AMERICAN ACADEMY OF OPHTHALMOLOGY
The Eye M.D. Association

COMPLEMENTARY THERAPY ASSESSMENT
ANTIOXIDANT VITAMIN AND MINERAL SUPPLEMENTS AND CATARACT PREVENTION AND PROGRESSION
LIMITED REVISION JANUARY 2002

SUMMARY

INTRODUCTION TO THE TOPIC

There is considerable interest in the role of antioxidant vitamins in the development of cataracts. Antioxidants neutralize the action of free radicals, thereby preventing damage to cells, and may be relevant to cataracts if oxidative damage to the lens is found to lead to cataract formation. Antioxidants are found naturally in food and include vitamin C (ascorbic acid), vitamin E (alpha-tocopherol), carotenoids, and anthocyanidins. The minerals selenium and zinc are cofactors for naturally occurring antioxidant enzymes.

CONCLUSIONS

The Age-Related Eye Disease Study (AREDS), a randomized, placebo-controlled trial of high-dose supplementation with vitamins C, E, and beta-carotene over 6 years has reported no apparent effect on the development or progression of age-related lens opacities in an older, relatively well-nourished, predominantly Caucasian American adult population. Several level II studies report that a lessened risk of cataract development is associated with higher serum levels of nutrients, higher reported intake of nutrients, or reported supplement use, while other studies report no statistically significant association for these factors. These inconsistencies may be due to different assessments of diet, supplement use, or cataract in the study designs. Two studies reported a slightly increased risk of developing cataracts with supplements, one for posterior subcapsular cataracts and one for cortical opacities.

At this time, the available evidence does not support a recommendation for healthy patients to use antioxidant vitamin and mineral supplements to prevent or treat cataracts. Patients can be encouraged to maintain a healthy diet by consuming fresh fruits and vegetables for a variety of health benefits, and can be informed of results of current studies.

BENEFITS

The AREDS reported no statistically significant effect of antioxidant supplements on the development or progression of age-related lens opacities. The Linxian Cataract Studies are two randomized double-masked controlled trials performed in a nutritionally deprived population in rural China, which demonstrated a positive effect of a nutritional supplement on the prevalence of nuclear cataracts. Results from observational studies report inconsistent findings.

RISKS

The adverse effects and toxicity, if any, of supplementation with antioxidants over a long-term period (10 years or more) is unknown. There were no statistically significant serious adverse effects associated with treatment in the AREDS. In two randomized controlled trials of supplementation for groups of individuals at high risk for cancer (smokers and asbestos-exposed workers), high levels of beta-carotene were associated with significantly higher cancer incidence and mortality rates. One theory on the risk of

supplementation with a single product is that protection may require multiple nutrients consumed in a balanced combination at nutritional doses.

There is also some economic risk of using antioxidant supplements, because the cost can be significant and is seldom covered by health insurance. The quality of supplements can vary by manufacturer and absorption can be affected by a variety of dietary factors.

REPORT

DESCRIPTION OF ANTIOXIDANT VITAMIN AND MINERAL SUPPLEMENTS

Antioxidants neutralize the damage to cells caused by free radicals and may be relevant to cataracts if oxidative damage to the lens leads to cataract formation. Antioxidant substances are found naturally in food and include vitamin C (ascorbic acid), vitamin E (alpha-tocopherol), carotenoids, and anthocyanidins. The minerals selenium and zinc are co-factors for naturally occurring antioxidant enzymes. Carotenoids are nutrients that are not classified as vitamins, and they include beta-carotene, alpha-carotene, the lycopenes, lutein, and zeaxanthin. The carotenoids are found in leafy green vegetables, corn, kiwi, and many other green, red, or yellow fruits and vegetables. The anthocyanidins are responsible for the blue color of blueberries and bilberries. Riboflavin (vitamin B2) and niacin, which occur in animal and plant tissues, have also been studied in relation to cataract development.

Many different brands of antioxidant supplements are sold singly and in various combinations as tablets, capsules, or sprays. The manufactured quality and formulation of the supplement can influence its absorption and therefore its potential benefit.

MECHANISM OF ACTION

The exact mechanism of antioxidants in the lens is not known. A hypothesis is that damage to the lens is caused by oxidative stress, leading to denaturation and precipitation of proteins and eventually to opacification. It is possible that oxidants damage the lens membranes and enzymes responsible for electrolyte balance and energy production. Antioxidants possibly prevent cellular damage in the lens by eliminating free radicals and harmful oxidants that are generated by light absorption and by normal metabolic processes.[1,2] Vitamins C and E are found in the lens, and it appears that higher vitamin C intake produces an increase in concentration in the lens. There is some evidence that shows a correlation between intake of vitamin E and its concentration in the lens, but it is not conclusive.[3]

DEFINITION OF THE PROBLEM

Cataract is the leading cause of blindness worldwide[4] and remains an important cause of blindness and visual impairment in the United States.[5,6] In the Baltimore Eye Survey, cataract was found to be the leading cause of blindness among the African American population over 40 years of age, and unoperated cataract was found four times more commonly among African Americans than Caucasian Americans.[6] Cataract surgery is a highly successful procedure, with nearly 90% of patients reporting increased visual function after surgery.[7]

There are several different types of cataract: nuclear, cortical, posterior subcapsular (PSC), and mixed. Each type has its own anatomical location, pathology, and risk factors for development. Several systems are available to classify and grade lens opacities systematically by imaging. Nuclear cataracts consist of a central opacification or coloration that interferes with visual function. There are different types of nuclear cataracts, accompanied by either brunescence, opalescence, or both. Nuclear cataracts tend to progress slowly and affect distance vision more than near vision. In advanced cases, the lens becomes brown and opaque.

