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WOMEN'S HEALTH

ABSTRACT & COMMENTARY

Prenatal Exercise for Pregnancy-induced Hypertension and Weight Gain

By William C. Haas III, MD, MBA

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Dr. Haas reports no financial relationships relevant to this field of study.

SYNOPSIS: Regular exercise throughout pregnancy exhibits a protective effect against the development of hypertension and excessive gestational weight gain without increasing the incidence of low birthweight infants.

SOURCE: Barakat R, et al. Exercise during pregnancy protects against hypertension and macrosomia: Randomized clinical trial. *Am J Obstet Gynecol* 2015 Dec 15; doi: 10.1016/j.ajog.2015.11.039. [Epub ahead of print].

Hypertensive disorders are some of the leading causes of maternal and fetal morbidity and mortality.[1,2] The precise mechanism for elevated blood pressure during pregnancy is not yet known; however, excessive gestational weight gain (GWG) and maternal obesity have been strongly correlated with developing a hypertensive disorder (i.e., gestational hypertension, pre-eclampsia).[3,4]

Implementing interventions to minimize excessive GWG have been recommended to reduce perinatal complications, including hypertension. Retrospective studies suggest that women engaging in regular exercise have a reduced risk of developing pregnancy-induced hypertension and pre-eclampsia.[5,6] In an effort to strengthen the evidence for physical activity in pregnancy, a group of researchers recently conducted a randomized, controlled trial evaluating the effect of exercise on pregnancy-induced hypertension as well as excessive GWG. Secondary outcomes included the incidence of infant macrosomia and low birthweight.

Based on calculations from a power analysis, 1100 pregnant women were recruited for the study. Inclusion criteria included women with singleton pregnancies and no history of diabetes mellitus (type 1, type 2,

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Summary Point

- Women not engaging in exercise during pregnancy are three times more likely to develop a hypertensive disorder and 1.5 times more likely to gain excessive weight compared to regular exercisers.

or gestational). After applying exclusion criteria (history of preterm delivery, contraindications to exercise, or plans to deliver at a hospital not associated with the study), 840 patients were identified and equally randomized to an exercise intervention or standard care.

The exercise intervention consisted of group training sessions (10-12 participants) that occurred 3 days/week for 50 minutes starting in the first trimester and continuing until delivery. Each session involved aerobic exercise, light resistance training, and stretching. The control group was given general advice about the positive effects of physical activity and questioned regarding their level of physical activity each trimester. Blood pressure was measured at every visit using a standardized protocol. Total GWG was calculated using the weight at the last clinic visit before delivery minus the pre-pregnancy weight. Birth weight was recorded from hospital perinatal records and classified according to standard definitions (macrosomia, > 4000 g; low birthweight, < 2500 g).

A similar number of patients completed the exercise (n = 383) and control interventions (n = 382). No statistical differences were noted between the groups at baseline. With regard to blood pressure, women who did not engage in formal exercise were three times more likely to develop hypertension during pregnancy compared to exercisers (odds ratio [OR], 2.96; 95% confidence interval [CI], 1.29-6.81; $P = 0.01$). Non-exercisers were also 1.5 times more likely to gain excessive weight compared to exercisers (OR, 1.47; 95% CI, 1.06-2.03; $P = 0.02$). Exercise was not significantly correlated with low birth weight at delivery; however, the lack of exercise was significantly correlated with macrosomy (OR, 2.53; 95% CI, 1.03-6.20; $P = 0.04$).

■ COMMENTARY

This study extends findings from correlative studies and suggests incorporating exercise into prenatal care to improve the health outcomes of both mother and child. Specifically, regular exercise during pregnancy can reduce the risk for developing hypertension and excessive gestational weight gain, all without affecting gestational age at birth or the method of delivery. These benefits also occurred without an increased risk for low birthweight among infants.

Although adherence to exercise was high in this study (> 80%), motivation and compliance with exercise always remain important considerations. Interestingly, none of the women in the control group were excluded as a result of self-increased physical activity. An organized and accountable exercise program might be an important requirement to achieve the beneficial effects resulting from regular exercise. Future studies should attempt to identify the minimal effective dose for exercise to maximize adherence.

One of the major limitations of the study was the lack of nutritional assessment. Both the quantity and quality of food ingested can drastically affect health metrics, such as blood pressure and weight. Without a clear record of nutritional information, the relative effect of exercise on the measured outcomes cannot be reliably determined.

Overall, this study should encourage physicians to recommend participation in regularly scheduled, well-supervised exercise programs throughout pregnancy. More specifically, recommendations should incorporate both aerobic and light resistance training for 150 minutes per week. ■

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ABSTRACT & COMMENTARY

Mind Over (Back Pain) Matter: An RCT

By David Kiefer, MD, Editor

SYNOPSIS: Mindfulness meditation training led to greater short-term function and less pain in adults with chronic low back pain when compared to a control group receiving only educational sessions.

