.
- Small, petechial hemorrhages, especially in the white matter.
- Diffuse axonal injury, seen as focal areas of white matter demyelination, and blood residua.

Normal Pressure Hydrocephalus

- Ventriculomegaly greater than the degree of cortical atrophy.
- Periventricular white matter increases in signal intensity (transependymal edema).
- Ballooning of the 3rd ventricle.
- Thinning of the corpus callosum.

If the routine ADRD diagnostic tests do not identify the etiology, then there are two possibilities:

1. The objectively established cognitive impairment is a false positive result and the patient does not have a progressive cognitive impairment.
2. The routine ADRD diagnostic tests were not sensitive enough (a false negative result), and more specialized ADRD diagnostic testing is needed.

There are five approaches to differentiating between these two possibilities.

a. Repeat the same cognitive test now. Look for variability in performance to identify whether the previous result was a false positive or false negative.

b. Repeat cognitive testing with the same tests in 4 to 6 months to look for change. This will establish whether there is a progressive cause of cognitive impairment or not.

c. Refer to a neuropsychologist for a more comprehensive battery of tests (if not already done) that can help better determine if there is evidence of a progressive cognitive impairment and can help differentiate AD from non-AD causes.

d. Refer to an ADRD specialist.

5.2 Other Differential Diagnostic Work Up

Tests that can be used to further confirm cognitive impairment not due to Alzheimer's disease (**AD**) depend upon the patient's underlying medical conditions and risks for possible:

Iatrogenic Causes

- Radiation therapy, chemotherapy, anticonvulsants, anticholinergics, antipsychotics, and chronic abuse or dependence upon benzodiazepines, tranquilizers, anxiolytics or sedatives.

  Action: Withdrawal, reduction or substitution of the potentially offending medication.

Organ and Systemic Disorders

- Neurotoxins
  - Lead, mercury, carbon monoxide, organophosphate insecticides, toluene, industrial solvents.
- Immunologic Disorders
  - Systemic lupus, temporal arteritis, cerebral arteritis.
  - Serum protein- and immuno-electrophoresis, specialized studies for cerebral vasculitis and immunodeficiency syndromes.

  Action: Refer to rheumatology or immunology.
- Severe Pain Syndromes: MR of the spine or other affected body part, EMG/NCV studies.

  Action: Refer to pain specialty.
- Metabolic Syndrome

  The US National Cholesterol Education Program Adult Treatment Panel III (2001) requires at least three of the following:
  - Central obesity: Waist circumference ≥ 102 cm or 40 inches (male), ≥ 88 cm or 36 inches (female) or body mass index > 30 kg/m2.
  - Fasting Lipid Panel:
    - Triglycerides: ≥ 150 mg/dl (≥ 1.7 mmol/L).
    - HDL-C < 40 mg/dL (male), < 50 mg/dL (female).
    - Blood Pressure ≥ 130/85 mm Hg
- Fasting plasma glucose ≥ 6.1 mmol/L (110 mg/dl).

  Action: Refer to endocrinology, internal medicine, diabetology.

- Diabetes or Pre-diabetes: Fasting glucose, HgbA1c.

  Action: Refer to diabetology, endocrinology.
- Thyroid Disorders: Hypothyroidism, hyperthyroidism
- Cerebrovascular disease: Small and large strokes, subdural, subarachnoid, cerebral, and intraventricular hemorrhages.
    - Orthostatic blood pressures, carotid/transcranial Doppler, MR angiography, sedimentation rate, PT/PTT, coagulopathy studies.

  Action: Refer to stroke neurology.
- Cardiovascular Disease: (Coronary artery disease, Arrhythmia, Valvular Disease, Congestive Heart Disease, Cardiomyopathy): CRP, ECG, Cardiac Doppler, Holter monitor and other appropriate cardiac studies.

  Action: Refer to cardiology.
- Sleep Disorders (Sleep Apnea, Myoclonus, REM Behavior Disorder, Restless Legs)

  Action: Refer to sleep specialist.
- Pulmonary Disease (COPD, restrictive lung disease, other hypoxic disorders)

  Action: Refer to internal medicine or pulmonology.
- Kidney Disease: GFR, urinalysis.

  Action: Refer to nephrology.
- Liver Disease: Liver enzymes, hepatic encephalopathy.

Disorders Affecting The Central Nervous System

- Depression, Anxiety, Obsessive Compulsive Disorder: appropriate history or standardized scale evaluation.

  Action: Refer to psychiatry.
- Other Psychiatric Disorders

  Action: Refer to psychiatry.
- Parkinson's Disease: Movement disorder followed by executive dysfunction, visual-spatial deficits and memory loss at least several years later.
- Lewy Body Disease: Marked fluctuation in level of confusion, loss of balance, difficulty walking, REM behavior disorder, visual hallucinations, visual problems, executive dysfunction, aprexia.

- Frontal Temporal Lobe Disease: Usually age of onset is 50-60 years old. Primarily affects frontal and temporal lobes. Loss of language, apraxia, personality changes, disinhibition or other behavioral abnormalities, and flat or inappropriate affect are early features.
- Hungtington's Disease: Usually age of onset is 30-40 years old. Choreoathetosis, executive dysfunction, memory loss.
- Creutzfeld-Jakob Disease: Movement disorder, insomnia, inattention, fatigue, and rapidly progressive dementia are characteristic. Any age can be affected. Abnormal periodic EEG activity.
- Traumatic Brain Injury: Can be progressive if multiple head injuries or very severe single head injury with loss of consciousness.
- Epilepsy: EEG studies.

  Action: Refer to neurology or epileptology.
- CNS Infection (HIV, Cryptococcus, cysticercosis, neurosyphyllis)

  Action: Refer to infectious diseases.
- CNS Demyelination (Multiple Sclerosis, Kufs disease, Adrenoleukodystrophy, Metachromatic leukodystrophy, other storage diseases)

  Action: Refer to neurology.

Section 6 Treatment

Optimal treatment follows accurate diagnosis of any underlying medical conditions. Guidelines for performing an accurate diagnosis of conditions that impair memory are available in sections 5 of this guideline.

Treating Alzheimer's disease and related disorders (**ADRD**) requires a robust approach that includes:

- Identification and treatment of common medical conditions
- Pharmacologic treatment
- Non-pharmacologic treatment

Identifying and Treating Common Medical Conditions

Untreated, or not well-controlled common medical conditions, such as thyroid disease, vitamin deficiency, heart disease, and diabetes frequently cause memory loss. Similarly menopause and testosterone deficiency, various medications, and depression can also cause memory loss. It is important to make sure that these conditions are well controlled and monitored regularly. Treatment guidelines for those conditions are widely available from a variety of sources.

Pharmacologic Treatment of ADRD

Like many other diseases, early detection and treatment of ADRD is the key to successful treatment outcomes. For Alzheimer's disease (**AD**), there is a substantial body of evidence showing disease-delaying effects using combined therapy of a cholinesterase inhibitor (Exelon®, Razadyne®, Aricept®) and memantine (Namenda®). Because these effects occur at all clinical stages of AD, it is imperative to initiate combined therapy as early as AD is detected, and continue patients on combined therapy until they reach the hospice terminal stage of AD.