Cortical cataracts are caused by changes in the ionic composition and hydration of the cortex. Cortical opacities can be central or peripheral, and sometimes may best be appreciated by retroillumination or retinoscopy. Patients with this type of

cataract commonly complain of glare. A mature cortical cataract occurs when the entire cortex becomes white and opaque.

Posterior subcapsular cataracts are associated with migration of lens epithelial cells to the PSC area and subsequent enlargement. The cell migration can cause signifycant visual impairment if it affects the axial portion of the lens. Posterior subcap-sular cataracts are found more often in younger patients than nuclear or cortical cataracts. Patients often have glare and poor vision with bright lighting, and their near vision is more affected than distance vision.

FDA/LEGAL STATUS

According to the National Institutes of Health Office of Dietary Supplements,[8] the Dietary Supplement Health and Education Act of 1994 defines a dietary supplement (other than tobacco) as a product that bears or contains one or more of the following dietary ingredients: a vitamin, mineral, amino acid, herb, or other botanical; as a substance that increases the total dietary intake; or as a concentrate, metabolite, constituent, extract, or combination of any ingredient described above. Any of these must be intended for ingestion in the form of a capsule, powder, tablet, softgel, liquid, or gelcap and must not be represented as a conventional food or as a sole item of a meal or the diet.

Dietary supplements are widely available through many commercial sources, including health food stores, grocery stores, and pharmacies, and by mail and on the Internet. Historically, in the United States, the most prevalent type of dietary supplement was a multivitamin/mineral tablet or capsule that was available in pharmacies by prescription or over the counter. Supplements containing strictly herbal preparations were less widely available. Currently in the United States, a wide array of supplement products are available, including vitamins, minerals, and other nutrients; botanical supplements; and ingredients and extracts of animal and plant origin. Producers of supplements are not allowed to attribute any potential health benefit to their products.

The Dietary Supplement Health and Education Act of 1994 limits the authority of the Food and Drug Administration (FDA) over dietary supplements since they are not classified as drugs. The FDA requirement for premarket review of these products is less than that over other products it regulates, such as drugs and many additives used in conventional foods. The FDA oversees safety, manufacturing, and product information such as claims in a product's labeling, package inserts, and accompanying literature. The Federal Trade Commission, which oversees advertising, has issued advertising guidelines and has taken a number of enforcement actions against companies whose advertisements contained false and misleading information.

SUMMARY OF EVIDENCE

Search Methods and Study Selection

MEDLINE and the Cochrane Library were searched using the keywords cataract, nutrition, antioxidants, bilberry, and vitamins. The MEDLINE search was restricted to the English language. The Cochrane Library had no completed systematic reviews on this subject. The International Bibliography Information on Dietary Supplements (IBIDS) was also searched using the keyword cataract, and the search was restricted to peer-reviewed articles.

Statistical Issues and Study Design

One randomized, placebo-controlled trial of high-dose supplementation with vitamins C, E, and beta-carotene over 6 years has reported results. This trial, the Age-Related

Eye Disease Study (AREDS), had overall adherence to the study medication regimen and follow-up of 75%.

Two additional randomized, double-masked, controlled trials were found in the literature, but there are limits to the generalizations that can be made about the findings because the studies were performed in a population with significant nutritional deficiencies in rural China. Moreover, follow-up was 70% to 78% of all participants, and cataract status was only assessed at follow-up and not at baseline. Another randomized controlled trial of vitamin E supplementation, the Vitamin E, Cataract, and Age-Related Macular Degeneration (VECAT) study, has reported results in abstract form only.

All other studies were observational, and several are limited in their interpretation because they did not measure cataract development or dietary and supplement intake in a standardized fashion.[1] It is difficult and imprecise to assess antioxidant nutrient status based on self-reported dietary intakes, partly because variations in absorption are not taken into account and because of recall bias.[9] Serum concentrations, which do not depend on participant recall, take into account differences in absorption, and they are typically representative of recent intake. Nonrandomized studies cannot adjust for all confounding factors that could affect the risk of developing cataracts, such as other differences between populations who take supplements and have healthier diets and populations who do not take supplements.[2] For example, patients who take supplements may represent a healthier population overall. Thus, observational studies can strongly suggest an association, but they cannot prove a causative effect.