SOURCE: Morone NE, et al. A mind-body program for older adults with chronic low back pain: A randomized clinical trial. *JAMA Intern Med* 2016;176:329-337.

Chronic low back pain afflicts many adults, a fact to which any clinician in primary care would attest. It is one of the most common reasons people turn to integrative therapies,[1] and has been widely studied to find effective treatments. The study reviewed here, financed by the National Institutes of Health, adds to the literature on the use of mind-body medicine for this condition.

The researchers randomized 282 English-speaking adults older than 65 years of age to either 8 weekly 90-minute mindfulness meditation sessions or "control" education sessions. Participants were included in or excluded from the trial as per the criteria in Table 1.

Functional limitation was measured using the Roland and Morris Disability Questionnaire (RMDQ), a 0-24 scale with higher numbers representing more disability. The mindfulness meditation sessions were fashioned after the mindfulness-based stress reduction (MBSR) program, a well-known and studied series of sessions that explores the aspects of four methods of mindfulness meditation. The "control" education session was a group health education program called "10 Keys to Healthy Aging," which provided 10 trainings on disease prevention surrounding blood pressure control, smoking cessation, cancer screening, immunizations, activity, cholesterol and glucose control, depression, healthy bones, and staying socially connected. Both groups also had six monthly "booster" classes at the end of the 8 weeks to reinforce the trainings and encourage participation.

The primary outcome for this study was the RMDQ, as described above. It was thought, based on prior work, that an improvement (lowering) of the RMDQ

Summary Points

- These researchers randomized 282 adults with chronic low back pain to either 8 weeks of mindfulness meditation training (fashioned after the MBSR course) or a "control" educational program.
- At the end of the intervention (8 weeks), the MBSR group fared better in the Roland and Morris Disability Questionnaire, but this improvement disappeared by 6 months post-intervention.
- The MBSR group showed some improvements at both 8 weeks and 6 months in sub-types of pain (current and most severe).

Table 1: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Age ≥ 65 years • English speaking • Mini-mental status exam ≥ 24 • Roland and Morris Disability Questionnaire (RMDQ) ≥ 11 • "Moderate" pain daily or almost every day for the previous 3 months* * This was a self-rated, five-part scale: extreme, severe, moderate, mild, no pain	• Previous mindfulness meditation program • Serious underlying illness causing the pain • Non-ambulatory or with severely limited mobility • Visual or hearing impairments (not allowing assessments to be done) • Pain in other locations more severe than low back pain • Acute or terminal illness • Moderate or severe depression as per the Geriatric Depression Scale

by 2.5-5.0 points would be clinically meaningful. Secondary outcomes assessed for pain, quality of life, depression, self-efficacy (to predict task performance), pain catastrophizing, and mindfulness, as per the validated scales listed in Table 2. All of the variables were assessed at the end of the program (8 weeks after the study began) and then 6 months after the study ended.

Of the 282 people randomized, 140 were in the MBSR group, and 142 were in the control group. All 282 were included in the final analysis of the primary outcome (intention-to-treat), even though only 118 in the MBSR group and 135 in the control group made it to the 6-month assessment. As would be expected, there was a better adherence to the protocol through 8 weeks: 132 people in the MBSR group and 138 in the control group. The researchers adeptly account for all dropouts in an included figure.

Baseline characteristics were statistically similar between the MBSR and control groups, including a relatively high baseline mindfulness score (4.6 and 4.4 in the treatment and control groups, respectively). Participants attended an average of 6.6 (out of eight) sessions and 2.4 (out of six) "booster" classes. Table 3 lists the RMDQ values for the different time points for each group, essentially showing a more significant lowering of the RMDQ for the MBSR group at the 8-week mark compared to the control group, a difference that was not sustained at 6 months. At the 8-week time point, 56.8% of the MBSR group and 44.9% of the control group achieved a 2.5 point improvement in the RMDQ, considered the cutoff for clinically significant findings. Of note, these percentages were not statistically different ($P = 0.51$). There were also a few participants who had at least a 2.5 point worsening in their RMDQ: in the MBSR, 5.3% (8 weeks) and 5.1% (6 months), and in the control group, 4.3% (8 weeks) and 4.4% (6 months).

For the secondary outcomes, the data of which are too voluminous to present here, there were some statistically significant improvements but few clinically significant effects. For example, the average Numeric Pain Rating Scale did not differ between the MBSR or control groups, although the Numeric Pain Rating Scale sub-groups of current and most severe pain over the last week was statistically and clinically significantly better in the MBSR group at both 8 weeks and 6 months. In addition, patient self-efficacy in the MBSR group improved more than the control group, but only at 8 weeks. Psychological measures and quality of life showed statistically significant, but not clinically significant, improvements in the MBSR group.

