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INSIDE

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Yeah, But How Are They Doing 6 Months from Now?

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

Professor of Medicine, University of Kentucky;
Director, Sleep Disorders Center, Samaritan Hospital, Lexington

Dr. Phillips is a retained consultant for Cephalon and Ventus, and serves on the speakers bureaus for Cephalon and Boehringer Ingelheim.

Synopsis: *Treatment with a low-calorie diet resulted in substantial weight loss, and improved obstructive sleep apnea in obese men, with the greatest improvement in patients who had severe sleep apnea.*

Source: Johansson K, et al. Effect of a very low energy diet on moderate and severe obstructive sleep apnea in obese men: A randomised controlled trial. *BMJ* 2009;339:b4609.

THESE INVESTIGATORS WANTED TO ASSESS THE EFFECT OF A VERY low-calorie diet on weight loss and obstructive sleep apnea (OSA). They sent a written invitation and screening questionnaire to patients who met entry criteria into the study. Patients who were interested in participating and who met the inclusion criteria had to attend an information meeting, and were screened by a physician to evaluate contraindications. Exclusions to participation were diabetes, current use of a weight-loss drug, previous bariatric surgery, or recent angina pectoris or atrial fibrillation. Of 291 patients invited to be in the study, the investigators were able to recruit 63, all men. These patients had a mean age of 49 years, a mean body mass index (BMI) of 34 kg/m^2, and a mean Apnea plus Hypopnea Index (AHI) of 37 events/hour. Of these, 30 were randomized to the very low-calorie intervention, and 33 were randomized to the control group. The intervention group received a liquid very low-energy diet (2.3 MJ, or about 549 calories per day) for 7 weeks, followed by 2 weeks of gradual introduction to normal food, reaching 6.3 MJ (about 1505 calories) per day at week 9. The actual protocol used was the Cambridge diet. Clinical examinations that included weight, waist circumference, neck circumference, and percentage

body fat were done every other week. Urinary ketosis was also tested at each visit. In addition, each visit included a 1-hour group session supervised by a research nurse and two study dietitians.

The patients in the control group were told to stick to their usual diet during the 9 weeks of the study, but they also attended clinical examinations at weeks 1, 3, 5, 7, and 9 that were identical to those of the intervention group. The controls did not have group sessions, but they were offered the same weight-loss program as the intervention group, once the 9-week follow-up was completed.

At the end of the study (week 9), the intervention group's mean body weight was 20 kg (44 pounds) lower than that of the control group. In the intervention group, the mean change in weight was -18.7 kg and mean change in BMI was -5.7 kg/m^2, compared with a weight gain of 1.1 kg and increase in BMI of 0.3 kg/m^2 in the control group. Twenty-two of 30 of the very low-calorie diet patients were no longer obese, but all of the control patients still were.

At the end of the study, the mean AHI in the intervention group was 12 events/hour, compared with 35 events in the control group. For the intervention group, there was a dose-response relationship between weight loss and change in AHI. In other words, the more weight they lost, the more their AHI improved. Five of 30 in the intervention group had an AHI < 5 events/hour, which is considered normal. On the other hand, only one of the patients in the control group had an AHI < 15 events/hour at the end of the study. There was a greater improvement in AHI in patients who had severe obstructive sleep apnea (AHI > 30 events/hour) at baseline compared to those with moderate (AHI 15-30 events/hour) sleep apnea, although the amount of weight they lost was similar. All patients in the intervention group had urinary ketosis at each visit, indicating adherence to the diet. Reductions in self-reported daytime sleepiness score at week 9 were greater in the intervention group than in the control group.

There were 8 adverse events in the intervention group that were believed to be due to the study diet. These included constipation (n = 3), elevated alanine aminotransferase concentrations (n = 2), dizziness (n = 1), gout (n = 1), and dry lips (n = 1). These adverse events were transient and resolved, without intervention, by the end of the study.