Specification of Level of Evidence

The Age-Related Eye Disease Study is rated as Level I evidence. Two additional randomized double-masked controlled trials performed in a population with nutritional deficiencies were conducted in such a manner as to produce accurate and reliable data, but they did not collect information on cataract status at baseline and therefore are rated as Level II evidence. All other studies are observational, and interpretation of them is limited because of deficiencies in study design.[1]

ONGOING STUDIES

There are four large ongoing studies, three in the United States and one in Australia, and initial results will become available in 2002. In the VECAT study in Melbourne, Australia, a total sample of 1,204 individuals 55 to 80 years old have been enrolled in a trial of vitamin E 500 IU/day and placebo over 5 years.[10]

Three additional trials in the United States will include cataract in the study outcomes. The Women's Health Study has randomized 39,876 healthy female health professionals 45 years old and older to low-dose aspirin and antioxidant vitamins (vitamin C, vitamin E, beta-carotene, and a combination of folate, vitamin B6, and vitamin B12). In the Physician's Health Study II, 15,000 male physicians will be randomized to one of four groups, including beta-carotene and placebo groups. The Women's Antioxidant Cardiovascular Study has 8,171 women at high risk for cardiovascular disease randomized to vitamin C, vitamin E, folate, vitamin B6, and vitamin B12 supplementation.

BENEFITS

Table 1 summarizes the results of the completed trials discussed in this assessment. The AREDS randomly assigned 4,629 participants to receive daily oral tablets containing either antioxidants (vitamin C, 500 mg; vitamin E, 400 IU; and beta-carotene, 15 mg) or no antioxidants.[11]

Participants were followed for an average of 6.3 years. No statistically significant effect of the antioxidant formulation was seen on the development of age-related lens opacities (odds ratio=0.97, *P*=0.55). There was also no statistically significant effect of treatment in reducing the risk of progression for any of the 3 lens opacity types or for cataract surgery. Study participants were predominantly Caucasian American (96%), relatively well nourished, and the median age was 68 years. At baseline, 8% were current cigarette smokers and 66% chose to take Centrum (Whitehall-Robins Healthcare, Madison, NJ), a multivitamin and mineral supplement with recommended daily allowance-level dosages.

The Linxian Cataract Studies are two randomized double-masked controlled trials with vitamin and mineral supplements conducted in rural China.[2] In the first trial (n=2,141), patients were randomly assigned to take either two multiple vitamin/mineral tablets and one beta-carotene capsule or matching placebos over a 6-year period. A total of 78% of participants were examined at follow-up. This study found that multivitamin supplements appeared to reduce the risk of nuclear cataracts for patients 65 to 74 years old by 36%. There was no significant effect found for patients 45 to 64 years old. The second trial (n=3,249) involved four different vitamin/ mineral combinations and eight treatment groups, including a placebo group, over a 5-year period, with 70% of patients examined at follow-up. This study found that the combination of riboflavin and niacin was associated with a reduced risk of nuclear cataract (44% decrease) in patients 65 to 74 years old. Cataract status was assessed only at follow-up.

A preliminary report from the VECAT Study, a trial of vitamin E supplementation versus placebo in 1,193 individuals, found no significant difference between the two groups in 4-year progression of either nuclear or cortical cataract, and no signify-cant difference in the proportion of cases of cataract extraction [Robman LD, McCarty CA, Tikellis G, et al. VECAT study: The effect of vitamin E on the progression of lens opacification (preliminary results). Invest Ophthalmol Vis Sci 2001; 42 (Suppl):S508].

A 1995 major review of cataract risk factors concluded that age-related cataract is a multifactorial disease and that there are different risk factors for different diseases.[12] It also showed that findings of antioxidant studies were conflicting, and that more data are required to establish an association with cataracts. A 1998 review of nutrition supplements and the eye stated that "Epidemiological studies give inconsistent support to the suggestion that nutrition plays a role in development of cataract in man."[3] A 1999 review on the same subject concluded, "Epidemiological evidence for the antioxidant hypothesis in humans has been conflicting."[1]

A review article on the recommended dietary allowance for vitamin C concluded that "At this stage it is difficult to propose a protective vitamin C intake with respect to cataract because of the limited number of prospective cohort studies and the wide range of protective concentrations reported."[13] A recent Institute of Medicine Study on Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium and Carotenoids noted, "A number of observational epidemiological studies have examined the relationship between intakes of vitamin C, vitamin E, and carotenoids and the presence of cataracts in humans. Several studies indicate a lowered risk of cataracts associated with either an increased serum level of these dietary components or supplement use. These studies, since observational in nature, do not constitute at this time a sufficient basis for a conclusion that these dietary components can prevent cataracts in humans."[14]

The Lens Opacities Case-Control Study (n=1,380) found high dietary intake (as reported by the patients) of vitamin C, vitamin E, riboflavin, and carotene appeared to have a protective effect for nuclear, cortical, and mixed cataracts, reducing the risk of developing cataracts by more than 50%.[15] It also found that a higher serum vitamin E level was associated with a lower risk of nuclear cataract, riboflavin appeared to be associated with a lower risk of any type of cataracts, and iron was associated with a lower risk of cortical cataract. A biochemical analysis for vitamin E and selenium in blood samples was subsequently performed in all patients.[16] This study found that lens opacities were associated with lower levels of vitamin E, iron, riboflavin, and protein. Another case-control study with similar methodology, The Italian-American Cataract Study (n=1,008), did not find linkages between any nutrients (intake information obtained by interview) or biochemical testing and lens opacities.[17] A third case-control study with similar methodology, the India-American Case-Control Study (n=1,441), did not find an association between vitamin E and cataract.[18]