Finally, at 8 weeks each participant was asked the following question: "How much have your back symptoms changed as a result of the treatment provided in this study?" Termed "global impression," reported improvement in back pain was significantly greater in the MBSR group compared to the control group ($P < 0.001$). This perceived improvement persisted in the MBSR group at 6 months, while more participants in the control group reported worsening symptoms.

Table 2: Secondary Outcomes and Validated Scales Used to Quantify Variables

Secondary Outcomes	Validated Scale Used to Qualtify Secondary Outcomes
Pain (present, average, and most severe during the week)	Numeric Pain Rating Scale: range 0-20, higher number for more pain
Quality of life	RAND-36 Health Status Inventory (Global Health Composite: range 9-67, higher number for better overall health; Physical Health Composite: range 20-65, higher number for better physical health)
Depression	Geriatric Depression Scale: range 0-30, higher number for worse depression
Self-efficacy	Chronic Pain Self-Efficacy Scale: range 0-100%, higher numbers for improved self-efficacy
Pain catastrophizing	Catastrophizing Scale of the Coping Strategies Questionnaire: range 0-6, higher number for more catastrophizing
Mindfulness	Mindful Attention Awareness Scale: range 1-6, higher numbers for more mindfulness
Comorbidities	Cumulative Illness Rating Scale: range 0-13, higher numbers for more comorbid conditions

Table 3: RMDQ (Primary Outcome), Results for MBSR vs Control Group

	MBSR baseline	MBSR 8 weeks	MBSR 6 months	Control baseline	Control 8 weeks	Control 6 months
RMDQ	15.6	12.1	12.2	15.4	13.1	12.6

RMDQ: Roland and Morris Disability Questionnaire; MBSR: mindfulness-based stress reduction

■ COMMENTARY

People with chronic low back pain commonly turn to the healthcare system for help. This study offers some ideas about what role mindfulness meditation might serve for this population. Most importantly, in the short term, function (less disability) is improved after an 8-week MBSR class. The researchers noted that this effect wasn't sustained, in comparison to the control group, at the 6-month mark. Were the participants in this study group going to improve anyway, regardless of the treatment offered? The researchers had strict inclusion criteria meant to find those adults with chronic pain, so that does not seem to be the explanation. Interestingly, the effect of the MBSR training on two subsets of pain did remain statistically and clinically significantly improved at 6 months, so some aspects of the MBSR training persist. One of the concluding sentences explores the need to adjust the training so that it persists longer; this would definitely be important.

It is difficult to tease out clinical pearls from the myriad of tests used to assess the secondary variables. It is possible, given the high baseline mindfulness scores in all participants, the extra "boost" to mindfulness given by the MBSR class was not sufficient to show benefits compared to the educational intervention. A somewhat concerning research finding was the high number of participants who were lost to follow-up at 6 months in the MBSR group. The researchers used intention-to-treat analyses, so these data were handled appropriately, but it still begs the question of how the data would have changed if all of the participants in the MBSR group had been located and analyzed at the 6-month mark. At least the adherence to the MBSR class was high; clinicians can feel confident that, if recommended, patients will stick to this approach for 8 weeks, at least according to this study. In some cases, perception is everything. With respect to the MBSR group, the global impression results were unequivocally better. Perhaps this is just what someone with chronic low back pain needs — a new outlook, hope, or a change in the status quo. In other words, even if the pain doesn't appreciably change, one's ability to cope with that pain improves, and that translates into an overall benefit. Perhaps less quantified than the rest of the study, this is nonetheless important and deserves attention.

Is there any reason not to recommend MBSR, or other versions of mindfulness meditation, for people with chronic low back pain? Cost, possibly, or inconvenience (90 minutes weekly for 8 weeks). Some participants showed a worsening of their RMDQ over time, but this also occurred in the control group. It would be difficult to call this an adverse effect; rather some patients, despite our best efforts, may be resistant to clinical improvement.

Overall, mindfulness meditation is worth exploring for patients with chronic low back pain. It may bring improvements in function, if not persistent benefits in pain and impressions of overall improvement. Hopefully, all clinicians have access to MBSR or related trainings to which they can refer patients who fit the bill. ■

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DEMENTIA

SPECIAL FEATURE

Integrative Approaches to Alzheimer's Disease

By Ellen Feldman, MD

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Dr. Feldman reports no financial relationships relevant to this field of study.

