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Detection and Prevention of Cognitive Decline

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Current diagnostic and treatment strategies for cognitive decline can help patients maintain cognitive ability and higher levels of function longer. Despite advances in detection and early treatment strategies, many patients do not receive proper assessments and available therapies. A systematic assessment strategy will increase the likelihood of an accurate diagnosis, which can facilitate pharmacologic and nonpharmacologic treatment plans that can have a meaningful impact on prognosis. Available data support the integration of healthy lifestyle strategies in the treatment plan to help to stabilize symptoms and potentially delay future cognitive decline. While investigators continue to pursue more effective detection, treatment, and prevention strategies, the scientific data support the use of symptomatic drug treatments and recommendations for healthy lifestyle behaviors to improve quality of life and potentially stave off future cognitive decline. Success of such healthy lifestyle programs involves educating participants on the connection between lifestyle and disease prevention, offering enjoyable exercises that target the patient's skill level, and providing feedback that motivates participants to continue their healthy behaviors so they become habits. (Am J Geriatr Psychiatry 2016; 24:1142–1150)

Key Words: cognitive decline, diagnosis, treatment, prevention

Thanks to advances in medical technology, people are living longer than ever before. Average life expectancy for an individual born in 1900 was less than 50 years. By contrast, those born today are likely to approach their 80th birthday.[1]

Although people are living longer, unfortunately they are not necessarily living better—age is the single greatest risk factor for developing cognitive decline. The risk for developing a major neurocognitive disorder (or dementia) is approximately 10% in people age 65 years and older. In 2011, the oldest of the 76 million Baby Boomers (those born 1946–1964) began to reach their 65th birthday; as they continue to age, their risk for dementia approaches 50% by age 85 years and older.[2] According to the Alzheimer's Association, nearly every 70 seconds another American is diagnosed with Alzheimer dementia. The annual costs to society exceed $200 billion in the United States alone, and these trends

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are expected to continue.[3] The number of Americans suffering from Alzheimer disease—5.4 million—is expected to triple by 2050.[2,4]

In this review, I will describe current methods for detection of cognitive decline and available drug treatments. In addition to pharmacologic interventions, I will discuss healthy behavior strategies that appear to delay the onset and progression of cognitive symptoms and possibly prevent future cognitive decline.

DISCOVERY OF ALZHEIMER DISEASE

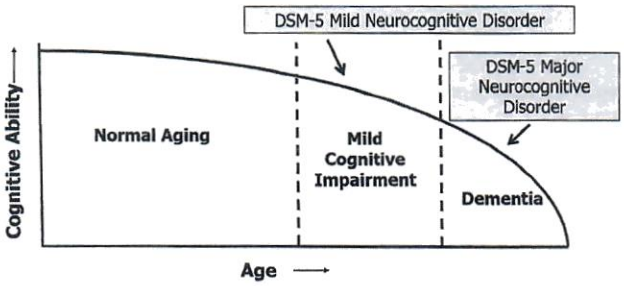
In 1906, Alois Alzheimer presented the first case of the disease to the medical community. The patient developed confusion accompanied by psychosis at age 51.[5] Her cognitive state continued to deteriorate until she died 4 years later. For the first time, Professor Alzheimer demonstrated waxy protein fragments and twisted fibers—amyloid plaques and tau tangles—that define the disease. These abnormal protein deposits were concentrated in brain regions that control memory, reasoning and other cognitive abilities, particularly in the frontal, parietal, and temporal lobes of the brain.

For many years, scientists and doctors assumed that Alzheimer disease was a rare presenile dementia because this initial case occurred in a middle-aged woman. In 1968, however, neuropathologists reported a series of cases of what was then termed "senility."[6] They found the same plaques and tangles in these older cases, which led to the idea that Alzheimer disease had two forms: early-onset and late-onset. The latter group makes up the major proportion of cases, and a new epidemic of Alzheimer disease was recognized. This caused tremendous anxiety among the public, but led to greater scientific focus on developing better methods for detection and treatment of age-related cognitive decline.