For more details, please review:

- Pharmacologic treatment of AD (Section 6.1)
- Rationale for Pharmacologic treatment of AD (Section 6.2)

Non-Pharmacologic Treatment of ADRD

Non-pharmacologic interventions have been recognized as important components of an optimal treatment strategy. Such interventions include, but are not limited to, life style modifications such as mental/physical exercise, and diet, as well as psychosocial

intervention, careful management of co-morbid conditions such as diabetes and hypertension, and integrating community resources for patients and families.

For more details on the psychosocial components of optimal treatment, please review:

- Psychosocial treatment of AD (Section 6.3)

Community resources that support appropriate psychological interventions are available at: www.OCBrain.org/physician/index.seam

6.1 Pharmacologic Treatment Strategies for Alzheimer's Disease

For a full discussion of the background for the pharmacologic treatment strategies given below, please see Section 6.2 "Background for Pharmacologic Treatment of Alzheimer's Disease." Also please note that the indicated treatment efficacy will differ from patient to patient, and may not be expected for all patients with Alzheimer's disease (**AD**).

Overall Treatment Strategy

Although there is considerable variability between patients with AD, there is a substantial body of evidence showing disease-delaying effects using combination therapy of a cholinesterase inhibitor (Exelon®, Razadyne®, Aricept®) and memantine (Namenda®). Because these effects occur at all clinical stages of AD, it is imperative to initiate combination therapy as early as AD is detected, and to continue patients on combination therapy until they reach the hospice terminal stage of AD.

Available evidence on the efficacy of the cholinesterase inhibitors in delaying AD progression indicates that:

- Aricept® is likely to provide disease-delaying effects for 1-3 years.
- Razadyne® is likely to provide disease-delaying effects for 1-3 years.
- Exelon® is likely to provide disease-delaying effects for 1-4 years.

Therefore, after 1-3 years of treatment with Namenda plus Aricept or Razadyne, patients may benefit by switching to Namenda plus the Exelon patch, particularly if more rapid decline has recently occurred.

Step 1: Set and Manage Expectation About Treatment

Before starting new medications, it is always helpful for patients and family members to understand what to expect from these treatments. Frequently patients and caregivers have unrealistic expectations and don't realize that "not getting worse" means that the medications are working. Since AD is a progressive degenerative disease, "stabilizing" the symptoms can be a positive outcome. Patients should also understand that finding the right combination of medications and dosages is a process that may take months. Finally, physicians should make it clear that some percentage of patients may not respond in any meaningful way to the treatment.

Therefore, setting the right expectations will help patients and family members approach the treatment process with a constructive mindset and a realistic idea about the course ahead.

Step 2: Start Cholinesterase Inhibitor (Aricept®, Exelon®, Razadyne®)

It is important to choose the correct cholinesterase inhibitor and its maximum, well-tolerated dose within the approved range. This process may take weeks to months, and it is always recommended to objectively measure the treatment effect on memory and function after achieving a stable optimal dose.

For more details, please see:

- Aricept Dosing Schedule
- Exelon Dosing Schedule
- Razadyne Dosing Schedule

Step 3: Add Memantine (Namenda®)

After reaching the optimal dose of the chosen cholinesterase inhibitor, add Namenda and find the maximal dose, from 5 to 20 mg, that is well tolerated without side effects. After achieving a stable optimal dose, it is always recommended to objectively measure the treatment effect on memory and function.

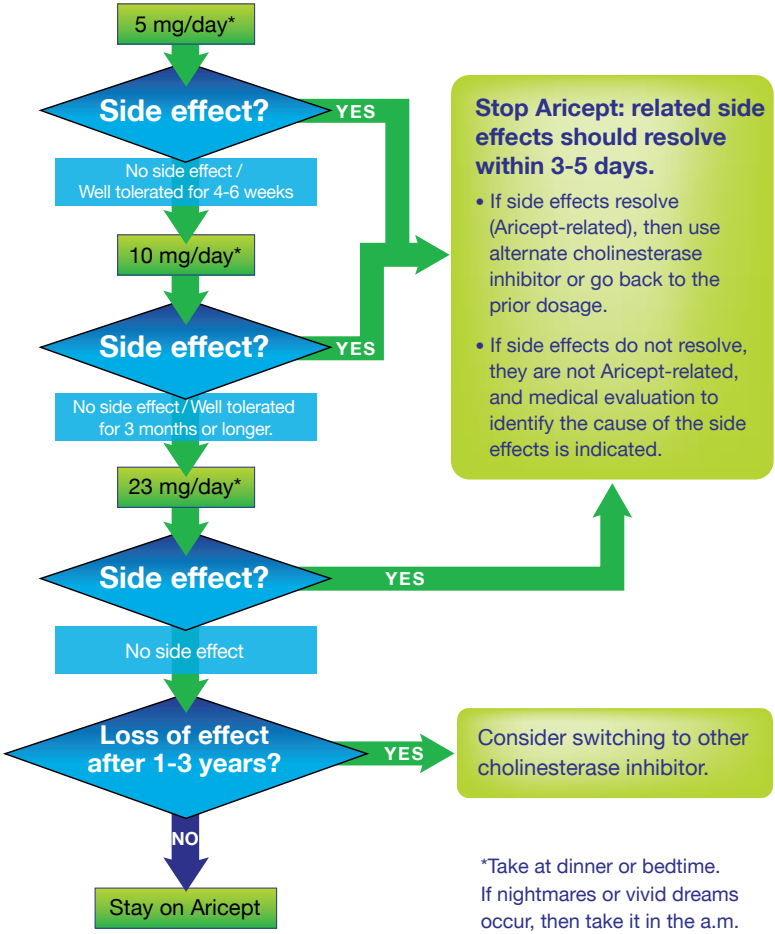
For more information, please see:

- Namenda Dosing Schedule

Aricept Dosing Schedule

Aricept® (donepezil HCl) Tablet

Aricept is a prescription medication to treat mild, moderate and severe AD. It is available in 5, 10, and 23 mg/day in tablet form. The starting dose is 5 mg/day and can be increased to 10 mg/day after 4-6 weeks of treatment and good tolerability. Similarly it can be increased to 23 mg/day after at least 3 months of treatment and good tolerability.

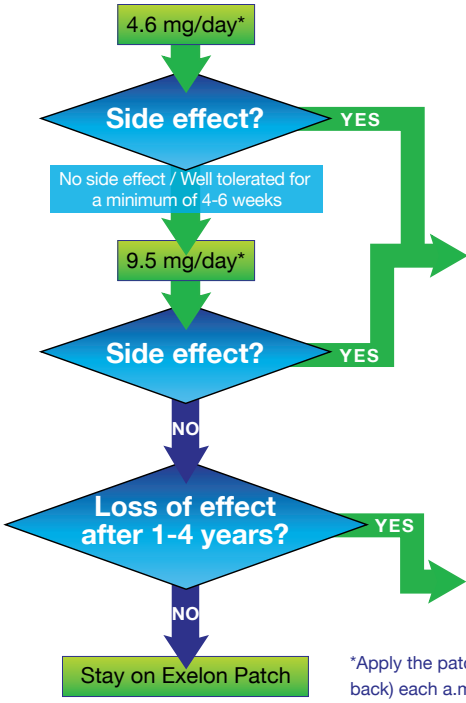


*Take at dinner or bedtime. If nightmares or vivid dreams occur, then take it in the a.m.

Exelon Patch Dosing Schedule

Exelon Patch® (rivastigmine transdermal system)

Exelon Patch is a prescription medication to treat mild to moderate AD. It is available in 4.6 and 9.5 mg/day. The starting dose is 4.6 mg/day and can be increased to 9.5 mg/day after a minimum of 4 weeks of treatment and good tolerability.