■ COMMENTARY

Obstructive sleep apnea is a prevalent and largely under-diagnosed condition, affecting, as a conservative estimate, at least 5% of North Americans.[1,2] Untreated obstructive sleep apnea is a multi-organ system disease, and is associated with increased risk of moving vehicle crash,[3] cardiovascular disease,[4,5] impaired glucose tolerance,[6] and cognitive impairment.[7] Indeed, obstructive sleep apnea is now first on the list of the causes of secondary hypertension promulgated by the Joint National Council on Hypertension (JNC 7).[8]

Most importantly, moderate-to-severe OSA is associated with increased all-cause mortality.[9]

The treatment of choice for obstructive sleep apnea is continuous positive airway pressure (CPAP), which is effective in relieving sleepiness and has been shown to improve or reverse many of the sequelae of sleep-disordered breathing. However, CPAP is burdensome treatment, and alternative treatments are eagerly sought by patients with OSA and their treating physicians. Although weight loss has been advocated as a primary treatment strategy for OSA, it is difficult to accomplish, and even more difficult to maintain.

This study is one of the first randomized controlled trials assessing weight loss as a treatment for sleep apnea, and the results are encouraging. In this paper, a very low-calorie diet resulted in a clinically important improvement of moderate-to-severe obstructive sleep apnea in obese men. AHI was cut by two-thirds in the intervention group compared with no change in the control group, and 17% of the intervention group patients had resolution of their disease.

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Because weight loss is so difficult to accomplish, much of what is known about the effects of weight loss on OSA has resulted from bariatric surgery studies,[10] and randomized controlled trials in this area are exceed ingly rare. A recent randomized trial of weight loss in patients with mild sleep apnea resulted in a 40% reduction in AHI from a weight loss of 10.7 kg after a year in patients with mild disease.[11] Another recent study of intensive lifestyle intervention vs group sessions about diabetes management resulted in a 10.8 kg weight loss in the intervention group, and a three-fold increase in resolution of OSA.[12]

So it can be done. The question is how best to do it. The authors of the current report note that "provision of bariatric surgery to all patients with this problem is not realistic." No kidding. They also argue that a systematic review of randomized weight-loss trials with a minimum follow-up of a year showed that very low-energy diets resulted in a greater (10%) weight reduction from baseline weight than drug treatment (8%). While that may be true, it implies a significant regain of weight after the termination of the very low-calorie diet. Indeed, a recent meta-analysis of very low-calorie diets, compared with low-calorie diets, concluded that very low-calorie diets produced greater short-term, but similar long-term weight loss.[13] What remains to be seen is the evolution of the sleep apnea in the patients in this study over time.

For now, maybe the message for our patients should be: Losing weight will help your sleep apnea, and you don't have to get thin again to get significant improvement. Every little bit helps. ■

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Importance of QRS Duration in Patients with Suspected Coronary Artery Disease

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

Dr. Karpman reports no financial relationship to this field of study.

Synopsis: *Resting QRS duration is an independent predictor of cardiac death and/or myocardial infarction in patients with suspected CAD.*

Source: Arend FL, et al. Prognostic significance of QRS duration in patients with suspected coronary artery disease referred for noninvasive evaluation of myocardial ischemia. *Am J Cardiol* 2009;104:1490-1493.

THE STANDARD 12-LEAD ELECTROCARDIOGRAM IS AN important first test for cardiac risk stratification because of its simplicity and wide availability. Several published studies in patients with previous myocardial infarctions and/or congestive heart failure have demonstrated that the QRS duration correlated strongly with the eventual clinical outcome.[1-3]

Because the prognostic impact of prolonged QRS duration in patients without known structural heart disease had not yet been evaluated, Arend and his colleagues mounted a study to evaluate the prognostic significance of the QRS duration in patients with suspected coronary artery disease (CAD) referred for non-invasive evaluation of myocardial ischemia by dobutamine stress echocardiography. During the mean follow-up period of 4.2 years, 280 patients died and 60 suffered a nonfatal myocardial infarction among the 1227 patients who were studied. Annualized event rates for cardiac death and/or myocardial infarction were significantly greater in patients who demonstrated QRS durations equal to or greater then 120 msec. QRS duration on the standard resting electrocardiogram therefore appears to be an independent predictor of cardiac death and cardiac death/nonfatal infarction in patients with suspected CAD.