CAUSES OF DEMENTIA

With increasing age, plaques and tangles gradually accumulate in the brain, and patients eventually develop cognitive impairments that impair their activities of daily living. Clinicians and investigators often consider three general degrees of cognitive decline: normal aging, mild cognitive impairment (MCI), and dementia (see Figure 1).[7,8] By age 50 years, most people develop normal aging or age-associated memory impairment, which includes such symptoms as forgetting names, misplacing keys or eyeglasses, and other cognitive complaints that do not interfere with daily function. These symptoms may gradually progress to MCI, which involves more severe short-term memory challenges. Patients with MCI (mild neurocognitive disorder according to the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* [DSM-5])[9] are able to compensate for their cognitive symptoms and remain functionally independent. MCI patients with memory issues (amnestic MCI), however, have a 10% risk of developing dementia (major neurocognitive disorder according to DSM-5)[9] within a year. After 5 years, approximately 50% of amnestic MCI patients will develop dementia.[10]

FIGURE 1. A plot of cognitive ability versus age shows the expected gradual decline, which can be categorized into three stages: normal aging, mild cognitive impairment (MCI or DSM-5 mild neurocognitive disorder), and dementia (DSM-5 major neurocognitive disorder). Adapted from Figure 1 in Small et al.[7]



Although Alzheimer disease is the most common cause of dementia, accounting for nearly 70% of cases, many other neurodegenerative, medical, and psychiatric conditions can lead to a dementia syndrome (Table 1). Sometimes treating such conditions as depression or discontinuing medications when cognitive side effects are suspected will improve or even reverse dementia symptoms. Moreover, early treatment of dementia appears to improve patient outcomes;[11] thus, it is important for patients and families to see a professional whenever age-related cognitive symptoms become a concern.

Nevertheless, stigma about diagnosis, nihilism regarding the benefits of treatment, and other factors lead

TABLE 1. Possible Causes of Cognitive Impairment in Older Adults

Alzheimer disease
Vascular disease
Lewy body disease
Parkinson disease
Huntington disease
Frontotemporal lobar degeneration
Head injury
Metabolic/nutritional causes
B_{12}, folate, thiamine deficiencies
Thyroid, hepatic, renal abnormalities
Medications (e.g., anticholinergic drugs, sedatives)
Alcohol
Toxins
Infectious (e.g., HIV, syphilis, meningitis)
Depression
Normal pressure hydrocephalus
Neoplasms
Autoimmune disorders

to diagnostic delays. In fact, only about half of individuals who meet diagnostic criteria for dementia have received a diagnosis from a physician.[12] Because Alzheimer disease is underdiagnosed, an estimated 2.5 million Americans with the condition may not know that they have it.

ASSESSMENT

The strategy for assessment of cognitive impairment involves obtaining an accurate history regarding the nature and course of cognitive complaints. Such histories can help to differentiate different causes. For example, a rapid onset of symptoms might be more consistent with depression or cerebrovascular disease than Alzheimer disease, which is characterized by a gradual onset and progression. Obtaining information from family members and caregivers who know the patient well is critical, and it is helpful for the clinician to spend time separately with each individual during the assessment.

Physical and neurological examinations as well as screening laboratory tests (e.g., complete blood count, thyroid level, B_{12}, folate, metabolic panel) may identify physical illnesses that can cause dementia (e.g., pneumonia, anemia), increase risk for developing dementia (e.g., diabetes, Parkinson disease), or worsen symptoms of Alzheimer disease (e.g., heart disease). A mental status examination can further characterize mental symptoms. Standardized rating instruments (e.g., Mini-Mental State Examination, Montreal Cognitive Assessment, Hamilton Rating Scale for Depression) can further document the degree of cognitive impairment and mood symptoms. Neuropsychological testing may be helpful for patients with unclear clinical presentations (e.g., overlapping mood and cognitive symptoms). Functional assessment is critical to understanding the degree of cognitive impairment and determining a diagnosis (e.g., differentiating MCI from dementia) as well as addressing practical and safety needs of patients and families.