Cross-sectional studies involving surveys based on participant recall included the Nutritional Factors in Eye Disease Study (n=2,152), the Barbados Eye Study (n=4,314), the Blue Mountains Eye Study (n=2,900), the Second National Health and Nutrition Examination Survey (NHANES II) (n=4,001) and a report from the ongoing VECAT study (n=1,111). The Nutritional Factors in Eye Disease Study found that in individuals without diabetes, regular use of multivitamins for 10 years was associated with a decreased risk of nuclear sclerosis.[19] It also assessed serum levels for 400 patients, and it did not find that higher serum levels of carotenoids or tocopherols were associated with less severe cortical or nuclear opacities.[20] Another random sample of 400 patients in this population with a 5-year follow-up did suggest that serum tocopherol concentrations were associated with cataract, but serum carotenoid concentrations were not.[9]

The Barbados Eye Study results indicated an association between a reduced risk for cortical cataract for patients under 70 years old and the regular use of nutritional supplements.[21] The Blue Mountains Eye Study found a decreased prevalence of nuclear cataract in persons reporting higher intakes of protein, vitamin A, niacin, thiamin (B1), and riboflavin.[22] Vitamin C was not found to be associated with reduced cataract prevalence. The study noted that "Numerous epidemiological studies have been conducted of the relationship between intake of antioxidant vitamins (vitamins A, C, and E) and risk of cataract in older people. These studies have produced conflicting findings, perhaps because of inadequate measurement of diet and/or cataract in many studies."[22]

In the Blue Mountains Eye Study, use of multivitamin supplements was associated with reduced prevalence of nuclear cataract. For both nuclear and cortical cataract, longer duration of multivitamin use was associated with reduced cataract prevalence. Folate and vitamin B12 supplements were protective against cortical cataract.[23]

A study of serum levels of vitamin C in individuals 60 to 74 old years enrolled in NHANES II found that each 1 mg increase in serum levels of vitamin C was associated with a 26% lower prevalence of self-reported cataracts.[24] There were no associations found for self-reported vitamin A and vitamin E supplement intake and prevalence of self-reported cataracts. However, NHANES II did not collect information on type of cataract and risk factors for cataract. Volunteers enrolled in the ongoing VECAT study were questioned about their past

vitamin E supplementation.[25] An association was found between prior supplementation and the absence of cortical opacity, but no association was found for nuclear opacity.

One study of 410 hypercholesterolemic men in Finland found that a low-plasma vitamin E level was associated with a 3.7-fold excess risk of progression of early lens opacities, compared with the highest plasma vitamin E level.[26] A cohort group of 1,354 persons from the Beaver Dam Eye Study was asked about their current and past antioxidant intakes using a questionnaire. Nuclear cataracts were not significantly related to vitamin E or C in the overall group. Patients with the highest reported intake of lutein were half as likely to have a cataract as patients with the lowest reported intake. The authors concluded that "While results of this short-term follow-up study are consistent with a possibly protective influence of lutein and vitamins E and C on the development of nuclear cataracts, the evidence in the present study provides weak support for these associations."[27]

A number of prospective cohort observational studies have examined the relationship of cataract and nutrition. The Physicians' Health Study (n=3,553) found a modest and marginally significant decrease in the risk of cataract with multivitamin supplementation as reported by questionnaire.[28] It did not find an effect for vitamins C and E. In the Health Professional Follow-Up Study, a group of 36,644 male health professionals was followed for 8 years and nutrient intake was reported by questionnaire.[29] The findings showed a modestly lower risk of cataract extraction in men with a higher dietary intake of zeaxanthin and lutein. No significant association was found for vitamin A or other carotenoids. The findings do support recommendations for eating vegetables and fruit rich in carotenoids.

The Nurses Health Study (n=50,828) found that use of vitamin C supplements for 10 or more years as reported by survey was associated with a 45% lower risk of cataract extraction compared to women who did not use vitamin C supplements.[30] There was no significant association found between multivitamins or vitamin A or E supplements and lessened risk of cataract extraction. A small study of 247 women from the Nurses Health Study also found that women who used vitamin C supplements for more than 10 years had a 77% lower prevalence of early lens opacities compared with women who did not use vitamin C supplements.[31] A large prospective cohort of female nurses (n=77,466) in the Nurses Health Study was followed for up to 12 years.[32] Information on nutrient intake was reported by questionnaire, and results indicated that those with the highest intake of lutein and zeaxanthin had a 22% reduced risk of cataract extraction compared with those with the lowest intake. Other carotenoids (beta-carotene, lycopene), vitamin A, and retinol were not associated with cataract extraction.