■ **COMMENTARY**

Prior studies have clearly demonstrated that the QRS duration in patients with suspected CAD (i.e., left ventricular dysfunction, heart failure, recurrent ventricular arrhythmias) provides incremental prognostic information regarding clinical outcomes.[1-3] The Arend study revealed that the QRS duration in patients with suspected (and not yet proven) CAD also provides incremental prognostic information not only for the prediction of cardiac death, but also for the combined endpoints of cardiac death and/or myocardial infarction. Therefore, this simple, inexpensive, and objective measurement can be used as an add-on to myocardial stress testing for risk stratification of patients with suspected and not already proven CAD. Although this study utilized a single, very specific type of provocative stress test, the findings suggest that careful measurements of the resting QRS duration is almost certainly of value in all patients and that the information derived will help clinicians determine CAD prognosis in the individual patient with or without known CAD. However, larger, carefully controlled and longer trials in these patients are needed to properly position the information derived by measuring QRS complex width into our prognostic armamentarium. ■

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Updates on Adult Immunizations

SPECIAL FEATURE

By Stan Deresinski, MD, FACP

Clinical Professor of Medicine, Stanford, Associate Chief of Infectious Diseases, Santa Clara Valley Medical Center

Dr. Deresinski serves on the speakers bureau for Merck, Pfizer, Wyeth, Ortho-McNeil (J&J), Schering-Plough, and Cubist, does research for the National Institute of Health, and is an advisory board member for Schering-Plough, Ortho-McNeil (J&J), and Cepheid. This article originally appeared in the February issue of Infectious Disease Alert. *At that time it was reviewed by Connie Price, MD, Assistant Professor, University of Colorado School of Medicine; she reports no financial relationship to this field of study.*

Source: Centers for Disease Control and Prevention. Recommended adult immunization schedule — United States, 2010. *Morbid Mortal Weekly Rep MMWR* 2010;59:1-4.

THE U.S. ADVISORY COMMITTEE ON IMMUNIZATION Practices (ACIP) has published its annual updated recommendations for routine immunizations of adults. The changes from the recommendations for 2009 are not extensive, but they are important.

Human Papillomavirus (HPV)

In October 2009, the FDA approved Cervarix®, a bivalent vaccine containing the oncogenic HPV types 16 and 18, for the prevention of cervical cancer and precancerous lesions in females ages 10-25. Gardasil®, a quadrivalent vaccine containing HPV types 6 and 8, which cause genital warts, in addition to types 16 and 18, has been available for several years with approval for use in the same general age group of females. Approval was also granted last October for its use in the vaccination of boys and men ages 9-26 for the prevention of genital warts caused by HPV types 6 and 11, and ACIP has now endorsed this use, if administered appropriately, cautioning that its efficacy is greatest when administered before initiation of sexual activity.

Measles, Mumps

Adults born before 1957 continue to be considered likely to be immune to measles and mumps as the result

of natural exposure, while those born during or after that year should receive 1 or more doses of vaccine with certain exceptions.

Those born during or after 1957 do not require MMR if they have a medical contraindication (e.g., significant immunocompromise), documentation of prior vaccination, laboratory evidence of immunity, or documentation of measles diagnosed by a physician. In an unchanged recommendation, ACIP states that a second dose of MMR vaccine, administered 4 weeks after the first dose, is recommended for adults who: 1) have been recently exposed to measles or are in an outbreak setting; 2) have been vaccinated previously with killed measles vaccine; 3) have been vaccinated with an unknown type of measles vaccine during 1963-1967; 4) are students in postsecondary educational institutions; 5) work in a health care facility; or 6) plan to travel internationally.

Similarly, adults born during or after 1957 should receive 1 dose of MMR vaccine unless they have: 1) a medical contraindication; 2) documentation of vaccination with 1 or more doses of MMR vaccine; 3) laboratory evidence of immunity; or 4) documentation of physician-diagnosed mumps. Also in an unchanged recommendation, a second dose of MMR vaccine, administered 4 weeks after the first dose, is recommended for adults who: 1) live in a community experiencing a mumps outbreak and are in an affected age group; 2) are students in postsecondary educational institutions; 3) work in a health care facility; or 4) plan to travel internationally.

Hepatitis A Virus

ACIP has added a recommendation that unvaccinated persons who anticipate close contact with an international adoptee should consider vaccination against hepatitis A virus infection.