Remove Exelon patch: Exelon-related side effects should resolve within 2 days.

- If side effects resolve (Exelon-related), reapply the patch over the abdomen. This will reduce the actual dose to 3.1 mg and 6.7 mg in 4.6 mg and 9.5 mg patch, respectively. If not well tolerated, then use alternate cholinesterase inhibitor.
- If side effects do not resolve, they are not Exelon-related, and medical evaluation to identify the cause of the side effects is indicated.

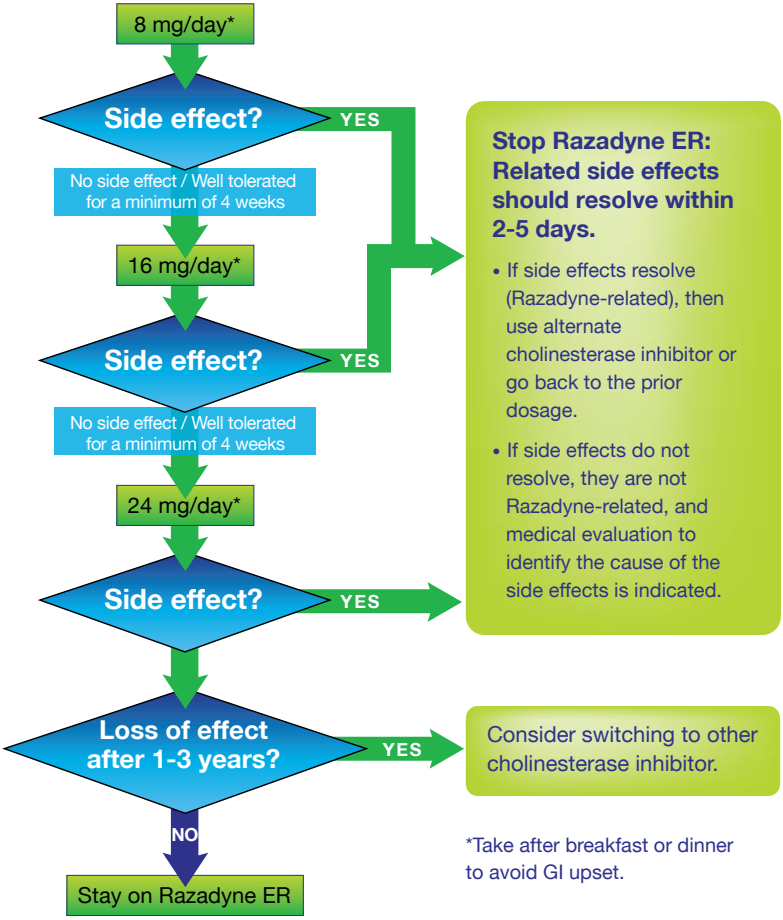
Consider switching to other cholinesterase inhibitor.

*Apply the patch to the upper body (chest, shoulder, back) each a.m., and remove the previous day's patch. Rotate the site to avoid skin irritation.

Razadyne ER Dosing Schedule

Razadyne® ER (galantamine hydrobromide extended-release) Capsule

Razadyne ER is a prescription medication to treat mild to moderate AD. It is available in 8, 16 and 24 mg/day. The starting dose is 8 mg/day and can be increased to 16 mg/day after a minimum of 4 weeks of treatment and good tolerability. Similarly, it can be increased to 24 mg/day after a minimum of 4 weeks of treatment and good tolerability.

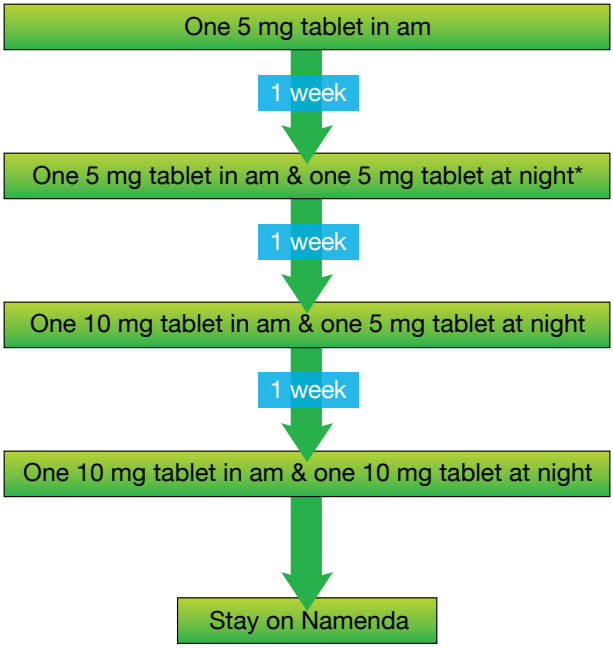


*Take after breakfast or dinner to avoid GI upset.

Namenda Dosing Schedule

(Recommended by manufacture)

Namenda (memantine HCl) is a prescription medication to treat the symptoms of moderate to severe AD. It is available in 5 and 10 mg tablets.

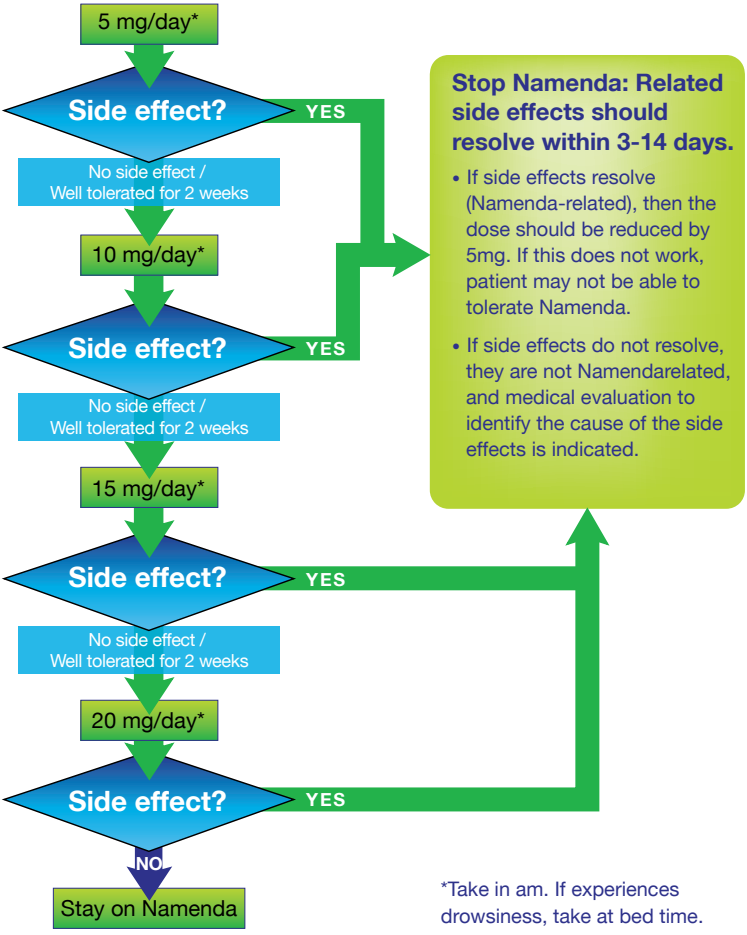


*For patients with severe renal impairment, 5 mg twice daily is the recommended dose.

