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Prevention of Dementia

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IA. Dementia

Dementia is a neurological condition that results in decline in multiple cognitive domains and is accompanied by a functional impairment. Individuals eventually lose their independence and will be unable to perform typical activities of daily living. Dementia is generally characterized by a decline in memory and at least one other cognitive function, and these difficulties are of sufficient magnitude to compromise daily function. Dementia if often the umbrella term under which there are several subcategories. Alzheimer's disease (AD) is the most common form of dementia in aging and is a degenerative disorder [1, 2]. The pathological hallmarks of AD include the deposition of amyloid in the brain producing amyloid plaques and the extracellular amyloid plaques in accompaniment with the intracellular misprocessed tau protein producing neurofibrillary tangles [3, 4].

Alzheimer's disease was first described in 1906 by Alois Alzheimer, and his index case was a 51-year-old woman with memory loss, behavioral difficulties and language problems. She ultimately progressed to death, and her autopsy revealed what are now called the beta-amyloid plaques and neurofibrillary tangles.

At present, AD can only be characterized definitively at the time of autopsy. However, a great deal of research is being conducted to define biomarkers characteristic of the underlying pathological process that can be identified in life [3, 5] [6]. It is not uncommon, especially in late life, to have the changes of AD accompanied by other neuropathologies such as concomitant Lewy bodies and vascular disease [3]. Currently, the neuropathological changes seen at the time of autopsy need to be accompanied by the clinical progression producing a dementia [7–9]. In the future, the clinical spectrum leading to the dementia of AD and the pathological spectrum may be separated to allow a more complete characterization of each continuum.

Currently, the cognitive decline associated with AD likely has a prodromal phase whereby individuals are affected by the underlying neuropathologic process, but the clinical manifestation does not reach the threshold for dementia. The construct of mild cognitive

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impairment (MCI) has come to represent this symptomatic pre-dementia stage of the Alzheimer process [10–14]. Mild cognitive impairment typically represents memory impairment beyond what one would expect for age, yet other cognitive processes and daily function are relatively well preserved. There has been an increase in literature accumulating on MCI over the last decade, and this research will likely influence future direction of the characterization of Alzheimer's disease.

Vascular cognitive impairment also represents a continuum from mild impairment through the fully developed dementia phase of vascular disease [15–18]. The prevalence of pure vascular disease producing dementia is relatively low, but the combination of vascular disease and neuropathological entities is quite common. The cognitive profile of vascular cognitive impairment can be quite variable, depending upon the specific location of the ischemic lesions. In general, there is more executive dysfunction from frontal lobe involvement of vascular disease, and gait disorder and urinary incontinence occur earlier in the dementing process than they do in AD [17, 19].

Dementia associated with Lewy bodies is also becoming increasingly well recognized. Individuals with this type of dementing disorder have features of parkinsonism, dream enactment behavior, daytime hallucinations, fluctuating cognition and behavior, and may have a somewhat different cognitive profile than AD [20–22]. Typically, in the early features of dementia with Lewy bodies, an individual may exhibit diminished speed of cognitive processing and visuospatial deficits early in the course. The extrapyramidal features are somewhat similar to parkinsonism, and a tremor is less common [22–24]. The combination of Lewy bodies and Alzheimer changes is quite common, and the overlap of the two diseases is well recognized [20–22].

Parkinson's disease in its advanced stages may be accompanied by cognitive and memory problems and, in many respects, share much of the neuropathologic features of dementia with Lewy bodies. The distinction between Parkinson's disease, dementia and dementia with Lewy bodies tends to revolve around the timing of the onset of the motor and cognitive symptoms. If these clinical features manifest themselves within approximately 12 months in duration, the picture is more likely associated with dementia with Lewy bodies. In Parkinson's disease dementia, the dementia occurs years after the onset of the parkinsonian motor features [25].