The medical community had warning. "Dementia in the Elderly: The Silent Epidemic," a 1982 *Annals of Internal Medicine* landmark article, looked at the "greying of America" and noted one natural consequence of longer life span would be an explosive impact on the prevalence of dementia.[1] Indeed, the epidemic has come — not only in the United States, but also globally, with dementia affecting an estimated 46 million people worldwide in 2015 and projected to affect 131 million by 2050.[2]

Despite these daunting numbers, more recent investigations have revealed promising news. Although there is still no cure for dementia, prevention efforts seem to be making an difference. While dementia remains a substantial health burden with risk increasing with age, the prevalence of this progressively impairing disorder is on a downward trend. First noted in 1988, subsequent

Summary Points

- A review of integrative interventions for Alzheimer's disease looks at pre-disease (prevention), early, middle, and late stages and emphasizes the importance of targeting interventions to each stage.
- Preventive efforts during midlife have potential to delay onset of this progressive deteriorating condition.

studies have consistently found a decreased incidence of dementia in specific geographical populations in the United States and Europe.[3,4]

Perhaps the most convincing evidence of this trend comes from a recently published analysis of Framingham Heart Study data.[5] These findings show a significant and steady decrease in incidence of dementia progressively in each of the three decades since the study began in 1975. It is important to understand that despite this decreasing trend, given the continued growth of the elderly population, sheer numbers of those affected by dementia are still projected to grow.[4]

As stated by the investigators of the Framingham Study data, the factors contributing to the decline in incidence of dementia among the study population are not completely understood but may be associated with several factors. These include advances in control of cardiovascular risk factors (including blood pressure and lipid status) and higher educational level. Interestingly, the downward trend of the incidence of new dementia diagnosis in the population investigated was found only in those with at least a high school education, leading to speculation and investigation into the effect of cognitive stimulation on prevention of dementia.[5]

Medical providers caring for elderly patients, their families, and/or their caregivers are in a unique position to observe, diagnose, and provide guidance to those affected by dementia. At this point, the medical system remains without a definitive cure to offer those with dementia; the decrease in incidence has strengthened the shift toward prevention, risk reduction, and early intervention, making an integrative approach to patient care particularly valued in effective treatment and management.[6,7]

There are multiple subtypes of dementia. In order of prevalence, these include Alzheimer's disease (AD), vascular dementia, mixed dementia, Lewy Body dementia, and frontotemporal lobar degeneration. All have a progressive, irreversible, and deteriorating effect on independent functioning.[2] AD, estimated to occur in 60-80% of all dementia cases, is the most common form of dementia. About 50% of AD cases are termed "mixed dementia," having symptoms or clinical evidence of pathology related to another dementia as well.[2]

HISTORIC AND RECENT FINDINGS IN ALZHEIMER'S (1901-2016)

Alzheimer's bears the name of the early 20th century physician Dr. Alois Alzheimer, who described this disorder in a 51-year-old woman and subsequently isolated neurofibrillary tangles (NFTs) and amyloid plaques (senile plaques [SP]) in sections of his patient's brain. Dr. Alzheimer published these findings in 1907, and they remain a hallmark of what is now known as AD.[8]

Advances in imaging techniques have since revealed evidence that the presence of SPs and NFTs are not specific to AD; NFTs are found in other types of dementias, and SPs may be found in adults with near-normal cognition. It appears that the quantity and distribution of the lesions have significant roles in making or confirming a diagnosis.[9] Currently, there are several hypotheses under investigation regarding the pathophysiology of AD. Most prominent are the amyloid hypothesis and the tau hypothesis.[10,11] Tau protein helps support healthy neurons. In AD, tau protein is hyperphosphorylated, contributing to the development of NFTs, which affects communication between neurons and eventually leads to cell death. Beta-amyloid are protein fragments that appear to be the main constituent of SPs. It is known that SP accumulation precedes clinical signs in AD and that accumulation of NFTs and cell death more closely correlate with progressive clinical decline.[11] As research progresses, the role of each of these in the development of AD, and eventually in the prevention and/or treatment of this disorder, should become more apparent and useful in clinical practice.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of AD includes treatable and reversible conditions such as depression, delirium, medication side effects, substance use (consider not only alcohol but also pain medication and other substances of abuse), specific vitamin deficiencies (folate and vitamin B12), thyroid abnormalities, chronic subdural hematoma, and normal pressure hydrocephalus.[6] A careful and complete history with collateral information from family or caregivers, appropriate lab tests, and imaging studies are used to distinguish conditions and determine diagnosis. Although not required for diagnosis, neuropsychological testing is often useful to better understand degree and extent of cognitive impairment, level of impairment of judgment and impulse control, and to aid in determination of the specific type of dementia.[12,13]