Namenda Dosing Schedule

(Possible alternative approach)

Alternatively, because the terminal elimination half-life is 60-80 hours, Namenda may be given as a once a day drug. Also, the time to steady state is 3 weeks. For this reason, Namenda may be better tolerated by changing dose every 2 weeks instead of every week during titration.



Step 4: Monitor Cognition and Function Every 3 to 6 Months

After optimizing the doses of both the cholinesterase inhibitor and namenda, schedule follow-up visits every 3-6 months and measure memory and function. See patients earlier if problems develop.

Regular monitoring is critical for:

- Measuring treatment efficacy
- Deciding if treatment modification is indicated
- Identifying co-morbid conditions (see **Step 5**)
- Educating patients and families about the importance of staying on treatment

Quite often, there is a misconception among patients and families that the treatment is not working because the patient is not getting better. However, in degenerative disorders such as AD, "being stable" or "getting worse at a slower rate" is a positive treatment effect that improves quality of life and can substantively reduce healthcare costs.

Regular monitoring can be quickly and accurately done within the constraints of a routine follow-up visit.

Functional Measurement

Assessment tools such as the Functional Assessment Staging (FAST), the Dementia Severity Rating Scale and the Clinical Dementia Rating Scale can be used. The FAST staging instrument which takes several minutes to complete, assesses the patient's level of severity and provides a variety of useful other pieces of information, such as the patient's developmental age, approximate MMSE score, and expected duration per FAST stage for untreated AD. The Clinical Dementia Rating Scale takes more time to administer in clinical practice (about 10 to 20 minutes) and is more widely used in clinical research settings.

Cognitive Measurement

Cognitive assessment tools such as MCI Screen, MOCA, MMSE and Clock Drawing can be used (see **Section 4**). Note that these tests differ greatly in their sensitivity and specificity. For example, the MMSE and Clock Drawing tests are not sensitive for detecting or monitoring the mild cognitive impairment stage of AD, and should be restricted to patients in the dementia stage. The MOCA is intermediate in sensitivity and specificity, and the MCI Screen has the highest sensitivity and specificity for discriminating normal aging from mild cognitive impairment and dementia. The MCI Screen has also been well validated as an effective tool for monitoring changes in mild cognitive impairment and dementia.

Depending on the structure of any given practice, reimbursement for performing cognitive assessment may be an important consideration in the selection of the most appropriate assessment tool. The MCI Screen is generally reimbursed by Medicare and most major insurers, the MOCA and the Clock Drawing Test may each be reimbursed in some situations, and the MMSE is almost universally not reimbursed.

Step 5: Evaluate Unexpected Changes

Sudden or subacute changes, or development of symptoms that are out of sequence with that expected by FAST staging, are not typical of AD progression. The most common reasons for such changes are:

- Infection: Urinary Tract infection, aspiration pneumonia.
- Trauma: Unobserved falls, particularly if head injury occurred.
- Metabolic: Dehydration due to altered patterns of eating and drinking.
- Iatrogenic: Compliance problems, anticholinergics, anti-anxiety, tranquilizers, antipsychotics.
- Exacerbation of an existing medical condition.
- Development of a new medical condition.
- Environmental: Changes in residence, light level, noise level, routine, caregiver, sleeping pattern or activity level.

Additional Information on Cholinesterase Inhibitors

Aricept® (Dopnepezil)

Optimal Dosing of Aricept (donepezil): The primary mechanism of action is likely to be acetylcholinesterase inhibition. However, clinically, this effect is observed to disappear within 1-2 years. One should find the highest dose among 5, 10 or 23 mg that causes no side effects. Because all of the Aricept 23 mg studies are 6 months, there are no published data to indicate that 23 mg prolongs the duration of acetylcholinesterase inhibition.

Potential Aricept Side Effects: Side effects occur in 9-19% of patients and are dose dependent. Loss of appetite, nausea, diarrhea, dizziness, syncope, lightheadedness and nightmares are the most common. These side effects usually resolve within 3-7 days of stopping Aricept because the elimination half-life is 70 hours. If side effects resolve, Aricept can be restarted at the next lower dose, and the side effects usually do not reappear.

For more information: www.aricept.com

Exelon® (Rivastigmine)

Optimal Dosing of Exelon Patch: The optimal dose is the highest well-tolerated dose, ranging from 3.1 mg to 14.3 mg per day. The dose of the patch is approximately 1/3 lower when applied over the abdomen compared to the upper body (i.e., 4.6 and 9.5 mg patches applied to the abdomen give 3.1 and 6.7 mg doses respectively). The FDA approved doses are 4.6 and 9.5 mg daily. However, the phase III FDA clinical trial showed further improvement in cognition for doses up to 19 mg daily, but there were more side effects above the 9.5 mg dose. When patients tolerate the 9.5 mg dose, then one can try increasing the dose to 14.3 mg (see below).

Potential Exelon Patch Side Effects: Side effects occur in 5-6% of patients and are dose dependent. Skin irritation is the most common one, followed by loss of appetite. These side effects usually resolve within two days of stopping the patch because the elimination half-life is 3 hours. If side effects resolve, the patch can be restarted at a lower dose, and the side effects usually do not reappear.

For more information: www.exelonpatch.com

Razadyne® (Galantamine)

Optimal Dosing of Razadyne ER (Galantamine ER): The primary mechanism of action is likely to be the presynaptic nicotinergic receptor modulation, which increases multiple neurotransmitters to a mild degree, and stimulates three neuroprotective mechanisms—reduced cholinergic neuron damage, increased degradation of amyloid precursor protein along the non-amyloidogenic pathway (s*APP-alpha*), and reduced glutamate-mediated excitotoxicity. One should therefore find the highest dose, from 8 to 24 mg, without side effects.

Potential Razadyne ER Side Effects: Side effects occur in about 4% of patients and are dose dependent. Loss of appetite, nausea, diarrhea, dizziness, syncope, lightheadedness and bradycardia are the most common. These side effects usually resolve within 2-5 days of stopping Razadyne ER because the elimination half-life is about 14-24 hours (for the non-extended release form of Razadyne, half-life is 7 hours). If side effects resolve, Razadyne ER can be restarted at the next lower dose, and the side effects usually do not reappear.

For more information: www.razadyneer.com.

Additional Information on Memantine

Namenda®

Optimal Dosing of Namenda: The optimal dose of Namenda is the highest one from 5 to 20 mg daily that is well tolerated. Because of Namenda's 72-hour half-life, it can be given once daily without difficulty. It usually does not cause drowsiness, so it can be given in the a.m. If it causes drowsiness, give at bedtime.

Potential Namenda Side Effects: Side effects occur in about 5% of patients, are dose dependent, and almost always occur within 3 to 7 days after a dose increase. The most common ones are agitation, irritability, confusion or a general worsening of function. If a side effect occurs, then lower the dose by 5 mg and continue that lower dose. If side effects are mild, they may resolve on their own over a few weeks without lowering the dose.