Frontotemporal lobar dementia (FTLD) is a degenerative disorder primarily involving the frontal and temporal lobes [19, 26–28]. These individuals present with early behavioral changes such as inappropriate behavior, apathy or hyperactive behavioral disorders constituting the behavioral variant of FTLD [29]. There are also language presentations of FTLD that present with primary progressive aphasia [30, 31]. This is a neurodegenerative disorder often with abnormalities in the tau protein [27].

The combination of these disorders is common aging and presents a significant problem for aging societies around the world. At present, there is a great deal of research going forward trying to understand the underlying nature of these disorders with the intention of developing disease modifying treatments. Many pharmacologic approaches are being

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entertained as well as the assessment of lifestyle factors. This review will address this literature.

IB. Prevalence of dementia/Alzheimer's disease

The prevalence of a dementia refers to the number of events, in this instance dementia, in a given population at a designated point in time. The incidence of the disease is defined as the number of new cases of a given disease during a defined period of time in a specified population [32]. The incidence of dementia has been reported to be 34.2 per 100,000 person-years for all dementias and 5–8 per 1000 person-years for AD [33–37]. These data would imply that there are 10–15 new cases of dementia for every 1000 persons in the population during one year, and more than half of these cases are due to AD. In the United States, 14% of all people age 71 years and older have some form of dementia. The Alzheimer's Association estimates that there are 5.3 million Americans who currently have Alzheimer's disease [1, 38, 39]. Approximately 10 to 13% of individuals over age 65 have AD, and age is the most prominent risk factor for AD, such that, by the time people reach their mid 80s, they have a 1 in 3 chance of having Alzheimer's disease. The risk of Alzheimer's disease doubles every five years after 65 years of age. In general, many studies indicate that there are more woman than men with AD, largely due to the greater longevity for women. When age adjustments are used, there does not appear to be a significant age effect with regard to the trends in AD over the past several decades [2] [37, 40, 41]. The Framingham study has calculated life-time risks of AD in the general population, and the risk of having AD was higher for women then men (about 17 versus 9%, respectively) and increased with age [2]. The projection for the number of cases of dementia and AD in the coming years is staggering and speaks to the importance of continued research with the development of therapeutic interventions. The worldwide prevalence of AD in 2010 was estimated to be 35.6 million and likely increasing to more than 65 million by the year 2030[42].

II. Prevention

Prevention can be considered as all actions that are performed to eradicate, eliminate or minimize the impact of an event. In medical science, this event is usually a disease or disability. When none of the approaches to prevention are effective, a secondary goal of delaying or reducing the frequency of the disease or reducing disability can be entertained. Typically, prevention in medical science can be defined as levels of prevention: primary, secondary and tertiary [32, 43].

Primary prevention refers to the efforts in public health to prevent the disease before symptom onset. True prevention would mean that the disease would never manifest itself later in life. In many respects, prevention may not be a realistic outcome, but can serve as a goal with intermediate targets being delay of onset or slowing of progression [44]. In neurodegenerative diseases, these actions would be performed to prevent the symptomatic phase and reduce the risk of disease. Medications and lifestyle factors are currently being investigated to determine their effectiveness at preventing disease onset.

Secondary prevention refers to the reduction or cessation of symptom progression once the symptoms have appeared. Again, the goal is to reduce the disability of the disease once the

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disease process has begun. In degenerative dementias, the secondary prevention stage might apply to the phase of MCI since, at this point, symptoms are present but are not sufficiently severe to constitute dementia. Therefore, treatment trials aimed at subjects with MCI could be considered secondary prevention studies.

Tertiary prevention refers to a treatment designed to halt the progression of the disease once it has been established. The goal, again, is to reduce the disability and improve the long-term prognosis for individuals with the manifest disease. Currently, in degenerative diseases, tertiary prevention would maintain an individual in an impaired state yet is worth pursuing.