Meningococcus

Menomune®, a polysaccharide meningococcal vaccine, was licensed in 1978, while Menactra®, a conjugate vaccine was approved in 2005. Each is quadrivalent, providing protection against meningococcal subtypes A, C, Y, and W-135. Menactra, although expected to provide longer-lasting protection than Menomune, received approval only for individuals ages 2-55, while the latter is approved for those age 2 and older, without an upper limit. Adhering to these formal strictures, ACIP now states that Menactra is preferred for adults with indications for vaccination who are ages < 55 years, while Menomune is preferred for adults ages > 55 years. Revaccination with Menactra after 5 years is recommended for adults previously vaccinated with Menactra or Menomune who remain at increased risk for infection (e.g., adults with anatomic or functional asplenia). Persons whose only risk factor is living in on-campus housing are not recommended to receive an additional dose.

***Haemophilus influenza* Type B**

Conjugate *Haemophilus influenzae* type B (Hib) vaccine is effective in and approved for the prevention of related infection in children age 6 weeks to 5 years. Only a small minority of *Haemophilus* infections in adults are due to type B, and the vaccine is specific to this type. Nonetheless, the vaccine is immunogenic in adults, and its use has been suggested in specific populations thought to be at increased risk, such as those with sickle cell disease, leukemia, or HIV infection, and those who are asplenic. ACIP does not specifically recommend the use of the vaccine in such individuals but now states: "Administering one dose of Hib vaccine to these high-risk persons who have not previously received Hib vaccine is not contraindicated." ■

Brief Report

Supersize My Bugs

By Carol A. Kemper, MD, FACP

Clinical Associate Professor of Medicine,
Stanford University, Division of Infectious Diseases,
Santa Clara Valley Medical Center

Carol A. Kemper, MD, FACP, does research for GSK Pharmaceuticals, Abbott Laboratories, and Merck. This article originally appeared in the February issue of Infectious Disease Alert.

Source: White AS, et al. Beverages obtained from soda fountain machines in the U.S. contain microorganisms, including coliform bacteria. *Int J Food Microbiol* 2010;137:61-66.

THIS ENGAGING EPIDEMIOLOGIC SURVEY ASSESSED microbial contamination of soda-fountain drinks, dispensed from nine different fountain machines, relative to current U.S. drinking water standards. Ninety drinks, including diet soda, regular soda, water, and ice were cultured. A follow-up survey examined the concentration of bacteria and other organisms found in an additional 27 drinks collected either in the morning or the afternoon. The beverages were self-dispensed or dispensed by a server.

Nearly half (48%) of the beverages contained coliforms, and one in 10 had bacterial colony counts > 500 colony-forming units per mL. The most common pathogen identified was *Chryseobacterium meningosep-*

ticum, found in 17% of the beverages, followed by *E. coli* in 11%. Other microbes isolated included *Klebsiella*, *Staphylococcus*, *Serratia*, *Stenotrophomonas*, and *Candida* spp. Ice alone did not exceed U.S. drinking water standards. No difference was observed in rates of bacterial contamination between self-dispensed drinks and those dispensed by a server, suggesting the machines are the source of the contamination. ■

Pharmacology Update

Tocilizumab Injection (Actemra®)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Elliott and Chan report no financial relationship to this field of study.

THE FIRST INTERLEUKIN-6 (IL-6) RECEPTOR ANTAGONIST has been approved for the treatment of rheumatoid arthritis (RA). Tocilizumab is a recombinant, humanized, monoclonal antibody that specifically binds to both soluble and membrane-bound IL-6 receptors. It was developed in Japan and has been available outside the United States since 2008. It will be marketed in this country by Genentech as Actemra®.

Indications

Tocilizumab is indicated for the treatment of adults with moderately to severely active RA who have not achieved adequate response to one or more anti-TNF drugs.[1]

Dosage

The recommended starting dose (as monotherapy or in combination with DMARDs) is 4 mg/kg every 4 weeks given by intravenous infusion over 1 hour.[1] The dose may be increased to 8 mg/kg based on clinical response. Tocilizumab should not be started in patients with an absolute neutrophil count < 2000/mm^3, platelet count < 100,000/mm^3, or ALT or AST > 1.5 times the upper normal limit.[1] Similarly, dose modification or interruption may be necessary with liver enzyme abnormalities, low neutrophil counts, or low platelet counts.