For more information: www.namenda.com

6.2 Background For Pharmacologic Treatment of Alzheimer's Disease

Abeta42, the 42-amino acid breakdown product of the amyloid precursor protein, self-aggregates to form oligomeric clusters of Abeta42. There is an extensive body of research supporting a major role for oligomeric Abeta42 in the pathogenesis and clinical expression of Alzheimer's disease (**AD**).[1-4] Human post-mortem studies have shown that patients receiving acetylcholinesterase (**AchE**) inhibitors have lower levels of cortical Abeta42 than those not receiving AchE inhibitors.[5] Furthermore, animal models of AD have shown that AchE inhibition reduces Abeta42 production. Studies from the Karolinska Institute have shown that cerebrospinal fluid levels of AchE and butyrylcholinesterase, which correlate very well with brain cholinesterase levels, remain inhibited by at least 50% below baseline after 1 year of Exelon treatment of AD patients.[6] Also, the type of AchE inhibited by Exelon favors protection against synaptic damage.[7] In contrast, after 3 months of treatment, cerebrospinal fluid AchE levels are 200% above baseline with Aricept, and are no longer reduced by Razadyne. AchE-R, the neuroprotective, or *read-through*, form of AchE, is reduced relative to AchE-S, the form associated with synaptic damage. The neuroprotective/neurodestructive ratios of Exelon, Aricept, and Razadyne are 1.4, 0.6 and 0.4 respectively.[7]

The longest prospective clinical study was done at Harvard by Atri et al.,[8] in which AD patients at all clinical stages received either no treatment (N=144, 1990-95), cholinesterase inhibitor (**Chel**) therapy only (N=122, 1998-2005), or Namenda plus a Chel (N=116, 1998-2005) for up to four years. Rates of cognitive and functional decline were carefully statistically analyzed. The Namenda plus Chel group showed a 33% delay in the rate of functional decline in AD patients starting with minimal functional impairment (equivalent to mild cognitive impairment), a 60% delay in AD patients starting with mild dementia, and a 50% delay in AD patients who were moderately severely demented. This finding was consistent with a 12-month, quantitative, volumetric MRI study in mild to moderately demented AD patients, in which monotherapy with either Namenda[9] or a Chel[10] delayed the rate of hippocampal atrophy.

In contrast to the disease-delaying effect of combined therapy, the Atri et al. study showed that AD patients receiving no treatment showed the same rate of decline as patients receiving Chel monotherapy. An independent study by the Pfizer global research team provided further information about the treatment effect of Chel monotherapy.[11] They performed a meta-analysis of randomized, placebo-controlled, Chel trials for up to 12 months, and found no difference between placebo and Aricept or Razadyne in the rate of cognitive decline. There was only one double-blind, placebo controlled, randomized trial of Exelon lasting 12 months, which suggested a delay in rate of cognitive decline.

Longer duration studies of rivastigmine (Exelon) support that it may delay AD progression, at least in certain sub-populations. A re-analysis in 2010 of the randomized, placebo-controlled, Exelon study lasting up to 4 years found a 25% reduction in the rate of conversion from MCI to AD for Exelon-treated patients, particularly females.[12,13] A 5-year open label extension study of Exelon in 32 AD-treated patients showed stabilization in cognition, function and severity for 2-3 years. Of the 8 patients who remained in the study at 5 years, 2/3 of them had started in the high dose Exelon group.[14] A 2-year study comparing Exelon to Aricept found that moderate-to-severe AD patients under 75 years old declined less in severity and functional abilities on Exelon. AD patients over 75 years old responded the same to Exelon and Aricept over 2 years.[15] Two open label extension studies, each lasting two years, compared the course of Exelon-treated AD patients vs. the expected cognitive decline from historical, untreated AD controls. Both studies found clinically meaningful reductions in the rate of cognitive decline on Exelon that influenced overall severity.[16] These longer duration Exelon studies provide the strongest support for a disease-delaying effect among the cholinesterase inhibitors.

Longer duration studies of galantamine (Razadyne) also support that it may delay AD progression. A 3-year open label extension of a randomized, double-blind trial of Razadyne vs. placebo showed a 50% reduction in the rate of cognitive decline compared to expected rate of decline on placebo using a matched patient sample.[17]

Longer duration studies of Aricept indicate that it may delay AD progression for up to 3 years in certain subgroups. The rate of conversion from MCI to AD dementia over 3 years was reduced in a subset of depressed AD patients.[18] A 1-year, open label extension in severe AD patients treated with Aricept found that they did not decline in behavior or functional abilities, but that these benefits were lost if treatment was discontinued for 1 month or longer.[19] A 1-year, double-blind, placebo-controlled trial of MCI patients treated with Aricept showed no difference in functional abilities and overall severity over the 2 years, but did show a slight reduction in rate of cognitive decline.[20] A 3-year open label extension of mild-to-moderate AD patients treated with Aricept showed cognitive and functional decline over the study that did not differ between patients initially treated during the first six months of the study (the duration of the randomized part of the trial) with Aricept or placebo.[21] Another 3-year open label extension study of AD patients treated with Aricept found small but statistically significant reductions in the rates of cognitive and functional decline, but not global decline.[22] Another open-label study of Aricept for up to 4 years found reduced rates of cognitive and functional decline for the first 2 years, but no change in rates of institutionalization at 3 years.[23] Overall, Aricept appears to slightly delay cognitive and/or functional decline for not longer than 2-3 years.

Although the above findings are not absolute, they suggest that the largest disease-delaying effect among the Chels is with Exelon, both in terms of amount and duration of delay (i.e., the only Chel with 5-year data for at least some patients). The evidence for Aricept and Razadyne suggests a smaller disease-delaying effect that can last for up to 2-3 years. More importantly, the Harvard study indicates that combined therapy with Namenda and a Chel delays rate of cognitive and functional decline at all clinical stages of AD by 33% to 60%, which means that one should attempt to detect AD as early as possible and maintain combined therapy as long as possible. A reasonable strategy, therefore, would use any of the Chels with Namenda during the first two to three years, depending upon the patient's course, and switch to one of the other Chels and Namenda when patients begin to show a more rapid decline.

6.3 Psychosocial Interventions in MCI and Early Alzheimer's Disease

Psychosocial interventions are a key component of treatment for the non-cognitive symptoms of MCI and early Alzheimer's disease. According to two recent literature reviews, 35-85% of individuals with MCI exhibit behavioral abnormalities.[24,25] Individuals with MCI exhibit an average of 2.3 neuropsychiatric disturbances, with some experiencing as many as 9.6 symptoms.[26] There is no typical profile of neuropsychiatric disturbances in MCI or mild AD as these symptoms are heterogeneous and unpredictable.[27] Across studies, depression, apathy, anxiety, and irritability are the most common neuropsychiatric symptoms in MCI.[24,25] Compared to cognitively intact older adults, persons with mild AD were at significantly greater risk for apathy (Odds Ratio = 42) and depression (OR = 17).[28] Neuropsychiatric disturbances, like the cognitive and functional symptoms of MCI and AD, worsen with disease severity.[29]

Psychosocial interventions to alleviate neuropsychiatric symptoms are critical given their deleterious consequences, including increased risk of conversion from MCI to AD,[30] greater functional dependence,[31] heightened risk for institutionalization,[32] shorter survival time,[33] and higher levels of burden and depression among caregivers.[34]

Evidence Base for Key Early Psychosocial Interventions

Caregiver Counseling and Support

In a series of studies, Mary Mittelman and her colleagues at New York University demonstrated that early access to a combination of counseling (i.e., 2 family and 4 individual sessions), a caregiver support group, and ad hoc telephone consultation lowered the rate of nursing home placement by 28.3%, delayed institutionalization by 557 days,[35] and resulted in other significant benefits for caregivers, including reduced depression,[36] better self-rated health,[37] improved satisfaction with support network,[38] and greater tolerance for a loved one's memory and behavior problems.[39]