Implicit in the discussion of, in particular, primary and secondary prevention, includes the concept of biomarkers. That is, since the disease process has not manifested itself clinically, such as in primary prevention, the clinical signals are absent. As such, the field needs to develop biomarkers as surrogates of the underlying disease process to allow the impact of the prevention [45, 46]. Clearly, reducing the likelihood that a person would progress to the symptomatic stage such as that seen in secondary and tertiary prevention studies would be a laudable goal, but biomarkers would be quite useful in characterizing the effects on the underlying disease process. When dealing with an underlying continuum of clinical progression and pathologic processes, these distinctions among primary, secondary and tertiary prevention are somewhat arbitrary.

This approach to prevention has been questioned in previous years. Geoffrey Rose supports the theory that current prevention is reductionistic and that a more efficacious strategy would be to act on the early causes of the disease in an entire population, appreciating the so-called, prevention paradox [43, 47]. The paradox is present the measure that produces a benefit to a subset of the population may offer little benefit to the overall population. For example, reducing cigarette smoking will likely improve the quality of life of some individuals but have no effect on others. Yet, the elimination of cigarette smoking is an example of prevention.

A challenge in the field of neurodegenerative diseases concerns the timing of the putative prevention strategy. That is, when potentially effective therapies are initiated too late in the underlying disease process, even in the asymptomatic stage, the true impact of prevention may not be appreciated. However, if one were to initiate therapies earlier in life, the overall effect of the prevention might be more appropriately realized. This is a theoretical dilemma since many studies that involve pure prevention would need to be initiated early in the lives of individuals, and the studies would need to continue for many years. As such, many investigators are choosing to address the disease in the secondary prevention stage, e.g., MCI, in an effort to exert some type of a disease-modifying effect on the underlying pathology.

This can be applied to the degenerative process of Parkinson’s disease. Currently, it is believed that Parkinson’s disease begins 20 to 30 years before the motor manifestations are apparent, and the disease spreads gradually [48, 49]. Tremor, bradykinesia and rigidity are the hallmarks of Parkinson’s disease, but they may not become manifest until many years after the degenerative process was initiated [48, 50]. At times, there are subtle symptoms

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such as constipation [51, 52], anosmia [53], anxiety [54, 55], autonomic dysfunction or sleep disturbances [56] that may appear decades before the classic motor symptoms, but they are likely indices of the onset of the degenerative process. Therefore, in this case, primary preventions start very early in life rather than close to the time of symptom onset.

One can imagine a similar problem in dementing disorders where true primary prevention would need to be initiated very early in life. Most investigators believe that the neuropathological process that characterizes AD begins years if not decades before clinical symptoms appear. This may be true for MCI as well insofar as the MCI stage is accompanied by significant pathology when it is described [57]. Once again, this speaks for the utility of biomarkers as assessing early stages of the disease process.

In summary, while true prevention is an ideal goal, intermediary targets such as delaying the onset and slowing the progression of the degenerative process might be more reasonable. As such, numerous studies have been performed and others are planned aimed at altering the trajectory of the clinical symptoms that constitute the onset of the disorder. A postponement in the onset of the clinical symptoms would have a significant impact on individuals and families as well as the healthcare in society. Similarly, reducing the rate of progression of the disease, even though the symptoms are present, will have a significant impact on improving the quality of life of the individuals, their families and will reduce the costs to healthcare systems. Therefore, numerous strategies are being investigated with the goal of altering the trajectory of the clinical course and the underlying pathology.