In the Baltimore Longitudinal Study on Aging, 660 patients were followed in a prospective cohort study,[33] and serum levels of vitamin E were measured. This study found that serum levels of vitamin E were associated with a lower risk of nuclear cataract.

The Longitudinal Study of Cataract assessed dietary intake, use of vitamin supplements, and plasma levels of vitamin E in 764 participants, with a median follow-up of 4.5 years.[34] The study used standardized methods to photograph and classify opacity type and severity. The results were that the risk of nuclear opacities was reduced by one-third in regular multivitamin supplement users, and the risk was reduced by one-half in regular users of vitamin E and those with higher plasma levels of vitamin E.

The AREDS provides Level I evidence of no apparent effect of high-dose antioxidant supplementation in an older, relatively well-nourished, predominantly Caucasian American adult population. Level II evidence provides conflicting results. It may be that targeted subgroups of the population are more suitable for supplementation.

RISKS

The risk, if any, of supplementation with antioxidant vitamins and minerals is unknown. There were no statistically significant serious adverse effects associated with treatment in the AREDS.[11] There are two randomized controlled trials of supplementation for groups of individuals at high risk for cancer (smokers and asbestos-exposed workers) in which high levels of beta-carotene were associated with signify-cantly higher cancer incidence and mortality rates.[35,36] One theory on the risk of supplementation with a single product is that protection may require multiple nutrients consumed in a balanced combination at nutritional doses.[37]

Some of the epidemiologic studies revealed an association of supplementation with an increased risk of cataracts. In the Linxian Cataract trials, there was a statistically significant association of riboflavin and niacin with an increased incidence of PSC cataracts, but the overall prevalence of PSC cataracts was low.[2] The Nutritional Factors in Eye Disease Study also found an association between regular use of multivitamins and increased risk of cortical opacities in some patients.[19] These effects could be due to temporal confounding, because patients improved their dietary intake recently after several years of deprivation.

There is also some economic risk of using nutritional supplements, because the cost can be significant and is seldom covered by health insurance. The quality of supplements can vary by manufacturer and absorption can be affected by a variety of dietary factors.

QUESTIONS FOR SCIENTIFIC INQUIRY

To understand the role of antioxidant supplements in the prevention and progression of cataracts, the following questions should be answered.

- What are the effects of biochemical oxidation on the lens?
- How does intake affect serum and lens levels of antioxidants?
- Is there a benefit to supplementation, and if so, in what amount and in what combinations? At what stage or age would supplementation be beneficial? How long would supplementation need to take place to remain effective?
- Which groups of people derive benefit from supplementation, e.g., smokers? Can we use objective testing to preselect these favorable responders?
- What constitutes an antioxidant-rich diet, and are there differences between consuming such a diet and taking supplements?

INFORMATION FOR PATIENTS

This material is excerpted from *An FDA Guide to Dietary Supplements*,[8] which is available at http://vm.cfsan.fda.gov/~dms/fdsupp.html.

- A healthy diet with a variety of fresh fruits and vegetables will have many overall benefits and also contain many of the antioxidant vitamins and minerals.
- Consumers who use dietary supplements should always read product labels, follow directions, and heed all warnings.

- To help protect themselves, consumers should do the following:
  - Look for ingredients in products with the U.S.P. notation, indicating the manufacturer followed standards established by the U.S. Pharmacopoeia.
  - Realize that the label term "natural" doesn't guarantee a product is safe.
  - Call a doctor or other health-care provider if they suffer a serious harmful effect or illness that they think is related to supplement use.
- If shoppers find dietary supplements with labels stating or implying the product can help diagnose, treat, cure, or prevent a disease, they should realize the product is being marketed illegally as a drug and as such has not been evaluated for safety or effectiveness.

CONCLUSIONS

The AREDs provides Level I evidence of no apparent effect of high-dose supplementation with vitamins C, E, and beta-carotene on development or progression of age-related lens opacities in an older, relatively well-nourished, predominantly Caucasian American adult population. Several Level II studies report that a lessened risk of cataract development is associated with higher serum levels of nutrients, higher reported intake of nutrients, or reported supplement use, while other studies report no statistically significant association for these factors. These inconsistencies may be due to different assessments of diet, supplement use, or cataract in the study designs. Two studies reported a slightly increased risk of developing cataracts by using supplements, one for PSC cataracts and one for cortical opacities.

At this time, the available evidence does not support a recommendation for healthy patients to use antioxidant vitamin and mineral supplements to prevent or treat cataracts. Patients can be encouraged to maintain a healthy diet by consuming fresh fruits and vegetables for a variety of health benefits, and can be informed of results of current studies.

DEVELOPMENT OF COMPLEMENTARY ASSESSMENTS

Complementary, or alternative therapies, are a growing part of health care in America. The National Institutes of Health National Center for Complementary and Alternative Medicine has broadly defined complementary and alternative medicine as those treatments and health care practices not taught widely in medical schools, not generally used in hospitals, and not usually reimbursed by medical insurance companies. Americans spend an estimated $14 billion a year on alternative treatments. Mainstream medicine is recognizing a need to learn more about alternative therapies and to determine their true value, and most medical schools in the United States offer courses in alternative therapies. The editors of the *Journal of the American Medical Association* announced that publishing research on alternative therapies will be one of its priorities. More scrutiny and scientific objectivity is being applied to determine whether evidence supporting their effectiveness exists.