Care Management

Effective management of MCI and early AD requires an integrated approach to care that encompasses medical care, psychosocial interventions, community services, and family resources.[40] Access to a care manager who can assess family needs, help caregivers

navigate the health care system and community resources, and serve as a coach has been shown to improve caregiver quality of life, social support, mastery of caregiving, and confidence.[41,42] Additionally, quality of care, as measured by adherence to guidelines, was dramatically higher in patients who were assigned a care manager than those who were not.[42]

Caregiver Education

Caregiver education has proven benefits for both the caregiver and person with MCI or early AD. Studies have investigated a variety of educational programs, which vary in content (e.g., caregiver self-care, behavior management), format (single- or multiple-session), and complexity (i.e., offered independently or as part of a multicomponent intervention). Key outcomes for caregivers include significant improvements in knowledge of Alzheimer's disease,[43] ability to cope with the dementia,[43] depression,[44,45] anger,[46] burden,[45] use of adaptive coping strategies,[44] self-efficacy[46] and response to difficult behaviors.[45] Additionally, caregiver education can also significantly reduce the actual frequency of behavior problems,[47] with key patient outcomes including stabilization,[43] and significantly reduced agitation and anxiety.[48]

Early-Stage Groups

Early stage groups that incorporate education and support for both individuals with MCI or early Alzheimer's disease and their care partners have proven beneficial in the literature. While early stage groups vary, they typically include parallel support sessions for persons with early memory loss and their care partners, and an educational component. A recent randomized controlled clinical trial demonstrated that participation in an early stage group can improve quality of life for the person with MCI or early AD, as evidenced in significantly reduced depression and behavioral symptoms, improved family communication, enhanced feelings of self-efficacy, and better emotional and social functioning.[49]

Cognitive Stimulation

A number of studies have now demonstrated that cognitive stimulation can have additive effects over and above those accrued by the acetylcholinesterase inhibitors and Namenda. In Requena et al.,[50] persons with mild AD who received a combination of cognitive stimulation and 10 mg of Aricept showed less decline on measures

of overall mental status (MMSE), cognitive functioning (ADAS-Cog), and functional abilities (FAST) across 2 years than their peers receiving no treatment or medication alone. Subsequently, Niu et al.[51] demonstrated that cognitive stimulation significantly improved apathy and depression/dysphoria in persons with mild-to-moderate AD. In MCI, a 4-week cognitive intervention that included activity planning, self-assertiveness training, relaxation techniques, stress management, use of external memory aids, memory training, and motor exercise, resulted in significant improvements on measures of activities of daily living, mood, and verbal and nonverbal episodic memory.[52] Options for cognitive stimulation include computer-based programs and participation in an early stage day program.

Exercise

Given the changes in motor[53] (e.g., walking speed, standing balance) and higher level functional abilities[54] that are already evident in MCI and early AD, in addition cognitive decline and neuropsychiatric symptoms such as depression, exercise can play an important role in maintaining physical, mental and emotional well-being. In MCI, walking 150 minutes per week for 6 months resulted in significant improvement on the ADAS-Cog,[55] better than that achieved by Aricept alone over the same period.[56] Aerobic exercise (e.g., treadmill, stationary bike) sufficient to elevate heart rate to 75-85% of reserve improved cognitive function, particularly executive skills, in women with MCI.[57] In AD, physical activity has also been associated with reduced depression,[58] better physical health[52] and longer survival time.[59] Among older adults, other health benefits of exercise have been documented for depression,[60] quality of life,[61] falls,[62] cardiovascular function,[63] and disability.[64]

Purposeful and Pleasurable Activities

Given the gradual loss of ability to engage in previously meaningful work and leisure activities, and the high frequency of apathy and depression in MCI and early AD, it is critical to encourage affected individuals to become involved in purposeful and pleasurable activities. Simply increasing the frequency and intensity of pleasurable activities in AD has been shown to alleviate depression.[65] In MCI and early AD, individuals may be able to continue participating in some activities relatively independently with encouragement and support (e.g., appropriate transportation) by caregivers. Early stage day programs, however, offer a venue for meaningful, pleasurable activities, cognitive stimulation, and peer support, while relieving the caregiver.

Examples – Psychosocial Interventions as a Component of Treatment in MCI and Early AD

1. A 56-year-old male corporate executive with multiple domain MCI who can no longer work or drive, is spending a lot of time sleeping at home, and exhibits depressed affect. Patient is receiving acytelcholinesterase inhibitor and anti-depressant. Patient has high degree of insight into how MCI has affected him. Caregiver is highly motivated to seek services for patient and self.
   - Refer patient for individual counseling
   - Refer patient and caregiver to early stage support group
   - Educate couple regarding need for meaningful, purposeful, and pleasurable activity, and suggest options such as volunteering and early stage day program
   - Educate couple regarding benefits of cognitive stimulation and options, including at-home computer-based programs and early stage day program
   - Promote exercise for positive benefits on cognition and mood
2. A 75-year-old homemaker with amnestic MCI being cared for by her 81-year-old spouse who is physically frail and has multiple chronic health conditions. Patient will not acknowledge memory loss, is resistant to services, and husband feels overwhelmed.
   - Refer for care management support to assist caregiver to assess both patient's and caregiver's needs, assist with patient's resistance and problem-solving, and coordinate care and community resources for patient and/or caregiver
   - Promote use of caregiver support group and educational opportunities related to caregiving
3. A 65-year-old man with early AD, living alone, estranged from family, and relying on support of neighbor. Patient retains some insight into his condition, but insists on living alone, has been the victim of a scam, and continues to drive short distances. It appears patient may be missing medications. Patient has minimal resources.
   - Refer to Adult Protective Services due to self-neglect for possible conservatorship and coordination of services.
   - Report patient to DMV for driving evaluation/license revocation.