Structural imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) is recommended for all patients undergoing assessment for cognitive impairment in order to identify potentially treatable causes of dementia, such as a tumor or normal pressure hydrocephalus.[7] In 2004, the Centers for Medicare & Medicaid Services (CMS) ruled to provide Medicare funding for positron emission tomography (PET) scanning using fluorodeoxyglucose (FDG) to assist with the differential diagnosis of frontotemporal and Alzheimer dementia.[13] Brain FDG-PET scans show regional glucose metabolic brain function, and patients with Alzheimer dementia demonstrate hypometabolism in the parietal, temporal, and frontal regions, which differs from the temporal and frontal hypometabolic pattern observed in patients with frontotemporal dementia.[7]

In recent years, scientists have developed PET scan technology using ligands that measure amyloid and tau in the brain, and the U.S. Food and Drug Administration (FDA) has cleared several of these technologies for clinical use.[8] CMS, however, determined that the evidence was insufficient to conclude that the use of amyloid-PET is reasonable and necessary for diagnosis or treatment for Medicare beneficiaries with dementia or neurodegenerative disease.[14] The agency did conclude that there was sufficient evidence that the use of amyloid-PET is promising for excluding Alzheimer disease for narrowly defined and clinically difficult differential diagnoses, such as Alzheimer disease versus frontotemporal dementia, and for enriching clinical trials seeking better treatments or prevention strategies for Alzheimer disease. Thus, CMS will cover one amyloid-PET scan per patient in certain clinical studies (e.g., those designed to develop better treatments or prevention strategies for Alzheimer disease or to resolve clinically difficult differential diagnoses).

GENETIC CONSIDERATIONS

In rare families that demonstrate autosomal inheritance patterns of Alzheimer disease (i.e., 50% of relatives eventually develop the disease), a genetic mutation on chromosomes 1 or 14 (presenilin) or chromosome 21 (amyloid precursor protein) causes the disease.[15,16] In such rare cases, genetic counseling can be helpful in guiding family members about whether to pursue genetic testing.

For most people, a genetic cause is not present but a variant (i.e., allele) of a common gene on chromosome 19 (apolipoprotein E-4 [APOE-4]) will increase the risk for Alzheimer disease. Approximately 20% of the population carries the APOE-4 allele, which is neither necessary nor sufficient to develop the disease. APOE testing is not recommended as a predictive test, and recent research indicates that revealing results of APOE-4 carrier status to nondemented individuals leads to poorer performance on neuropsychological testing compared with APOE-4 carriers who are not informed of their genetic status.[17]

BIOMARKER PREDICTION OF DEMENTIA

Several imaging and other biomarkers have been studied to determine their predictive value in people at risk for dementia. In addition to the clinical use of structural (CT and MRI) scans and FDG-PET scans, quantitative regional brain structures, functional MRI, diffusion tensor imaging, magnetic and resonance spectroscopy have been assessed, as well as cerebrospinal fluid concentrations of proteins associated with Alzheimer disease, olfactory identification tests, and other measures.[7,18,19]

The positive predictive value of these various measures will vary depending on the methods of each study, and limited data are available on the utility of these biomarkers for individuals in daily clinical use. There is ongoing debate among experts about whether such biomarkers in development provide added value beyond the standard clinical assessment, in part because data are derived from select subject groups and results may not apply to general populations. Whenever pursuing any test or procedure, it is important to consider the available evidence as to whether the results of that test will improve diagnostic accuracy and/or alter treatment planning.