In the fall of 1998, the Board of Trustees appointed a Task Force on Complementary Therapy to evaluate complementary therapies in eye care and develop an opinion on their safety and effectiveness, based on available scientific evidence, in order to inform ophthalmologists and their patients. A scientifically grounded analysis of the data will help ophthalmologists and patients evaluate the research and thus make more

rational decisions on appropriate treatment choices.

The Academy believes that complementary therapies should be evaluated similarly to traditional medicine: evidence of safety, efficacy, and effectiveness should be demonstrated.[38] Many therapies used in conventional medical practice also have not been as rigorously tested as they should be. Given the large numbers of patients affected and the health care expenditures involved, it is important that data and scientific information be used to base all treatment recommendations. In this way, we can encourage high-quality, rigorous research on complementary therapies.[39]

Ideally, a study of efficacy compares a treatment to a placebo or another treatment, using a double-masked controlled trial and well-defined protocol. Reports should describe enrollment procedures, eligibility criteria, clinical characteristics of the patients, methods for diagnosis, randomization method, definition of treatment, control conditions, and length of treatment. They should also use standardized outcomes and appropriate statistical analyses.

The goal of these assessments is to provide objective information of complementary therapies and provide a scientific basis for physicians to advise their patients, when asked.

To accomplish these goals, the assessments, in general, are intended to do the following:

- Describe the scientific rationale or mechanism for action for the complementary therapy.
- Describe the methods and basis for collecting evidence.
- Describe the relevant evidence.
- Summarize the benefits and risks of the complementary therapy.
- Pose questions for future research inquiry.
- Summarize the evidence on safety and effectiveness.

TABLE 1. Summary of Findings of Completed Studies

Study	Date Published	Type of Study	Sample Size	Measure	Results
High-Dose Vitamin C, E, and Beta-Carotene Supplement					
AREDS[11]	2001	Randomized placebo-controlled	4.629	Supplement use	No effect on the development or progression of lens opacities
Multivitamin Supplement					
Linxian Cataract [2]	1993	Randomized controlled	2,141	Supplement use	36% reduction in nuclear cataract
Blue Mountains Eye Study[23]	2001	Cross-sectional	2,873	Supplement use	Reduced prevalence of nuclear cataract
Nutritional Factors in Eye Disease [19]	1994	Cross-sectional	2,152	Supplement use	Decreased risk of nuclear sclerosis
Barbados Eye Study[21]	1997	Cross-sectional	4,314	Supplement use	Reduced risk of cortical cataract in patients over 70 years old
Physicians Health Study[28]	1994	Prospective cohort	17,744	Supplement use	Modest, marginally significant decrease
Nurses Heath Study[30]	1992	Prospective cohort	50,828	Supplement use	No association
Longitudinal Study of Cataract[34]	1998	Prospective cohort	764	Supplement use	33% reduction in nuclear opacities
Riboflavin/Niacin					
Linxian Cataract[2]	1993	Randomized controlled	3,249	Supplement use	44% reduction in nuclear cataracts
Lens Opacities Case Control[15]	1991	Case-control	1,380	Total dietary intake	Lower risk of any type of cataract
Blue Mountains Eye Study[22]	2000	Cross-sectional	2,900	Total dietary intake	Lower risk of nuclear cataract
Nurses Health Study[30]	1992	Prospective cohort	50,828	Total dietary intake	No association
Vitamin E					
VECAT* (abstract)	2001	Randomized controlled	1,193	Supplement use	No significant difference
Nutritional Factors in Eye Disease Study[9]	1999	Prospective cohort	400	Serum tocopherol level	Association with nuclear cataracts
Lens Opacities Case Control[16]	1991	Case-control	1,380	Serum level	Serum levels associated with lower risk of nuclear cataract
Italian-American Case Control[17]	1991	Case-control	1,008	Serum level	No association
India-American Case Control[18]	1989	Case-control	1,441	Serum level	No association