Table 1: Two Types of Alzheimer's Disease and Their Characteristics

Early-onset Familial Alzheimer's Disease (FAD)
- Individuals between the ages of 30 and 60 years
- < 5% of all Alzheimer's cases
- Usually caused by genetic mutation
- Strong inheritance pattern

Late-onset Alzheimer's Disease
- Develops after the age of 65 years
- Most of the cases of Alzheimer's
- Multifactorial risk factors: genetics, lifestyle, environment
- Genetic risk factor related to apolipoprotein gene (APOE 4) and the number of alleles present

GENETIC FACTORS IN AD[14]

Genetic factors influencing the development of AD has become a promising area of research. Researchers now know there are at least two forms of AD with different genetic patterns of inheritance and risk. The early-onset form, occurring in < 5% of all AD is almost always inherited and has onset between the ages of 30 and 60 years of age. In contrast, the more common late-onset AD is multifactorial in origin; the genetic risk here is related to carriers of the APOE4 allele, which is found in 10-15% of the general population. It appears that the number of copies of this allele increases risk of AD by 3- to 8-fold. However, the presence or absence of this allele does not correlate 1:1 with disease occurrence. Thus, it is known as a "risk-factor" gene.[14] (*See Table 1.*)

CONVENTIONAL DIAGNOSIS AND TREATMENT

There are several stages of AD. These stages may be distinguished by scores on the Mini Mental State Exam (MMSE), commonly used in general medical practice. The MMSE is an office-administered standard scoring tool with a maximum score of 30.[15] Scores of 21-25 generally are found in early-stage AD, scores of 11-20 imply a progression to mid-stage, and scores of ≤ 10 are indicative of severe or late-stage AD.[16]

Mild cognitive impairment (MCI) is a term used to indicate a stage in the "grey area between intact cognitive functioning and clinical dementia."[17] This time period has evolved into a rich area of investigation for prevention of AD. There are efforts in progress to subtype MCI and clarify risk for progression to specific types of full-blown dementia, including AD. A 2015 review article looked at promising results from 23 randomized controlled trials involving nonpharmacological interventions aimed at delaying progression to AD; cognitive training and exercise figure most prominently here.[18] The Montreal Cognitive Assessment (MoCA) is an office-based screen with specific utility used to differentiate early stages of AD from MCI.[19] The Alzheimer's Association provides a "cognitive assessment toolkit" containing links to several other quick screens useful for general clinicians as alternatives to the MMSE.[20]

There are several FDA-approved medications for AD but not for MCI. Cholinesterase inhibitors used during early-mid stages include donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne). These work to increase availability of acetylcholine, a neurotransmitter crucial in memory and learning. Studies show cholinesterase inhibitors lend a modest but significant benefit in slowing cognitive and functional decline in early stages of AD. It is important to understand and convey to patients and families that these agents neither target nor affect the ongoing destructive progression of the disease.[21,22] As AD progresses, memantine (Namenda), an N-methyl-D-aspartate (NMDA) antagonist or glutamate regulator, may be used to attempt to preserve functioning as long as possible. The newest agent, Namzaric, combines donepezil and memantine, both of which are approved individually for treatment at this stage. Clinical studies with all of these agents indicate responses tend to vary in individuals.[23]

INTEGRATIVE APPROACHES TO AD

As noted, there remains no known agent to definitively treat and cure AD. The decreasing incidence of dementia of all types in the elderly suggests efforts toward prevention and early intervention have been successful. Integrative medicine combines the best of conventional medication and treatment with non-conventional approaches, including nutritional, behavioral, and other nonpharmacological interventions. Given the limited efficacy and effect on the progression of AD from available pharmacotherapy, many patients, families, and practitioners look to adjunct or alternative treatments. Although limited information is available regarding specific numbers of patients with AD seeking such treatments, several studies note the use of alternative therapies among elderly in general reaches 40-45% in the United States.[24]

A thoughtful holistic approach to the patient with AD involves consideration of multiple dimensions. A recognition of the role and health of not only the identified patient but also the caregiver becomes important, especially as the disease progresses. In discussing an integrative approach, it is helpful to distinguish interventions during each of several stages of disease progression. Treatment approaches for at-risk populations, including those with MCI (prevention), early- to mid-stage AD, and late-stage AD, are described below. Although the most robust evidence points to the value of integrative approaches in the preventive arena, there are emerging studies and evidence suggesting that integrative treatment of AD is useful at all stages.[25]

PREVENTION

Age remains the largest risk factor for development of late-onset AD. The expected incidence rate in the United States ranges from 0.2% among people 65-74 years of age to 1.3% among people 75-84 years of age, and finally to 3.9% among those > 85 years of age. Second to age, genotype (APOE4) is the next most significant risk factor in the development of AD.[2] There can be little done in the way of prevention regarding the above unmodifiable risk factors; prevention work revolves around the known modifiable risk factors. At the London G8 summit in December 2013, an international group of scientists presented conclusions that AD can be prevented and recommended the following:

"Public health policies should encourage middle-aged people to stop smoking; exercise; eat diets rich in fruit and vegetables and fish (Mediterranean foods); avoid becoming obese and diabetic; avoid excessive alcohol intake; treat high blood pressure. In other words — tell people that adopting a healthy lifestyle may help to ward off dementia as it does for other diseases."[23]

Physical Activity: Studies suggest the effect of exercise and physical activity goes beyond mitigation of cardiovascular risk. A 2011 meta-analysis of studies looking at physical activity and cognitive decline suggests a decline in risk of cognitive deterioration of > 30% through moderate- to high-intensity exercise.[27]

Diet/Nutrition: This is a very active and exciting area of investigation and research. Data from observational studies suggest a role for specific heart-healthy diets, while randomized, controlled trials fail to show a consistent effect for nutritional intervention. There is no evidence that omega-3 fatty acids directly help cognition in the elderly, but there is evidence that control of cardiac risk factors in mid-life aids prevention. Promising results from a 2015 observational study of a hybrid diet are noted below.[28,29]

Mediterranean-DASH Diet Intervention for Neurodegenerative Delay (MIND diet).[30] Rush University Medical Center researchers developed and investigated the MIND diet, which combines elements of two heart-healthy diets with neuroprotective foods. (*See Table 2.*) Results from a large observational study are encouraging and point to a delay in cognitive decline in adults who follow this modification of the Mediterranean and DASH diets. Evidence suggests a preventive effect even with only moderate adherence and further suggests the preventive effect may mirror the length of time adhering to the dietary pattern. (See https://www.rush.edu/news/diet-may-help-prevent-alzheimers.)

Hypertension Control. This is important in mid-life, with some emerging evidence that hypotension becomes a risk factor in the elderly.[31]

Table 2: MIND Diet

Components of MIND diet include:
- Whole grains, 3 times daily
- Green leafy vegetables daily
- Other vegetables daily
- Berries (strawberries and blueberries)
- Nuts
- Beans
- Fish
- Poultry
- Olive oil
- Wine

Eliminate or significantly reduce:
- Red meats
- Butter
- Cheese
- Sweets/pastries
- Fast food/fried food

Obesity. Longitudinal studies have identified mid-life obesity as a risk factor for AD.[32]

Hypercholesterolemia. There appears to be a link between cholesterol, plaque formation, and hyperphosphorylation of tau protein. A recent randomized, controlled trial involving almost 1000 elderly males during an 8-year period found convincing evidence that consistent statin use reduced AD risk.[33]

Cardiovascular Risk Factors. Better control of diabetes, heart disease, and metabolic syndrome are associated with AD risk reduction, although studies are not clear regarding cause and effect.[34]

Cognitive Training and Social Engagement. Multiple randomized, controlled trials have tried to measure the effect of cognitive stimulation programs on persons with and without cognitive impairment, but results have been mixed. Researchers who performed a robust study with 2832 randomized participants and multiple intervention arms published a 10-year follow-up of their patients in 2014. These results point to a positive impact of cognitive intervention on reasoning, speed of processing, and self-reported activities of daily living, but no effect on memory.[35]

Sleep. Many believe that sleep disturbances during midlife may affect amyloid deposits in the brain. Improvement of sleep during midlife may help prevent AD.[36]

Relevant Negatives

Ginkgo evaluation of memory study. More than 3000 community volunteers with normal cognition or early changes were involved in a prospective study (2000-2008); median follow-up was 6 years. *Ginkgo biloba*, at

120 mg twice daily, was not effective in reducing the rate of development of dementia or AD.[37]

Vitamin B12. This trial of 201 participants, which looked at correction of moderate vitamin B12 deficiency (no anemia; serum level 107-210 pmoL/L), found no evidence of improved cognitive functioning in AD.[38]

Take Home Message for Those at Risk
The biggest single risk factor for AD is age.

- Increase physical movement.
- Eat more whole grains, berries, vegetables, nuts, and beans while decreasing red meat.
- Control weight.
- Address cardiovascular risk factors in midlife.
- Keep brain active and stimulated.
- Watch for and correct sleep disturbances in midlife.

EARLY TO MID-STAGE AD

Look carefully at a complete picture.