III. Pharmacological approaches

A. Acetylcholinesterase inhibitors

There is a reduction in the cholinergic system in the brains of patients with AD [58]. Acetylcholinesterase is the enzyme that breaks down acetylcholine, and the inhibition of this enzyme can help to increase cholinergic activity. There are currently three drugs that have been approved for the treatment of AD that are cholinesterase inhibitors: donepezil, rivastigmine and galantamine. In general, these three compounds have similar efficacy and are approved for either mild to moderate AD or the entire AD spectrum. The drugs have a modest effect at improving symptoms in the disease but can be useful in individual patients. The compounds have similar side effect profiles, largely increasing gastrointestinal system motility, but generally are well tolerated. However, none of these drugs delays the ultimate underlying progression of the AD process [59]. When these drugs were used in secondary prevention studies, particularly in MCI, none of them was demonstrated to reduce the rate at which individuals progressed to the dementia stage of AD [59–63]. One study involving donepezil and high-dose vitamin E demonstrated that donepezil was shown to reduce the risk of progressing from MCI to AD for 12 months in all subjects and up to 24 months in subjects who were apolipoprotein E4 carriers [63]. However, over the 36-month duration of the study, none of the interventions was documented to be effective.

B. NMDA antagonists

The NMDA antagonists have been studied in AD and have been improved for the treatment of moderate to severe AD [64, 65]. Memantine is the only approved drug at this time in the

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United States, and it acts on the glutamate receptors. If NMDA receptors are up regulated, the release of glutamate leads to neuronal toxicity and neuronal damage. NMDA receptors are thought to play a role in the pathologic cascade of AD, and NMDA antagonists may act as neuroprotectors, preventing this cascade [65]. There have not been any trials that have demonstrated that memantine is effective at reducing the risk of developing either MCI or AD [66]. Some studies have shown that the combination of memantine with an acetylcholinesterase inhibitor may improve functional abilities [67], but again, even the combination has not been shown to have a disease modifying effect on the underlying pathologic process.

All four of these drugs have been approved for symptomatic treatment of the dementia phase of AD, but none has been demonstrated to alter the disease process itself. Therefore, while somewhat useful in treating individuals with AD, these compounds do not appear to have any effect on prevention of the symptomatic phase of AD [59].

C. Vitamins

Numerous studies have been conducted concerning the possible protective role of vitamins in treating or preventing dementia [68]. Many vitamins are considered to be antioxidant agents that may prevent or reduce the oxidative stress that has been described as part of the neuronal degeneration [69, 70]. The biochemical cascade that starts in the brain during AD leads to the increase of oxygen-free radicals and reactive oxygen species (ROS)[71]. Several different components of the neurodegenerative cascade may contribute to generating ROS; furthermore, the tissue injury itself can produce these compounds [72–74]. In order to retard this mechanism, the use of antioxidants was a reasonable strategy to treat AD and cognitive decline [71]. Various vitamins including B-12, folate [75–79], B-6, B-3[78], vitamin E and others have been extensively investigated; however, the studies do not show consistent results in the reduction of AD or cognitive decline. Most studies have used the fully developed dementia of AD and followed the cohort for variable periods of time to see if there was a reduced risk of progression in AD. The measurement of the vitamins was performed either directly by pill counts or by blood sample tests or, occasionally, inferred from responses to food questionnaires.

Some preliminary evidence indicated that low folate levels may be associated with an increased risk of AD [75, 79]. One study reported a possible reduced risk of AD in a population that used the high intake of folate [73]; however, these results were not confirmed in another study [76]. There is a good deal of methodological variability in these studies, and consequently, the relation between B-12 and AD was uncertain (recent study). A higher intake of Niacin (B-3) was suggested to reduce the risk of AD in one study; however, these findings have not been replicated subsequently [78]. Other studies have suggested the possible reduction in the risk of AD or cognitive decline with the use of vitamin C, vitamin E or the combination of them [73, 80–85]. However, once again, there have not been consistent results from these. As mentioned above, in one study comparing donepezil and vitamin E in the MCI stage of the disease process, no benefit of vitamin E was determined to slow the rate of progression from MCI to AD [86]. However, another study by the same group did show that vitamin E might be effective at slowing the rate of

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progression in the fully developed dementia phase of AD [87]; these findings were also recently confirmed by some other authors [88]. There has been some discrepancy between studies that have used supplemental vitamin E and vitamin E in dietary intake, indicating that the latter may be preferable.