SHARING DIAGNOSTIC FINDINGS WITH PATIENTS AND FAMILIES

Disclosing the diagnosis of Alzheimer disease to patients and family members can be beneficial, although variability in understanding diagnostic information can pose challenges—especially in situations of diagnostic ambiguity.[20] When discussing results, including family members or others likely to provide care can help facilitate the process and clarify misunderstandings about the diagnosis and prognosis. How clinicians share results of the assessment and reveal the diagnostic findings can have an important impact on families. Many people are frightened about the implications of a diagnosis and confused about the terminology. The process takes times and requires attention to these concerns and anxieties.[21]

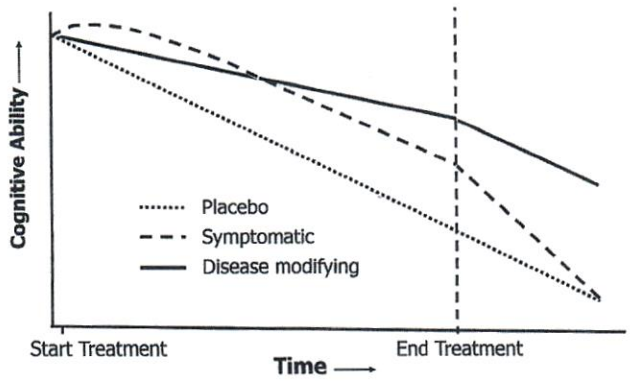
Finding a private and quiet location and scheduling ample time for the feedback visit(s) is essential. Also, the clinician needs to determine the family's specific concerns and understanding of the disease and meaning of the test results. Clear explanations about the definitions of terms, implications and limitation of test results, and providing realistic expectations about the future are essential. These discussions also lead to conversations about available treatment strategies and those under development.

MEDICATION TREATMENT

For patients with Alzheimer dementia, several medications provide modest symptomatic benefits.[8] The FDA has cleared four cholinesterase inhibitors (tacrine [Cognex], donepezil [Aricept], rivastigmine [Exelon], and galantamine [Razadyne]) and one *N*-methyl d-aspartate–receptor antagonist (memantine [Namenda]) for the treatment of Alzheimer disease. These medications have demonstrated benefits for cognition, behavior, and function, but their modest effect sizes and temporary benefits leave room for improvement. Because of the side effects and dosing requirement of tacrine, it is rarely used today.

When prescribing these symptomatic treatments, it is important to first describe their potential benefits and

FIGURE 2. Plot of level of cognitive impairment versus time indicates the predicted cognitive impairment trajectories of Alzheimer's disease patients treated with placebo, symptomatic, or hypothesized disease-modifying drug treatments.



side effects. It is helpful to inform families that not all patients will experience improvement in their cognitive symptoms when taking the medicines, but as long as they tolerate the treatment, remaining on the medication will keep patients at a higher level of functioning for a longer period of time. Eventually, symptoms of the disease worsen, but discontinuing medication too early will lead to a more rapid decline in cognition and function (Figure 2). When patients and families are informed of realistic medication results, they are more likely to adhere to treatment recommendations.

Although some clinicians and experts have expressed concern about the modest clinical benefits of available symptomatic treatments for dementia, meta-analyses of cholinesterase inhibitor clinical trial data indicate small to moderate effect sizes ranging from 0.03 to 0.78, depending on the medication dose and method of treatment and data analysis.[22] A comparison of the cholinesterase inhibitor donepezil for the outcome of loss of activities of daily living to a common geriatric treatment (angiotensin-converting enzyme [ACE] inhibitor) for the outcome of death in congestive heart failure indicated that the number needed-to-treat for 1 year of donepezil treatment was three, and the number needed-to-treat for 1 year of ACE treatment was six.[23]

Comparisons of expected outcomes from the commonly used symptomatic drug treatments to placebo (Figure 2) indicate that the symptomatic treatments do not change the slope of cognitive decline. Recent research has focused on developing disease-modifying treatments, which would be expected to decrease the slope of cognitive decline and provide sustained benefits if the treatment were withdrawn.