Tocilizumab is supplied in single-use 20 mg/mL concentrate vials (packaged in 4 mL, 10 mL, and 20 mL).

Potential Advantages

Tocilizumab inhibits a different proinflammatory cytokine (IL-6). The addition of tocilizumab to a DMARD provides additional benefit compared to the DMARD alone. It may slow the progression of structural joint damage.[2,3]

Potential Disadvantages

As with other biologic agents that affect the immune system (e.g., anti-TNF drugs), there is a warning for increased risk of serious infections such as tuberculosis, bacterial, viral, and fungal infections.[1] Tocilizumab has been associated with increased risk of GI perforation (complication of diverticulitis), reduction of neutrophil and platelet counts, and elevation of liver transaminase and lipid parameters.[1] Serious hypersensitivity reaction and demyelinating disorders have been reported. Leukoencephalopathy with cognitive impairment was reported in one patient during the Phase III trials in Japan.[4]

Comments

The safety and efficacy of tocilizumab was evaluated in five randomized, double-blind trials in adult patients (n = 4087) with moderately to severely active rheumatoid arthritis (at least 8 tender and 6 swollen joints at baseline).[1,5-8] The primary endpoint was achieving a 20% response on the American College of Rheumatology criteria (ACR20). In patients with no recent use of methotrexate or no previous treatment failure with methotrexate or an anti-TNF drug, 70% of patients on tocilizumab 8 mg/kg achieved ACR20 at 24 weeks compared to 53% for methotrexate.[1,5] In patients with longstanding RA, tocilizumab 4 mg/kg and 8 mg/kg plus methotrexate or a DMARD were more efficacious than methotrexate or a DMARD alone.[6,7] Results were similar in patients with one anti-TNF failure.[8] In patients with inadequate response to methotrexate monotherapy, the addition of tocilizumab showed inhibition of progression of structural joint damage compared to the addition of placebo.[2] In a 52-week study, more patients treated with tocilizumab had no radiographic disease progression compared to DMARDs, 56% vs 39% (P < 0.01).[3] Tocilizumab is generally well tolerated. The discontinuation rates during clinical trials due to adverse events were 4%-10% for monotherapy and 4%-12% as combination therapy.[9] The most common adverse events were upper respiratory tract infection, nasopharyngitis, headache, and hypertension. Changes in laboratory parameters included increased ALT and plasma lipids,

and decreased neutrophils and platelets. ALT and AST levels and neutrophil and platelet counts should be monitored every 4-8 weeks. Lipid levels should be monitored every 4-8 weeks after initiation of treatment and approximately every 6 months thereafter. There are currently no comparative studies with other biological agents such as anti-TNF drugs.

Clinical Implications

Currently there are numerous antirheumatic biological agents with different mechanisms of action. Currently, anti-TNF drugs are first-line biological agents. Tocilizumab may be an effective option for patients who have long-standing, treatment-refractory moderate-to-severe RA or those who have failed at least one anti-TNF drug. ■

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CME Questions

7. Weight loss in patients with sleep apnea:
a. occurs so rarely that not much is known about its effects on the AHI.
b. happens occasionally, but cannot result in cure.
c. confers the greatest improvement in those with the most severe disease.
d. can only be accomplished to a significant degree with bariatric surgery.

8. Measurements of QRS duration in patients with suspected CAD:
a. are of little value in predicting the occurrence of cardiac death/nonfatal myocardial infarction.
b. are an independent predictor of cardiac death and cardiac death/nonfatal myocardial infarction.
c. are abnormal if the duration is between 80-120 msec.
d. are prognostically significant if the duration is more than 120 msec.
e. Both b and d are correct.

Answers: 7. c, 8. e.

CME Objectives

Upon completion of this educational activity, participants should be able to:
- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

Clinical Briefs

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville
Dr. Kuritzky is a consultant for Sucampo Pharmaceuticals, Takeda, Boehringer Ingelheim; and is a consultant and on the speaker's bureau for Novo Nordisk, Lilly, Daiichi Sankyo, Forest Pharmaceuticals, Cephalon, Novartis, and Sanofi Aventis.