Therefore, although experimental and laboratory models suggest that the oxidative cascade may play a role in AD, the currently clinical trials do not provide strong support for the role of vitamins in reducing the risk of dementia or its prodromal phases. Once again, however, the time of intervention may be critical insofar as perhaps the reduction of ROS at an earlier point in life may be beneficial rather than waiting until symptoms appear.

IV. Physical activity

Physical activity has been associated with a reduced risk of developing cognitive disorders and mental diseases (ANN of General Psychiatry). Several observational studies have reported that people who are physically active were at lower risk of developing cognitive impairment or AD later in life [89–95]. Abott and colleagues observed that men who walk for at least two miles per day were less likely to develop dementia over a six-year period [89]. These findings were confirmed in the Nurses' Health Study that showed that increased physical activity was associated with higher cognitive scores [96]. Subsequent prospective studies have supported the role of physical activity in protecting against AD and cognitive decline [89, 90, 93, 94, 97–101]. Most of these studies use physical exercise in self-reported questionnaires of frequency of these activities, such as swimming, hiking and running. There was a reduction of risk of AD in those subjects who exercised regularly as opposed to those people who did not exercise on a routine bases [90]; moreover, these authors reported that the protective effective was increased as the number of activities increased; i.e., the risk was lower when four activities were performed as opposed to fewer. In addition, the protective effect of physical exercise in dementia or cognitive decline was also present when exercise was limited to later in life.

There have also been a number of clinical trials involving physical exercise. In the Fitness for Aging Brain Study, individuals older than 50 years of age were randomly allocated to 24 weeks of physical exercise or to an educational program [102]. The subjects in the exercise group had better cognitive scores compared to the subjects in the educational program over the 18 months of followup [102]. The mechanism by which physical activity may improve cognition in older subjects is unknown [103], but a study involving transgenic mice indicated that exercise may increase the metabolism of the amyloid beta protein and actually reduce its deposition in animals predisposed to Alzheimer's-like lesions in the brain [104]. It is possible that physical activity increases synaptogenesis, plasticity and neural response to stress through the induction of endorphins, brain derived growth factor, insulin-like growth factors and vascular endothelial growth factor [105–108]. Another proposed mechanism includes the possible stimulation of angiogenesis and brain perfusion [109]. Colcombe demonstrated that, in humans, physical exercise increases blood perfusion of brain regions that modulate attention [110, 111].

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There is a prominent body of research demonstrating possible positive effect of exercise in aging. One of the major aims of physical exercise is to decrease morbidity and mortality and increase the quality of life in individuals. Spirduso and colleagues reviewed the literature on this topic and demonstrated that physical activity is consistently associated with a better quality of life [112]. Higher physical activity increased independence and improved activities of daily living.

An impressive study on the role of physical activity and cognitive function in older adults has recently been reported from Australia [102]. This study was a randomized control trial of 24-week physical activity intervention conducted on individuals who reported memory problems but did not meet criteria for dementia. This was a double blinded study, and participants were randomly assigned to an education or usual care group for a 24-week home-based program of physical activity. An intent-to-treat analysis reveals that the intervention group improved over the usual care group on a typical scale used in AD clinical trials, the Alzheimer's Disease Assessment Scale – Cognitive Subscale. At 18 months, the participants in the intervention group improved on the scale to a greater extent than those in the usual care group. This study demonstrated that, in subjects with a subjective memory impairment, a six-month program of physical activity provided modest improvement in cognition over 18 months.

The National Institute on Aging encourages the role of exercise to prevent diseases, to maximize independence and improve mobility while reducing depression. The National Institute on Aging suggests exercise programs such as 30 minutes of endurance activity, strength exercises, exercise to improve balance and stretching exercises. They encouraged participation in these activities on a regular basis to promote quality of life [113].