Much of the research on disease-modifying drug development has focused on clearing amyloid plaques from the brain. Other disease mechanisms have been pursued as well, including anti-tau treatments, anti-inflammatory interventions, insulin-nasal spray, and statin drug treatments. To date, these treatment studies have failed to uncover an effective disease-modifying intervention.[8] Patients and family members appreciate when their clinician can offer a realistic perspective about new investigational treatments when they are discussed.

BRAIN HEALTHY LIFESTYLE STRATEGIES ASSOCIATED WITH A LOWER RISK FOR DEMENTIA

Genetics account for only part of the risk for cognitive decline, which means that nongenetic factors have a greater impact on brain health than previously appreciated.[24–26] Recent research in this area of modifiable risk factors for dementia has yielded compelling results, and clinicians are already beginning to encourage their patients to alter their behaviors to reduce their future risk for cognitive decline. The following include some of the strategies that appear to impact brain health as people age.

Physical Exercise

Animal and human studies indicate that physical exercise not only improves mood and memory, but also increases brain size.[25] Investigators at the University of Illinois studied older volunteers who began a brisk walking program and compared them with a control group that did stretching and toning exercises.[27] Brain MRI scans showed that after 6 and 12 months, hippocampal volume was significantly greater in the walkers compared with stretchers and toners. Aerobic conditioning increases levels of brain-derived neurotrophic factor, or BDNF, which repairs damaged neurons and stimulates healthy branching of neuronal dendrites. In addition, high blood levels of BDNF are associated with a lower risk for developing Alzheimer disease. Studies of strength training indicate

additional benefits perhaps beyond aerobic workouts. Investigators at the University of British Columbia demonstrated memory benefits in women with MCI after 6 months of strength training.[28] For older adults, balance training is helpful in steadying gait and preventing falls that can impair cognitive functioning through head trauma and mental morbidities associated with other injuries.

Mental Stimulation

People who engage in mentally stimulating activities, such as reading, doing puzzles, going to school, or playing board games, have a lower risk for cognitive decline. Functional MRI studies show that Internet searching and learning and recall tasks activate and potentially strengthen neural circuits.[29]

In addition to the general benefits of mental stimulation, cognitive training helps people with normal aging to compensate for their cognitive challenges. In the ACTIVE (Advanced Cognitive Training in Vital Elderly) study,[30] nearly 3,000 older volunteers were randomized into four groups: three with focused training in memory, reasoning, or speed-of-processing, and the fourth a control group. Group training was provided over 5–6 weeks. The benefits were specific to the type of training and several cognitive gains were still apparent after 5 and 10 years of follow-up.[30]

Many of these memory training methods involve teaching people to focus attention on what they want to learn and to use visual images and associations for better recall. When people with mild memory complaints can make information personally meaningful, the experiences become more memorable.

Stress Reduction

Animal studies indicate that chronic stress impairs memory and leads to hippocampal atrophy.[31] Some neuroscientists conclude that stress hormones may be damaging the brain by increasing a chronic inflammatory response. People prone to stress are at greater risk for cognitive decline, and human volunteers injected with the stress hormone cortisol will experience memory decline. Fortunately, such cognitive impairment resolves after cortisol levels return to normal.

Meditation, tai chi chih, yoga, deep breathing, or other relaxation exercises can improve mood as well as memory abilities. In a functional MRI study of the effect of yoga on cognitive decline and resting-state functional connectivity, Eyre and co-workers[32] found that yoga improved symptoms of depression as well as visuospatial memory. Moreover, verbal memory improvements correlated with increased neural connectivity.

An effective way to reduce stress and bolster brain health is to ensure adequate sleep.[33] Memories consolidate during sleep, which improves recall abilities the next day. Poor sleep is associated with worse cognitive ability, and longer sleep latency is correlated with greater amyloid-β burden in the prefrontal cortex.[34] Strategies for better sleep include an active lifestyle, cognitive behavioral therapy, and relaxation techniques. In a study comparing the effects of cognitive behavioral therapy, tai chi chih, and a sleep seminar education control, Irwin and associates[35] found that cognitive behavioral therapy performed better than the other interventions in remission of clinical insomnia and also showed greater and more sustained improvement in sleep quality, sleep parameters, fatigue, and depressive symptoms.