Reference

1. Rabinovici GD, Jagust WJ. Amyloid imaging in aging and dementia: testing the amyloid hypothesis in vivo. Behav Neurol 2009; 21:117-28.
2. Iacono D, Markesbery WR, Gross M, Pletnikova O, Rudow G, Zandi P, Troncoso JC. The Nun study: clinically silent AD, neuronal hypertrophy, and linguistic skills in early life. Neurology 2009; 73:665-73.
3. Nimmrich V, Ebert U. Is Alzheimer's disease a result of presynaptic failure? Synaptic dysfunctions induced by oligomeric beta-amyloid. Rev Neurosci 2009; 20:1-12.
4. Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, Petersen RC, Trojanowski JQ. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010; 9:119-28.
5. Ballard CG, Chalmers KA, Todd C, McKeith IG, O'Brien JT, Wilcock G, Love S, Perry EK. Cholinesterase inhibitors reduce cortical Abeta in dementia with Lewy bodies. Neurology 2007; 68:1726-9.
6. Darreh-Shori T, Almkvist O, Guan ZZ, Garlind A, Strandberg B, Svensson AL, Soreq H, Hellström-Lindahl E, Nordberg A. Sustained cholinesterase inhibition in AD patients receiving rivastigmine for 12 months. Neurology 2002; 59:563-72.
7. Nordberg A, Darreh-Shori T, Peskind E, Soininen H, Mousavi M, Eagle G, Lane R. Different cholinesterase inhibitor effects on CSF cholinesterases in Alzheimer patients. Curr Alzheimer Res 2009; 6:4-14.
8. Atri A, Shaughnessy LW, Locascio JJ, Growdon JH. Long-term course and effectiveness of combination therapy in Alzheimer disease. Alzheimer Dis Assoc Disord 2008; 22:209-21.
9. Schmidt R, Ropele S, Pendl B, Ofner P, Enzinger C, Schmidt H, Berghold A, Windisch M, Kolassa H, Fazekas F. Longitudinal multimodal imaging in mild to moderate Alzheimer disease: a pilot study with memantine. J Neurol Neurosur Psychiatry 2008; 79:1312-7.
10. Hashimoto M, Kazui H, Matsumoto K, Nakano Y, Yasuda M, Mori E. Does donepezil treatment slow the progression of hippocampal atrophy in patients with Alzheimer's disease? Am J Psychiatry 2005; 162:676-82.
11. Ito K, Ahadieh S, Corrigan B, French J, Fullerton T, Tensfeldt T; Alzheimer's Disease Working Group. Disease progression meta-analysis model in Alzheimer's disease. Alzheimers Dement 2010; 6:39-53.
12. Ferris S, Nordberg A, Soininen H, Darreh-Shori T, Lane R. Progression from mild cognitive impairment to Alzheimer's disease: effects of sex, butyrylcholinesterase genotype, and rivastigmine treatment. Pharmacogenet Genomics 2009; 19:635-46.
13. Ferris S, Lane R, Sfikas N, Winblad B, Farlow M, Feldman HH. Effects of gender on response to treatment with rivastigmine in mild cognitive impairment: A post hoc statistical modeling approach. Gend Med 2009; 6:345-55.

14. Farlow MR, Lilly ML; ENA713 B352 Study Group. Rivastigmine: an open-label, observational study of safety and effectiveness in treating patients with Alzheimer's disease for up to 5 years. BMC Geriatr 2005; 5:3.
15. Bullock R, Bergman H, Touchon J, Gambina G, He Y, Nagel J, Lane R. Effect of age on response to rivastigmine or donepezil in patients with Alzheimer's disease. Curr Med Res Opin 2006; 22:483-94.
16. Grossberg G, Irwin P, Satlin A, Mesenbrink P, Spiegel R. Rivastigmine in Alzheimer disease: efficacy over two years. Am J Geriatr Psychiatry 2004; 12(4):420-31.
17. Raskind MA, Peskind ER, Truyen L, Kershaw P, Damaraju CV. The cognitive benefits of galantamine are sustained for at least 36 months: a long-term extension trial. Arch Neurol 2004; 61:252-6.
18. Lu PH, Edland SD, Teng E, Tingus K, Petersen RC, Cummings JL. Alzheimer's Disease Cooperative Study Group. Donepezil delays progression to AD in MCI subjects with depressive symptoms. Neurology 2009; 72:2115-21.
19. Homma A, Imai Y, Tago H, Asada T, Shigeta M, Iwamoto T, Takita M, Arimoto I, Koma H, Takase T, Ohbayashi T. Long-term safety and efficacy of donepezil in patients with severe Alzheimer's disease: results from a 52-week, open-label, multicenter, extension study in Japan. Dement Geriatr Cogn Disord 2009; 27:232-9.
20. Doody RS, Ferris SH, Salloway S, Sun Y, Goldman R, Watkins WE, Xu Y, Murthy AK. Donepezil treatment of patients with MCI: a 48-week randomized, placebo-controlled trial. Neurology 2009; 72:1555-61.
21. Winblad B, Wimo A, Engedal K, Soininen H, Verhey F, Waldemar G, Wetterholm AL, Haglund A, Zhang R, Schindler R. 3-year study of donepezil therapy in Alzheimer's disease: effects of early and continuous therapy. Dement Geriatr Cogn Disord 2006; 21:353-63.
22. Burns A, Gauthier S, Perdomo C. Efficacy and safety of donepezil over 3 years: an open-label, multicentre study in patients with Alzheimer's disease. Int J Geriatr Psychiatry 2007; 22:806-12.
23. Courtney C, Farrell D, Gray R, Hills R, Lynch L, Sellwood E, Edwards S, Hardyman W, Raftery J, Crome P, Lendon C, Shaw H, Bentham P; AD2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet 2004; 363:2105-15.
24. Apostolova LG, Cummings JL. Neuropsychiatric manifestations in mild cognitive impairment: A systematic review of the literature. Dement Geriatr Cogn Disord 2008; 25:115-26.
25. Monastero R, Mangialasche F, Camarda C, Ercolani S, Camarda R. A systematic review of neuropsychiatric symptoms in mild cognitive impairment. J Alzheimers Dis 2009; 18:11-30.
26. Edwards ER, Spira AP, Barnes DE, Yaffe K. Neuropsychiatric symptoms in mild cognitive impairment: Differences by subtype and progression to dementia. Int J Geriatr Psychiatry 2009; 24:716-22.

27. Spalletta G, Baldinetti F, Buccione I, Fadda L, Perri R, Scalmana S, Serra L, Caltagirone C. Cognition and behavior and are independent and heterogeneous dimensions in Alzheimer's disease. J Neurol 2004; 251:688-95.

28. Di Iulio F, Palmer K, Blundo C, Casini AR, Gianni W, Caltagirone C, Spalletta G. Occurrence of neuropsychiatric symptoms and psychiatric disorders in mild Alzheimer's disease and mild cognitive impairment subtypes. Int Psychogeriatr. 2010; 22:629-40.

29. Fernández-Martinez M, Molano A, Castro J, Zarranz JJ. Prevalence of neuropsychiatric symptoms in mild cognitive impairment and Alzheimer's disease, and its relations with cognitive impairment. Curr Alzheimer Res 2010; 7:517-26.

30. Teng E, Lu PH, Cummings JL. Neuropsychiatric symptoms are associated with progression from mild cognitive impairment to Alzheimer's disease. Dement Geriatr Cogn Disord 2007; 24:253-59.

31. Feldman H, Scheltens P, Scarpini E, Hermann N, Mesenbrink P, Mancione L, Tekin S, Lane R, Ferris S. Behavioral symptoms in mild cognitive impairment. Neurology 2004; 62:1199-201.

32. Yaffe K, Fox P, Newcomer R, Sands L, Lindquist K, Dane K, Covinsky KE. Patient and caregiver characteristics and nursing home placement in patients with dementia. JAMA 2002; 287(16):2090-97.

33. Weiner MF, Hynan LS, Bret ME, White I. Early behavioral symptoms and course of Alzheimer's disease. Acta Psychiatrica Scandinavia 2005; 111:367-71.

34. Mohamed S, Rosenheck R, Lyketsos CG, Schneider LS. Caregiver burden in Alzheimer disease: Cross-sectional and longitudinal patient correlates. Am J Geriatr Psychiatry 2010; 18:917-27.

35. Mittelman MS, Haley WE, Clay OJ, Roth DL. Improving caregiver well-being delays nursing home placement of patients with Alzheimer's disease. Neurology 2006; 67:1592-9.

36. Mittelman MS, Roth DL, Coon DW, Haley WE. Sustained benefit of supportive intervention for depressive symptoms in caregivers of patients with Alzheimer's disease. Am J Psychiatry 2004; 161:850-56.