V. Intellectual activities

Several recent studies have suggested that there is a positive association between intellectual activity and reduction of the risk for cognitive decline or AD [92, 93, 114–120]. The Seattle Longitudinal Study explored a possible link between higher intellectual activities in AD [121, 122]. The Seattle Longitudinal Study included over 5000 subjects in 1956 and followed them for more than four decades. The study found that higher levels of intellectual activities and an intellectually stimulating environment may reduce the risk of cognitive decline later in life, and suggested that reducing mental activities might be a risk factor for subsequent cognitive decline. In addition, several studies have documented the role of higher education in reducing a risk for cognitive decline in AD, and numerous observational studies have also supported this contention [33, 117–120, 123–128].

A systematic review of the literature indicated that there are several good quality studies associated education and risk for AD [129]. These authors concluded that a lower level of education increases the risk of having AD by approximately 30% [129]. In addition, some studies explored the possible role of higher education in subjects who were carriers of the apolipoprotein E4 allele, but these studies have often showed inconsistent results [130–132]. Higher education may be a protective factor but may also be related to higher

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socioeconomic status and perhaps a healthier lifestyle, so the association may not be straightforward.

There is also the construct of cognitive reserve, indicating that individuals with higher education may be able to compensate for a considerable neuropathological burden and may be able to postpone the diagnosis for a greater period of time [133, 134]. However, when these individuals eventually reach the stage of dementia, their cognitive decline may be more precipitous [135]. A recent neuropathological study suggested that the education does provide an element of reserve such that the clinical expression of cognitive impairment was delayed [136]. Therefore, education and/or cognitively stimulating activities may be somewhat protective against cognitive decline and dementia later in life [136].

VI. Cognitive training

Mental exercise and training have been described as a possible strategy to increased so-called “brain reserve” later in life [137]. Several clinical trials have been performed to assess the role of cognitive training in delaying or even preventing subsequent cognitive decline. [138–143]. The ACTIVE study has been influential in defining the role of cognitive training. This trial investigated the effect of ten weekly sessions of cognitive exercises on 2,832 elderly individuals using four tasks: memory, reasoning, processing and wait-and-see controls. After five years of followup, this study demonstrated that specific mental activities can produce benefits not only on cognitive performance but also on instrumental activities of daily living [139, 140, 144]. The reasoning task was reasonably protective against decline in instrumental activities of daily living.

Moreover, some studies have assessed the complex relationship between cognitive training and quality of life and depression. One study showed that cognitive training was more helpful at maintaining mood rather than enhancing cognitive abilities [145]. Apparently, the SMART trial demonstrated that progressively increasing the level of training over time was more efficacious at delaying cognitive decline than using a fixed and standardized training regimen [146].

The biological mechanism underlying the effect of cognitive training is unknown. However, some experimental evidence indicates that, in animals, there is actually an increase in brain volume after prolonged mental activity [147]. In humans, there is some evidence that mental activities related to a decrease in atrophy of the hippocampal formations and indicates a complex time-dependent change in cortical function as revealed by functional MRI [148, 149]. Some animal models have indicated that cognitive training may be associated with a reduction in amyloid pathology which could imply a disease modifying effect of these activities [104, 150]. In humans, it has also been described that mental activity may reduce the establishment of alternative compensatory pathways in spite of a certain burden of pathology [151].

VII. Mediterranean Diet

The Mediterranean Diet involves certain nutritional and behaviorally recommendations that have been inspired by the food and lifestyle of the coastal regions of the Mediterranean areas

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(southern Italy, Crete and Greece) in the 1960s. In addition to regular physical activity, the diet consists of fresh fruit, plant foods, olive oil, dairy products, fish and poultry with limited amounts of eggs and red meat. A moderate amount of wine is also included in this diet.