Remaining socially active in the later years further reduces stress and promotes healthy brain aging. A stimulating conversation will increase memory performance and mental speed.[36] Talking with an empathic friend can lower stress and further protect brain cells. Social support provides practical assistance that improves health and longevity, and stronger social networks are associated with longer life expectancy.[37]

Nutrition

Nutrition has an important impact on age-related cognitive ability.[38] Brain-healthy diets emphasize anti-inflammatory omega-3 fats from fish, nuts, and flaxseed, as well as antioxidant fruits and vegetables. Moreover, high glycemic index carbohydrates, processed foods, and refined sugars are de-emphasized.

Mediterranean-style diets are not only heart-healthy but brain-healthy as well. Investigators at Rush University Medical Center in Chicago, Illinois, devised a diet that combines a Mediterranean-style diet with the Dietary Approach to Systolic Hypertension (or DASH) diet. The combined diet is called the Mediterranean-DASH Intervention for Neurodegenerative Delay, or MIND diet, which focuses on neuroprotective dietary elements.[39] This diet emphasizes beans, fruits, vegetables, nuts, olive oil, poultry, whole grains, and fish,

and minimizes butter, cheese, margarine, fast or fried foods, pastries, and sweets. In a recent 5-year study[39] of over 900 older volunteers, the investigators found that adherence to the MIND diet significantly slowed cognitive decline equivalent to a 7.5-year younger brain age.

A major challenge is to help people achieve their ideal body weight, because midlife overweight or obesity increase the risk for late-life dementia.[40] Studies of obese volunteers who lose weight indicate that their cognitive abilities improve. A prospective study of 150 obese subjects (109 bariatric surgery patients enrolled in the Longitudinal Assessment of Bariatric Surgery project and 41 controls who had not undergone bariatric surgery) indicated that the surgery patients were less likely to exhibit a decline on two or more cognitive tests after 3 months than were obese controls.[41] Such cognitive benefits continued following 3 years of follow-up.[42]

Weight loss from gastric bypass surgery may result from fewer absorbed calories, but also from a change in the balance of intestinal bacteria.[43] Some gastrointestinal bacteria increase fat metabolism; thus, future novel treatments may be designed to increase the proportion of gut bacteria that metabolize fat and potentially improve cognition without the need for a surgical intervention.

Moderation in portions is a theme of several brain healthy nutritional strategies. For example, moderate consumption of alcohol[44] or caffeinated beverages[45] is associated with better brain health and cognitive abilities.

COMBINING HEALTHY LIFESTYLE STRATEGIES

Our research group has conducted several studies supporting the cognitive benefits of combining brain-healthy lifestyle strategies. A short-term healthy lifestyle program combining mental and physical exercise, stress reduction, and healthy diet was associated with significant effects on cognitive function and brain metabolism.[46] We also found that a 6-week healthy lifestyle program can improve both encoding and recalling of new verbal information, as well as self-perception of memory ability in older adults residing in continuing care retirement communities.[47]

In collaboration with Gallup Poll and Healthways investigators, we obtained data on memory problems and healthy behaviors in a representative sample of 18,552 respondents across the United States, ranging in age from 18 to 99 years.[48] Reports of memory problems were inversely related to the Healthy Behavior Index, which is a measure of smoking, eating, and exercise habits. These results further support the benefit of lifestyle behavior habits for protecting brain health and possibly delaying the onset of memory symptoms as people age.