37. Mittelman MS, Roth DL, Clay OJ, Haley WE. Preserving health of Alzheimer caregivers: Impact of a spouse caregiver intervention. Am J Geriatr Psychiatry 2007; 15:780-9.

38. Roth DL, Mittelman MS, Clay OJ, Mandan A, Haley WE. Changes in social support as mediators of the impact of a psychosocial intervention for spouse caregivers of persons with Alzheimer's disease. Psychol Aging 2005; 20:634-55.

39. Mittelman MS, Roth DL, Haley WE, Zarit SH. Effects of a caregiver intervention on negative caregiver appraisals of behavior problems in patients with Alzheimer's disease: Results of a randomized trial. J Gerontol 2004; 59B:P27-P34.

40. Callahan CM, Boustani M, Sachs GA, Hendrie HC. Integrating care for older adults with cognitive impairment. Curr Alzheimer Res 2009; 6:368-74.

41. Belle SH, Burgio L, Burns R, Coon D, Cazja SJ, Gallagher-Thompson D, Gitlin LN, Klinger J, Koepke KM, Lee CC, Martindale-Adams J, Nichols L, Schulz R, Stahl S, Stevens A, Winter L, Zhang S. Enhancing the quality of life of dementia caregivers from different ethnic or racial groups: A randomized, controlled trial. Ann Intern Med 2006; 145:727-38.

42. Vickrey BG, Mittman BS, Connor KI, Pearson ML, Della Penna RD, Ganiats TG, DeMonte RW, Chodosh J, Cui X, Vassar S, Duan N, Lee M. The effect of a disease management intervention on quality and outcomes of dementia care: A randomized, controlled trial. Ann Intern Med 2006; 145:713-26.

43. De Rotrou J, Cantegreil K, Faucounau V, Wenisch E, Chausson C, Jegou D, Grabar S, Rigaud AS. Do patients diagnosed with Alzheimer's disease benefit from a psychoeducational programme for family caregivers? A randomized controlled study. International Journal of Geriatric Psychiatry 2010. Advance online publication.

44. Gallagher-Thompson D, Coon DW, Solano N, Ambler C, Rabinowitz Y, Thompson LW. Change in indices of distress among Latino and Anglo female caregivers of elderly relatives with dementia: Site-specific results from the REACH national collaborative study. Gerontologist 2003; 43:580-91.

45. Hepburn KW, Tornatore J, Center B, Ostwald SW. Dementia family caregiver training: Affecting beliefs about caregiving and caregiver outcomes. J Am Geriatr Soc 2001; 49:450-57.

46. Coon DW, Thompson L, Steffen A, Sorocco K, Gallagher-Thompson D. Anger and depression management: psychoeducational skill training interventions for women caregivers of a relative with dementia. Gerontologist 2003; 43:678-89.

47. Hébert R, Lévesque L, Vézina J, Lavoie J-P, Ducharme F, Gendron C. Préville M, Voyer L, Dubois M-F. Efficacy of a psychoeducative group program for caregivers of demented persons living at home: A randomized controlled trial. J Gerontol 2003; 58B:S58-S67.

48. Haupt M, Karger A, Jänner M. Improvement of agitation and anxiety in demented patients after psychoeducative group intervention with their caregivers. Int J Geriatr Psychiatry 2000; 15:1125-9.

49. Logdson RG, Pike KC, McCurry SM, Hunter P, Maher J, Snyder L, Teri L. Early-stage memory loss support groups: Outcomes from a randomized controlled clinical trial. J Gerontol 2010; 65B:691-697.

50. Requena C, Maestú F, Campo P, Fernández A, Ortiz T. Effects of cholinergic drugs and cognitive training on dementia: 2-year follow-up. Dement Geriatr Cogn Disord 2006; 22:339-45.

51. Niu YX, Tan JP, Guan JQ, Zhang ZQ, Wang LN. Cognitive stimulation therapy in the treatment of neuropsychiatric symptoms in Alzheimer's disease: a randomized controlled trial. Clin Rehabil 2010. Advance online publication.

52. Kurz A, Pohl C, Ramsenthaler M, Sorg C. Cognitive rehabilitation in patients with mild cognitive impairment. Int J Geriatr Psychiatry 2009; 24:163-8.

53. Aggarwal NT, Wilson RS, Beck TL, Bienias JL, Bennett DA. Motor dysfunction in mild cognitive impairment and the risk of incident Alzheimer's disease. Arch Neurol 2006; 63:1763-9.

54. Farias ST, Mungas D, Reed BR, Harvey D, Cahn-Weiner D, DeCarli C. MCI is associated with deficits in everyday functioning. Alzheimer Dis Assoc Disord 2006; 20:217-23.

55. Lautenschlager NT, Cox KL, Flicker L, Foster JK, van Bockxmeer FA, Xiao J, Greenop KR, Almeida OP. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease. JAMA 2008; 300:1027-37.

56. Petersen RC, Thomas RG, Grundman M, Bennett D, Doody R, Ferris S, Galasko D, Jin S, Kaye J, Levey A, Pfeiffer E, Sano M, van Dyck CH, Thal LJ; Alzheimer's Disease Cooperative Study Group. N Engl J Med. 2005; 352(23):2379-88.

57. Baker LC, Frank LL, Foster-Schubert K, Green PS, Wilkinson CW, McTiernan A, Plymate SR, Fishel MA, Watson GS, Cholerton BA, Duncan GE, Mehta PD, Craft S. Effects of aerobic exercise on mild cognitive impairment: A controlled trial. Arch Neurol 2010; 67:71-9.

58. Teri L, Gibbons L, McCurry SM, Logsdon RG, Buchner DM, Barlow WE, Kukull WA, LaCroix AZ, McCormick W, Larson EB. Exercise plus behavioral management in patients with Alzheimer disease: A randomized controlled trial. JAMA 2003; 290:2015-22.

59. Scarmeas N, Luchsinger JA, Brickman AM, Cosentio S, Schupf N, Xin-Tang M, Gu Y, Stern Y. Physical activity and Alzheimer Disease Course. Am J Geriatr Psychiatry 2010. Advance online publication.

60. Netz Y, Wu M-J, Becker BJ, Tenenbaum G. Physical activity and psychological well-being in advanced age: A meta-analysis of intervention studies. Psychol Aging 2005; 20:272-84.

61. Spirduso WW, Cronin DL. Exercise dose-response effects on quality of life and independent living in older adults. MSSE 2001; 33: S598-S608.

62. Chang JT, Morton SC, Rubenstein LZ, Mojica WA, Maglione M, Suttorp MJ, Roth EA, Shekelle PG. Interventions for the prevention of falls in older adults: Systematic review and meta-analysis of randomized clinical trials. BMJ 2004; 328:680-6.

63. Thompson PD, Buchner D, Pina IL, Balady GJ, Williams MA, Marcus BH, Berra K, Blair S, Costa F, Franklin B, Fletcher GF, Gordon NF, Pate RR, Rodriguez BL, Yancey AK, Wenger N. Exercise and physical activity in the prevention and treatment of artherosclerotic cardiovascular disease: a statement from the Council on Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Actvity). Circulation 2003; 107:3109-16

64. Keysor JJ. Does late-life physical activity or exercise prevent or minimize disablement? Am J Prev Med 2003; 25(suppl 2):129-36.

65. Teri L, Logsdon RG, Uomoto J, McCurry SM. Behavioral treatment of depression in dementia patients: A controlled clinical trial. J Gerontol 1997; 42B,:P159-P166.

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