Some cohort studies have examined the association between the Mediterranean Diet and cognitive decline of AD [152–155]. The exposure to the diet was assessed with self recorded food questionnaires, and one study reported that a higher adherence to the Mediterranean Diet was associated with a lower risk of progression from cognitively normal persons to MCI [152]. The other study showed that subjects exposed to the Mediterranean Diet had better scores on the Mini-Mental State Exam and less decline on a memory test [154]. The mechanisms of risk reduction are thought to be related to role of antioxidants present in this diet and its potential relationship at reducing reactive oxygen species.

VIII. Social networks

Social engagement can be defined as the participation of social activities and maintain social connections. Martial status, loneliness, participation in social and political events in the community, contact with family and friends have been used by several studies to measure and quantify the degree of social engagement and its association with AD or cognitive decline. A number of cohort studies in the U.S. and Europe have explored social engagement as a possible risk for the future development of AD [91, 156–164]. These studies indicated that, through observing populations for several years and following them longitudinally, self-reported questionnaires tended to imply that social activities may be protective against developing a cognitive decline. In particular, being single and not cohabitating with partner in life has been associated with an increased risk of AD; however, these findings could not be applied to individuals who were divorced or widowed. The latter result, however, was not confirmed in a study that showed that being widowed in mid-life or later life was associated with a higher risk of AD as compared to people who were cohabitating either in mid-life or later life [159]. Moreover, the degree of loneliness, decreased social networking and activities seem to be associated with a higher risk [165].

Some caution is warranted to interpret these findings because a reduction in social engagement can be an early sign of AD rather than a risk factor. Patients with early AD may have reduced social activity because they are less functional and are tending to withdraw. Although evidence is not definitive with respect to social activity, there seems to be a reasonable degree of support for maintaining social networks. Consequently, this recommendation is often provided by healthcare workers as a means of maintaining a high quality of life.

IX. Meta-analysis

The Agency for Healthcare Research and Quality (AHRQ) prepared a systematic review of the available literature and a meta-analysis to better understand the current evidence on cognitive decline and AD [165]. The authors prepared a list of inclusion criteria excluding small to moderate observational studies and randomized control trials and studies with less than one year of observation. A challenging problem in this type of study pertains to the lack

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of homogeneity across the studies in defining AD or cognitive decline; there was not a consistent diagnostic definition provided in many of these studies.

In the analysis, 25 systematic reviews and 250 primary research studies were included. Most factors did not show a significant and consistent association with a reduction in the risk of AD or cognitive decline. Alternatively, physical activities and cognitive engagements seem to be factors that were more consistently associated with a reduction in AD and cognitive decline, although a strict length with causality was not found. The reduction of the risk was small to moderate in AD and small in cognitive decline. While there was some evidence for a reduction in late life cognitive loss, there appeared to be insufficient evidence to draw definite conclusions. However, it must be realized that some of the issues addressed in this type of analysis may not be amenable to randomized control trials, and consequently, the available data were based on relatively short-term observational studies. As such, this type of analysis may not be entirely appropriate for these topics. The authors concluded that further research needs to be done to better understand factors associated with a risk of AD and cognitive decline and suggested that a more homogeneous definition of the diagnostic entities would be helpful.

X. Comments on meta-analyses

A meta-analysis is a “quantitative approach for systematically assessing the previous research in order to arrive at conclusions about the body of research.” In other words, this is a research technique that tries to combine different studies on the same topic to provide a quantitative result that might address the questions under study. The unit of a meta-analysis is not the population of subjects but rather individuals. An important step in initiating a meta-analysis is to perform an extremely thorough review of the current literature on the selected topic in order to find all of the relevant papers. Moreover, it is necessary to clearly state the inclusion criteria to define studies that would be used for the analysis. It is difficult to interpret studies using different designs and combining studies that may have had different foci. For example, combining cohort studies and case control studies may lead to uninterpretable results. Meta-analyses are very helpful to provide a quick and easy interpretation for a large body of literature pertaining to clinical practice or for addressing certain scientific issues. However, there are limitations of meta-analyses. The variable quality of the different studies may severely impact the quantitative meta-analytical result. It is not always possible to have high quality studies across the field, yet often, meta-analyses combine these various investigations as if they were done equally well. This may lead to results that are difficult to interpret. The ideal studies for meta-analyses are randomized clinical trials. These studies have defined onsets and ends, and the criteria for inclusion are clearly defined. However, observational studies are less precise by nature and, consequently, often do not meet the strict criteria that are observed in randomized clinical trials. Nevertheless, some of the issues that are very important to address can only be done adequately through observational studies. However, the techniques used in meta-analyses downgrade the quality of a study if it is purely observational.