Study	Date Published	Type of Study	Sample Size	Measure	Results
NHANES II[24]	2000	Cross-sectional	4,001	Supplement use	No significant association
VECAT[25]	2000	Cross-sectional	1,111	Supplement use	Association with absence of cortical opacity
Kuopio Atherosclerosis Prevention Study[26]	1996	Prospective cohort	410	Serum level	Low plasma E associated with increased risk of progression of early lens opacities
Beaver Dam Eye Study[27]	1999	Prospective cohort	1,354	Total dietary intake	No association in overall group
Physicians Health Study[28]	1994	Prospective cohort	3,533	Supplement use	No association
Nurses Health Study[30]	1992	Prospective cohort	50,828	Total dietary intake and supplement	No significant association
Baltimore Longitudinal Study on Aging[33]	1993	Prospective cohort	660	Serum level	Serum levels associated with lower risk of nuclear cataract
Longitudinal Study of Cataract[34]	1998	Prospective cohort	764	Supplement use and serum levels	50% reduction in nuclear opacities in regular supplement users and higher serum levels
Vitamin C					
Blue Mountains Eye Study[22]	2000	Cross-sectional	2,900	Total dietary intake	No association
NHANES II[24]	2000	Cross-sectional	4,001	Serum level	1 mg increase in serum level was associated with 26% lower risk
Beaver Dam Eye Study[27]	1999	Prospective cohort	1,354	Total dietary intake	No association with overall group
Physicians Health Study[28]	1994	Prospective cohort	3,553	Supplement use	No association
Nurses Health Study[30]	1992	Prospective cohort	50,828	Supplement use	45% lower risk of cataract extraction with 10 years or less use
Nurses Health Study[31]	1997	Prospective cohort	247	Supplement use	77% lower prevalence of early lens opacities with use of supplements for more than 10 years
Vitamin A					
Blue Mountains Eye Study[23]	2001	Cross-sectional	2,873	Supplement use	Protective against nuclear cataract
Blue Mountains Eye Study[22]	2000	Cross-sectional	2,900	Total dietary intake	Lower risk of nuclear cataract
NHANES II[24]	2000	Cross-sectional	4,001	Supplement use	No association
Health Professional Study[29]	1999	Prospective cohort	36,644	Total dietary intake	No association
Nurses Health Study[30]	1992	Prospective cohort	50,828	Total dietary intake	No significant association

Study	Date Published	Type of Study	Sample Size	Measure	Results
Nurses Health Study[32]	1999	Prospective cohort	77,466	Total dietary intake	No association
Carotenoids					
Nutritional Factors in Eye Disease[9]	1999	Prospective cohort	400	Serum levels	No association
Beaver Dam Eye Study[27]	1999	Prospective cohort	1,354	Total dietary intake	Highest lutein levels were half as likely to have cataract as lowest lutein levels
Health Professionals Study[29]	1999	Prospective cohort	36,644	Total dietary intake	Modestly lower risk of cataract extraction with zeaxanthin and lutein
Nurses Health Study[32]	1999	Prospective cohort	77,466	Total dietary intake	22% reduced risk of cataract surgery with zeaxanthin and lutein, not with beta-carotene or lycopene

*Robman LD, McCarty CA, Tikellis G, et al. VECAT study: The effect of vitamin E on the progression of lens opacification (preliminary results). Invest Ophthalmol Vis Sci 2001; 42 (Suppl):S508

REFERENCES

1. Congdon NG, West KP Jr. Nutrition and the eye. Curr Opin Ophthalmol 1999; 10:464–73.

2. Sperduto RD, Hu TS, Milton RC, et al. The Linxian cataract studies. Two nutrition intervention trials. Arch Ophthalmol 1993; 111:1246–53.

3. Brown NA, Bron AJ, Harding JJ, Dewar HM. Nutrition supplements and the eye. Eye 1998; 12:127–33.

4. Foster A, Johnson GJ. Magnitude and causes of blindness in the developing world. Int Ophthalmol 1990; 14:135–40.

5. Dana MR, Tielsch JM, Enger C, et al. Visual impairment in a rural Appalachian community. Prevalence and causes. JAMA 1990; 264:2400–5.

6. Sommer A, Tielsch JM, Katz J, et al. Racial differences in the cause-specific prevalence of blindness in east Baltimore. N Engl J Med 1991; 325:1412–17.

7. Steinberg EP, Tielsch JM, Schein OD, et al. National study of cataract surgery outcomes. Variation in 4-month postoperative outcomes as reflected in multiple outcomes measures. Ophthalmology 1994; 101:1131–41.

8. NIH Office of Dietary Supplements. http://ods.od.nih.gov/index.asp. Accessed November 1, 2001.

9. Lyle BJ, Mares-Perlman JA, Klein BE, et al. Serum carotenoids and tocopherols and incidence of age-related nuclear cataract. Am J Clin Nutr 1999; 69:272–7.

10. Garrett SK, McNeil JJ, Silagy C, et al. Methodology of the VECAT study: vitamin E intervention in cataract and age-related maculopathy. Ophthalmic Epidemiol 1999; 6:195–208.

11. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS Report No. 9. Arch Ophthalmol 2001; 119:1439-52.

12. West SK, Valmadrid CT. Epidemiology of risk factors for age-related cataract. Surv Ophthalmol 1995; 39:323-34.

13. Carr AC, Frei B. Toward a new recommended dietary allowance for vitamin C based on antioxidant and health effects in humans. Am J Clin Nutrition; 1999:69:1086-107.

14. Food and Nutrition Board. Institute of Medicine. Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids. http://www.nationalacademies.org. Accessed November 1, 2001.

15. Leske MC, Chylack LT Jr, Wu SY. The Lens Opacities Case-Control Study Group. Risk factors for cataract. Arch Ophthalmol 1991; 109:244–51.

16. Leske MC, Wu SY, Hyman L et al. Biochemical factors in the lens opacities case-control study. Arch Ophthalmol 1995; 113:1113–19.