Evaluate and simplify a medication list. Many older patients are on anticholinergic agents (i.e., diphenhydramine, oxybutynin), which contribute to confusion and counteract the effect and action of cholinesterase inhibitors. Carefully evaluate a patient's medication list and eliminate or minimize such agents when possible.[39]

Treat Comorbid Illnesses. These are common in this population of elderly patients. Look particularly for signs and symptoms of depression and anxiety. Monitor sugar control in diabetics and address if necessary.[40]

Discuss medication adherence and compliance with the patient and caregiver, recognizing that with cognitive deterioration, old strategies for managing medications may no longer work.[41]

Reveal a Diagnosis. Informing patients and/or caregivers of an AD diagnosis is an important, difficult, and often neglected step in management of this disorder. A large-scale analysis of Medicare records from 2008, 2009, and 2010 found a diagnosis disclosure rate of 45% among persons diagnosed with AD (and even lower for other forms of dementia.) Multiple studies explore the benefits of disclosing a diagnosis early and clearly. These point to implicit advantages for patients, including having the time to plan for the future financially and legally while still cognitively able; being able to provide informed consent for treatment options; providing a sense of autonomy and control; and allowing patients and families the time to develop positive coping strategies by putting a name to the changes they are experiencing or noticing. Contrary to many providers' beliefs, there is little evidence that revealing this diagnosis increases the likelihood of depression or suicide.[41]

Selected Supplements with Potential for Use in Alzheimer's Disease

Ginkgo biloba
Plant extract; antioxidant and anti-inflammatory.
A 2015 meta-analysis looked at results from nine adequately sized randomized, controlled trials investigating the use of *Ginkgo biloba* in dementia. All studies used standardized *Ginkgo biloba* extract EGb761 at varying doses; dementia was subtyped to AD and/or vascular dementia. Safety, in terms of side effects, did not differ markedly from placebo. *Ginkgo biloba* at 240 mg daily outperformed placebo in specific measures of cognitive improvement in most of the studies.[45]

Huperzine A
Chinese herb extract; acetylcholinesterase inhibitor.
A review article in 2013 looked at results of 20 randomized, controlled trials and concluded that there may be evidence of efficacy in AD but methodology of studies does not allow clear recommendations or conclusions. There were no serious adverse effects noted in the studies.[46]

Vinpocetine
Semi-synthetic ester of a compound obtained from the leaves of the vinca plant (Lesser Periwinkle).
Vinpocetine's theoretical efficacy in AD derives from its action as a phosphodiesterase inhibitor. It has been used as a folk remedy around the world in a variety of disorders, including treatment of diabetes in Europe and as a diuretic in Asia. There have been limited studies in AD, although the basic science is starting to drive investigation. A 2003 Cochrane analysis showed limited beneficial effect in dementia at doses of 30-60 mg/day and no adverse effects, and recommended larger well-designed studies moving forward.[47]

Phosphatidylserine (PS)
Phospholipid contributing to integrity of cell membranes.
Promising studies were conducted with bovine-derived PS, which is no longer available due to safety concerns regarding the risk of bovine spongiform encephalopathy. Soybean-derived PS represents a safer alternative and is being actively investigated for efficacy and safety in humans. A promising exploratory study in 2013 gave soybean-derived PS in 30 volunteers with memory impairment at a dose of 300 mg/day. Recommendations are to move forward with more broad-based, robust studies.[48]

Exercise. Exercise has long been thought to be important in treatment, with few evidence-based studies supporting clinical impression. A recent Danish randomized, controlled trial involving 200 community-dwelling patients with mild AD (mean MMSE score of 24 and all scores > 19) is considered the first "rigorously conducted study of moderate-to-high intensity aerobic exercise in mild AD." Findings from this study are promising but mixed, pointing to a need to conduct more studies and to differentiate the effect of socialization from the effect of exercise. In this study, high-intensity exercise seemed the

most effective in leading to measurable improvements in cognition.[42]

Stress Management. Promising results from several studies have examined the effect of meditation, yoga, sleep quality and quantity, and control of depression symptoms in early AD. Music may have a neuroprotective effect; participation in music-related activities may help with short-term recall in early-stage AD.[43,44]

SELECTED INVESTIGATIONAL STUDIES IN EARLY-MID STAGE AD

Acupuncture. A meta-analysis published in June 2015 looked at 10 randomized, controlled trials (585 patients; all studies were published in Chinese). The authors found that acupuncture alone (six trials) showed greater improvement on MMSE scores than acetylcholinesterase inhibitors alone. Acupuncture in addition to donepezil (three trials) showed greater improvement on MMSE than donepezil alone. There were few reported adverse side effects related to acupuncture. Limitations of the studies included no follow-up, moderate sample sizes, and unclear diagnostic criteria.[49]

Cognitive Training/Cognitive Rehabilitation. These consist of specific, usually individualized, approaches to address impairments in cognition. A review article in 2013 looked at 11 randomized, controlled trials. The authors found no association with positive or negative outcomes in AD. Limitations of the studies included design and methodology.[50]

Multi-pronged, Individualized Approach with Diet, Exercise, and Stress Reduction. Reversal of cognitive decline was reported in a series of case studies in the September 2014 issue of *Aging*. The authors reported reversal of cognitive decline in nine out of 10 patients using dietary changes (eliminating simple carbohydrates and processed foods and increasing fruit and vegetable intake), vitamin supplementation, stress reduction, hormone replacement, and exercise.[51] This was not a randomized, controlled trial, and its individualized approach makes replication difficult.