Another concern with meta-analyses can pertain to the sample sizes of the studies. Meta-analyses tend to place a great deal of weight on studies with large sample sizes. As discussed

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above, the quality of the study might not be in direct proportion to the size of the study. For example, a study with a large sample size but of marginal clinical assessment might be combined with a smaller study with a better clinical assessment, and the larger study will carry more weight in the analysis in spite of the rather cursory clinical features. This can compromise the interpretation of the results. Finally, meta-analyses tend to be more effective when a specific question is being addressed rather than a more general scientific issue. As noted above, the randomized control trial addressing a particular question carries the greatest amount of weight in a meta-analysis, and studies that are addressing a more diffuse issue are more difficult to conduct.

XI. National Institutes of Health State of the Science Conference

The National Institutes of Health recently organized a meeting to assess the available scientific evidence related to the prevention of AD and cognitive decline. In this meeting, there was an independent panel of health professionals and public representatives who evaluated the results of a systematic literature review and considered the presentations of investigators in the field of aging and dementia. The meeting focused on the identification of risk factors that may be associated with AD and cognitive decline including the therapeutic effects of any medications that are available. The focus was to determine if there are any factors that may maintain or improve cognitive function over the lifespan and the relationship between those factors and AD in cognitive decline [166].

Although the panel recognized the magnitude of the progress and knowledge over the past decades, they did not draw any firm conclusions about modifiable risk factors for AD or cognitive decline. Moreover, they indicated that there was inconsistent evidence regarding the diagnoses of AD, MCI and cognitive decline and concluded that no pharmaceutical agents or dietary supplements were noted to be preventive. They suggested that additional randomized control trials should be performed in a representative population to identify factors that might delay the onset or slow the progression of cognitive decline or AD.

The feedback concerning the State of the Science report was mixed. Critics felt that the panel failed to recognize the distinction between causal relationships and associations. There are numerous studies that indicate that there is an association between exercise and AD, for example, but since definitive clinical trials were unavailable to document this distinction, the panel rejected this information. On the one hand, certain factors may be associated with increasing a risk of getting AD but not definitely indicate that those factors cause the disorder. Nevertheless, the relationship between several of the factors involving exercise and intellectual activity were underestimated. All agreed that additional research needs to be conducted in this area.

XII. Conclusions and recommendations

The importance of defining factors that may delay the onset, slow the progression or even prevent AD and cognitive decline cannot be overestimated. With the aging of world populations, the burden of individuals with all degrees of cognitive impairment on societies will be enormous. A great deal of research has been conducted concerning these factors over the past decades. While it is true that there are no definitive interventions that have been

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defined to prevent or slow the cognitive decline in aging, there are very strong trends in the literature. The available evidence suggests that physical activity, intellectual activity and social engagement are the most helpful factors at reducing AD and cognitive decline and, at the same time, these factors may be helpful for enhancing quality of life. Clearly, further studies are needed to better understand the early pathological changes related to the symptoms of AD and cognitive decline, and these studies need to be conducted in a prospective fashion in representative populations. There is optimism in the field with respect to possible disease modifying effects that can be achieved through a variety of nutritional, pharmacological and lifestyle modifications.

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