17. Risk factors for age-related cortical, nuclear and posterior subcapsular cataracts. The Italian-American Cataract Study Group. Am J Epidemiol 1991; 133:541–53.

18. Mohan M, Sperduto RD, Angra SK, et al. India-US case-control study of age-related cataracts. Arch Ophthalmol 1989; 107:670–6.

19. Mares-Perlman JA, Klein BEK, Klein R, Ritter LL. Relation between lens opacities and vitamin and mineral supplement use. Ophthalmology 1994; 101:315–25.

20. Mares-Perlman JA, Brady WE, Klein BE, et al. Serum carotenoids and tocopherols and severity of nuclear and cortical opacities. Invest Ophthalmol Vis Sci 1995; 36:276–288.

21. Leske MC, Wu SY, Connell AM, et al. Lens opacities, demographic factors and nutritional supplements in the Barbados Eye Study. Int J Epidemiol 1997; 26:1314–22.

22. Cumming RG, Mitchell P, Smith W. Diet and cataract: the Blue Mountains Eye Study. Ophthalmology 2000; 107:450-6.

23. Kuzniarz M, Mitchell P, Cumming RG, Flood VM. Use of vitamin supplements and cataract: The Blue Mountains Eye Study. Am J Ophthalmol 2001; 132:19-26.

24. Simon JA, Hudes ES. Serum ascorbic acid and other correlates of self-reported cataract among older Americans. J Clin Epidemiol 1999; 52:1207–11.

25. Nadalin G, Robman L, McCarty A, et al. The role of past intake of vitamin E in early cataract changes. Ophthalmic Epidemiol 1999; 6:105–12.

26. Rouhiainen P, Rouhiainen H, Salonen JT. Association between low plasma vitamin E concentration and progression of early cortical lens opacities. Am J Epidemiol 1996; 144:496-500.

27. Lyle BJ, Mares-Perlman JA, Klein BK, et al. Antioxidant intake and risk of incident age-related nuclear cataracts in the Beaver Dam Eye Study. Am J Epidemiol 1999; 149:801-9.

28. Seddon JM, Christen WG, Manson JE, et al. The use of vitamin supplements and the risk of cataract among US male physicians. Am J Public Health 1994; 84:788–92.

29. Brown L, Rimm EB, Seddon JM, et al. A prospective study of carotenoid intake and risk of cataract extraction in US men. Am J Clin Nutr 1999; 70:517–24.

30. Hankinson SE, Stampfer JM, Seddon MJ, et al. Nutrient intake and cataract extraction in women: a prospective study. BMJ 1992; 305:335–9.

31. Jacques PF, Taylor A, Hankinson SE, et al. Long-term vitamin C supplement use and prevalence of early age-related lens opacities. Am J Clin Nutr 1997; 66:911-16.

32. Chasan-Taber L, Willett WC, Seddon JM, et al. A prospective study of carotenoid and Vitamin A intakes and risk of cataract extraction in US women. Am J Clin Nutr 1999; 70:509–16.

33. Vitale S, West S, Hallfrisch J, et al. Plasma antioxidants and risk of cortical and nuclear cataract. Epidemiology 1993; 4:195-203.

34. Leske MC, Chylack LT, He Q, et al. Antioxidant vitamins and nuclear opacities: the longitudinal study of cataract. Ophthalmology 1998; 105:831–6.

35. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. N Engl J Med 1994; 330:1029–35.

36. Omenn GS, Goodman GE, Thornquist MD, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med 1996; 334:1150–5.

37. Hercberg S, Galan P, Preziosi P. Antioxidant vitamins and cardiovascular disease: Dr Jekyll or Mr Hyde? (editorial). Am J Public Health 1999; 89:289–91.

38. Fontanaros PB, Lundberg GD. Alternative medicine meets science (editorial). JAMA 1998; 280:1618–19.

39. Margolin A, Avants SK, Kleber HD. Investigating alternative medicine therapies in randomized controlled trials (editorial). JAMA 1998; 280:1626–8.

WEB RESOURCES

- NIH Office of Dietary Supplements available at http://ods.od.nih.gov/index.asp
- FDA Consumer: *An FDA Guide to Dietary Supplements*. Available at http://www.cfsan.fda.gov/~dms/fdsupp.html
- Federal Trade Commission available at http://www.ftc.gov
- USDA Agricultural Research Service Phytochemical and Ethnobotanical Databases at http://www.ars-grin.gov/duke/

Prepared by the American Academy of Ophthalmology Complementary Therapy Task Force

Ivan R. Schwab, MD, Chair
Roger Husted, MD
Jeffrey Todd Liegner, MD
Harold P. Koller, MD
William F. Mieler, MD
Sayoko E. Moroi, MD, PhD
Denise Satterfield, MD
Peter R. Holyk, MD, Consultant

Academy Staff: Flora C. Lum, MD
Nancy Collins, RN, MPH
Margo Leslie
Kellie Campbell

Approved by the Quality of Care Secretariat September 15, 2000
Last revision November 11, 2001
Approved by the Quality of Care Secretariat January 24, 2002