Anti-Tau Vaccine.[52] In this Phase I trial of 30 patients with early to moderate AD (mean MMSE = 20), the authors noted stable cognition over 6 months. Limitations include that the study was clearly investigational, limited subjects, limited follow-up, no statistical analysis, and some adverse effects.

Take Home Message for Early-Mid Stage AD

- Keep up or increase physical activity.
- Address medication compliance strategies.
- Consider cholinesterase inhibitors.
- Simplify medication regime and look for interactions.
- Treat comorbidities, including stress and anxiety.
- Consider dietary changes and vitamin supplementation.
- Consider use of dietary supplements after full discussion of known benefits and risks.
- Plan for future needs.

MIDDLE–LATE-STAGE AD

Manage Secondary Symptoms. Delusions or hallucinations may emerge and interfere with functioning and autonomy. Treatment with pharmacologic agents must be balanced with understanding of side effects. An FDA black box warning cautions that treatment with atypical antipsychotics (and with many of the older neuroleptics as well) increases the risk of stroke or death in this population. The consensus is that it best to use these agents in low doses and only as needed to improve or maintain level of functioning.[53]

Consider Behavioral Interventions. Look at manipulation of environment (assistive devices, door alarms, electronic monitoring, and pill dispensers, for example) and behavioral plans within nursing homes or as developed with a caregiver. These can address behavioral concerns without the risk associated with pharmacologic interventions, or can be used in combination with agents as clinically indicated.[53]

Attend to the Emotional Needs of the Caregiver. Educate caregivers about signs and symptoms of burnout; refer to support groups or community agencies; and reinforce the need for self-care.[2,54]

Take Home Message for Middle-Late Stage AD

- Consider appropriate pharmacologic interventions for primary or secondary symptoms and behaviors that impair functioning.
- Consider changing or modifying environment to manage these same behaviors with less pharmacologic agents.
- Manage comorbidities.
- Address self-care of caregiver(s).

CONCLUSION

Integrative approaches to AD are at the forefront of treatment of this devastating and progressive disorder. Although neither conventional nor integrative medicine offer a single curative agent or procedure, the dual goals of prolonging stable functioning and postponing cognitive deterioration are clearly within the realm of integrative agents and techniques. Of particular interest to the integrative practitioner is the mounting evidence of the importance of preventive interventions during pre-disease or midlife. ■

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We Need Your Help!

The *Integrative Medicine Alert* editors are planning topics for 2016 issues and would like your feedback on topics recently covered. Please help us by answering three questions at the following link: https://www.surveymonkey.com/r/AMA2016. Thank you for your help!

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

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CME QUESTIONS

1. **According to the results of the Barakat et al study, pregnant women who regularly exercised reduced their risk for developing which of the following?**
   a. Gestational diabetes
   b. Preterm delivery
   c. Hypertensive disorder
   d. All of the above

2. **In the study on chronic low back pain, mindfulness meditation training led to which of the following outcomes?**
   a. A decrease in the score of the Roland and Morris Disability Questionnaire at 8 weeks
   b. An increase in the overall score of the Numeric Pain Rating Scale
   c. More catastrophizing as per the Catastrophizing Scale of the Coping Strategies Questionnaire
   d. Statistically equal global impression score when compared with the control group.

3. **Which of the following is recommended for the prevention of dementia?**
   a. Low-fat/low-carb diet, exercise, social engagement
   b. High vitamin E supplement, vitamin B12, and *Ginkgo biloba* 40 mg three times daily
   c. Exercise, MIND diet, correction of cardiovascular risk factors
   d. There are no good preventive interventions for late-onset Alzheimer's disease

4. **Which of the following is appropriate when treating patients with early to mid-stage Alzheimer's disease?**
   a. Let the caregiver know the diagnosis and let the caregiver decide if the patient can handle the information.
   b. Look carefully for medication interactions (especially anticholinergics) and address strategies for medication compliance.
   c. Limit outside stimulation to reduce anxiety.
   d. Prescribe cholinesterase inhibitors (i.e., donepezil or Aricept) to halt disease progression.

[IN FUTURE ISSUES]

- Mediterranean diet and breast cancer
- Herbal viagra
- Alexander technique and chronic neck pain
- Integrative approaches for autism