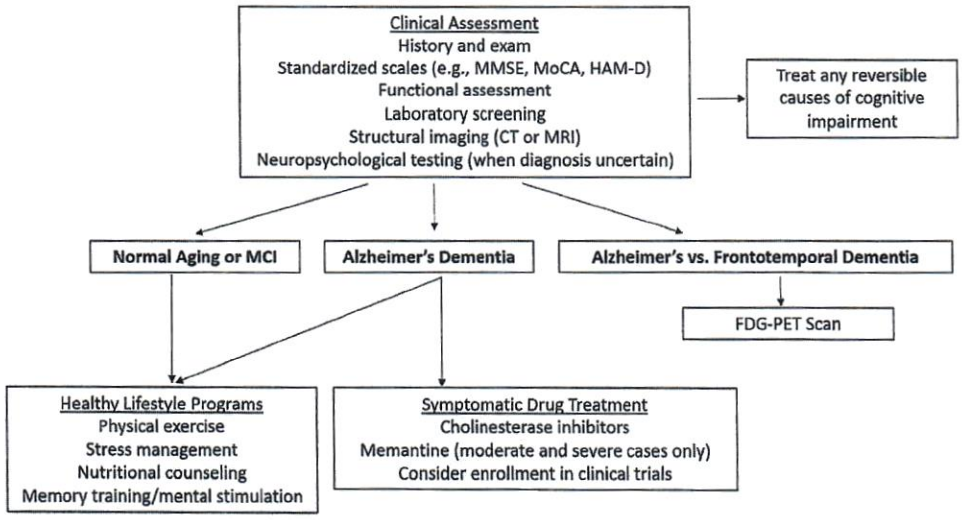
Evidence points to several potentially modifiable risk factors for Alzheimer disease, including diabetes, midlife hypertension, midlife obesity, smoking, depression, cognitive inactivity or low educational attainment, and physical inactivity. Barnes and Yaffe[49] have projected the effect of risk factor reduction on prevalence of the disease by calculating the percent of cases attributable to a given factor and the number of potentially preventable cases by risk factor reductions. They concluded that up to half of Alzheimer disease cases are potentially attributable to such modifiable risk factors.

The effect sizes of these strategies vary depending on the intervention and study methods. For example, a previous meta-analysis demonstrated overall mean effect sizes between physical exercise and non-exercise groups for all outcomes was 0.62 (95% confidence interval: 0.55–0.70).[50] Long-term effect sizes for cognitive training in the ACTIVE study varied depending on the form of training, ranging from 0.23 for memory to 0.76 for speed of processing, and the latter increased to 0.85 when booster training was included.[51]

CONCLUSIONS

A systematic assessment and diagnostic approach to cognitive decline will help to pinpoint treatable conditions and increase diagnostic accuracy. With an accurate diagnosis, clinicians can then proceed to devising a treatment plan that includes both pharmacologic and nonpharmacologic interventions that can have a meaningful impact on prognosis (Figure 3). Integrating healthy lifestyle strategies in the treatment plan may stabilize current symptoms and potentially delay the onset of future cognitive decline. Healthy lifestyle programs are more effective when

FIGURE 3. Summary of diagnostic and treatment strategies.
Notes: **CT: computed tomography; FDG-PET: flurodeoxyglucose-positron emission tomography; HAM-D: Hamilton Rating Scale for Depression; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; MRI: magnetic resonance imaging.**



they educate participants on the connection between lifestyle and disease prevention; provide a fun and easy method to complete the exercises; and offer feedback to motivate participants to continue healthy behaviors so they become habits.

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The University of California, Los Angeles, owns a U.S. patent (6,274,119) titled "Methods for Labeling ß-Amyloid Plaques and Neurofibrillary Tangles"; this has been licensed to TauMark, LLC. Dr. Small is among the inventors and is a co-founder of TauMark, LLC. Dr. Small also reports having served as an advisor to and/or having received lecture fees from Allergan, Axovant, Cogniciti, Forest Laboratories, Forum Pharmaceuticals, Herbalife, Janssen, Lilly, Novartis, Otsuka, and Pfizer.

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