Aspirin for primary prevention in diabetes? Maybe

Source: Calvin AD, et al. Aspirin for the primary prevention of cardiovascular events: A systematic review and meta-analysis comparing patients with and without diabetes. *Diabetes Care* 2009;32:2300-2306.

The syllogism seemed so simple: 1) The CV risk reduction of aspirin (ASA) in primary prevention is linearly related to baseline risk; 2) DM is a high-risk population for CV events; and therefore, 3) ASA should be really good for primary prevention in diabetics. Well, it's not quite so simple.

The authors of this report in *Diabetes Care* performed a random-effects meta-analysis and Bayesian logistic regression (whatever that means, you ask?) to provide an opinion about whether aspirin is beneficial for primary prevention in diabetes. Their conclusion, based upon 8 trials that included patients with diabetic subgroups among the overall cohort (5 trials) as well as diabetes-only trials (3 trials), is that the benefits of aspirin are similar in persons with or without diabetes.

I don't really know what "a random-effects meta-analysis and Bayesian logistic regression" means, but it would appear encouraging that this analysis, which incorporates data from 8 major clinical trials totaling more than 90,000 study subjects, suggests that aspirin might be a good thing.

Trouble is, I'm just not so sure. First, it is a matter of debate whether there is really any such thing as primary prevention in diabetes; after all, adult type 2 diabetics are considered a CV risk equivalent, since their CV risk (without ever having an MI) is as great as a person who has already had one. So, is aspirin in a diabetic primary or secondary prevention?

Secondly, the only 2 recent trials that studied only diabetics and were primarily designed to study the effects of aspirin in diabetics (the JPAD and POPADAD trials) both failed to find a beneficial effect of aspirin.

For the time being, popular opinion suggests that aspirin is a good thing. I'm not so sure. ■

Secondary prevention of depression: Cognitive therapy

Source: Bockting CL, et al. Long-term effects of preventive cognitive therapy in recurrent depression: A 5.5-year follow-up study. *J Clin Psychiatry* 2009; 70:1621-1628.

For mild-to-moderate depression, the literature indicates that cognitive therapy (COG) and pharmacotherapy have similar beneficial effects, although pharmacotherapy is often less expensive and may provide symptomatic improvement more quickly. Because depression is recurrent, it is important to identify whether long-term cognitive therapy is helpful to prevent such recurrences.

To investigate this issue, Bockting et al enrolled major depressive disorder patients who had achieved remission (n = 172) and compared usual care with usual care plus COG. The COG was administered as weekly 2-hour group sessions over a 2-month period. After this 2-month COG intervention, both groups were followed for 5.5 years.

The group that had received 8 weeks of COG had a 21% relative risk reduction for recurrence over the next 5 years. Suicide (60% of cases are related to depression) remains in the top 10 causes of death. The value of COG treatment for even as brief a period as 8 weeks might have substantial long-term clinical payoff. ■

Dementia: We all wish for a simple answer

Source: Snitz BE, et al. *Ginkgo biloba* for preventing cognitive decline in older adults: A randomized trial. *JAMA* 2009;302:2663-2670.

The burgeoning population of advanced seniors (age > 75 years) includes an ever-growing population of persons with cognitive impairment and dementia. Popular complementary and alternative interventions to forestall dementia abound, among which it has been suggested that ginkgo has memory-preserving qualities.

Unfortunately, the data supporting long-term favorable outcomes for cognitive function are lacking. Nonetheless, because *Ginkgo biloba* has a popular impression of being favorable for mental faculties, and because earlier trials have faced limitations of trial duration, size, and population age, more conclusive insights have been sought.

A study sample of community-dwelling seniors (n = 3069; mean age, 79 years) was administered either 120 mg of ginkgo or placebo twice daily for a median follow-up of 6.1 years. Rates of decline in cognitive function, and numerous other metrics including attention, language, executive function, and others, were not statistically improved by administration of ginkgo. Although there were no significant adverse effects attributable to ginkgo, there is no sound basis for advocating the use of ginkgo for long-term cognitive improvement. ■