



Supplements Combat AMD

An ever-increasing wealth of documented evidence suggests nutritional supplements may help treat AMD. **By Diana L. Shechtman, O.D., and Paul M. Karpecki, O.D.**

Age-related macular degeneration (AMD) is a leading cause of vision loss in the elderly.¹ AMD is largely characterized by a progressive deterioration of the retinal pigment epithelium (RPE) and the photoreceptors.

Although the exact pathogenesis of AMD is still unknown, researchers have identified various risk factors. These risk factors include age, ethnicity, gender, genetics, cardiovascular disease, smoking and sun exposure.¹⁻³ Cumulative oxidative stress may also play a contributory role by leading to apoptosis of the photoreceptor cells.^{3,4}

Several studies have demonstrated the benefits of nutritional supplements, such as antioxidants, for patients with existing AMD.⁴⁻⁸ For example, nutritional supplements have been associated with a decline in the progression of the disease.^{7,8} We will look at some studies here.

AREDS

The majority of current nutritional guidelines for managing patients with AMD come from the Age-Related Eye Disease Study (AREDS).⁸⁻¹⁰

AREDS was the first large-scale, randomized, double-masked clinical trial that answered the question: "What effect do antioxidants have on the progression of AMD?"

AREDS included nearly 4,000 subjects from 11 centers. The results showed that high intake levels of antioxidants and zinc lowered the risk for disease progression by 25%

in patients with intermediate or advanced AMD (*figures 1 and 2*).⁷ Additionally, these nutritional supplements reduced the overall risk of moderate vision loss by 19%.⁷

But, remember that these results were only apparent in patients with intermediate or advanced AMD. Due to the slow, progressive nature of early AMD, nutritional supplements were unable to show any statistical benefit for patients in less advanced stages of AMD (*figure 3*).

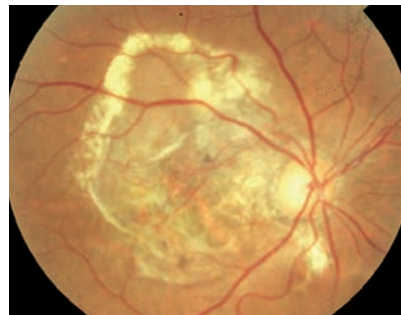
Today, the AREDS formula is widely available through a variety of companies, and is commonly used to manage patients with AMD.

Beyond AREDS

Since AREDS results were published, researchers have focused greater attention on the ocular health benefits of other nutrients.^{5,10-15} Several smaller studies have demonstrated the effects of lutein, zeaxanthin and omega-3 fatty acids.

Lutein and zeaxanthin are carotenoids that selectively accumulate within the macular pigment. These carotenoids are exclusively derived from nutritional origin, and are found in greater quantities in leafy, green vegetables. Heightened dietary intake of lutein and zeaxanthin is associated with increased macular pigment density.¹⁰ Thus, carotenoids may serve as a preventive mechanism against AMD, to optimize ocular health.¹⁰

Lutein absorbs blue light, quenches free radical formation, and diminishes oxidative retinal stress. In



1. The end stage of exudative age-related macular degeneration is associated with a fibrovascular scar.

1994, Johanna Seddon, M.D., and associates concluded that 6mg of lutein per day reduced the risk for developing AMD by up to 43%.⁶

In 2004, Stuart Richer, O.D., Ph.D., and associates reported results of the Lutein Antioxidant Supplementation Trial (LAST).¹⁰ This 12-month study evaluated the effects of lutein alone and/or in combination with antioxidants and other vitamins and minerals on visual function in 90 male patients with atrophic AMD.¹⁰

Results showed that supplementation with lutein alone or in combination with other nutrients significantly improved visual function and macular pigment density.¹⁰

Omega-3 is a polyunsaturated fatty acid that is obtained from oily fish, such as salmon, as well as flaxseed and walnuts. High concentrations of these polyunsaturated fatty acids are found in the outer segment membranes of photoreceptors, and have both a structural and functional role.



2. This patient demonstrates the end stage of non-exudative AMD. Note the associated severe retinal atrophy that appears in a geographic pattern.

The anti-angiogenic and anti-inflammatory properties of omega-3 fatty acids have been inversely associated with the risk of developing advanced AMD.^{16,17}

In patients with non-exudative AMD, these anti-angiogenic properties protect against progres-

sion to the exudative form.^{16,17}

In 2007, the Taurine, Omega-3 fatty acids, Zinc Antioxidant, Lutein (TOZAL) Study reported the effects of omega-3 fatty acids and other nutrients on mitigating the progression of AMD.¹¹

Thirty-six patients from five evaluation sites participated in the TOZAL study. Visual acuity stabilized or improved in two-thirds of the patients who took nutritional supplements that consisted of omega-3 fatty acids and antioxidants.¹¹

In 2006, researchers began enrolling subjects with intermediate or advanced AMD for AREDS 2. This new study will evaluate the effects of lutein, zeaxanthin and omega-3 long-chain polyunsaturated fatty acids (docosahexaenoic acid, or DHA, and eicosapentaenoic acid, or EPA) on disease progression.^{18,19}

AREDS did not evaluate the effects of these carotenoids on AMD progression, since lutein and zeaxanthin were not commercially available when the study began. Additionally, due to the undesirable side effects associated with a high intake of some antioxidants and minerals, AREDS 2 will refine the existing AREDS formula.

High levels of beta-carotene have been linked to an increased incidence of lung cancer among heavy smokers.^{8,20} Also, high volumes of zinc have been associated with genitourinary disorders and gastrointestinal disorders.²⁰

AREDS 2 will evaluate the impact of lutein, zeaxanthin and omega-3 long-chain polyunsaturated fatty acid supplements on the development of advanced AMD. Additionally, the study will assess the effects of reducing zinc and eliminating beta-carotene on the progression of AMD. Currently, AREDS 2 is still recruiting participants.

During the last two decades, we have gained a

Vigamox®

(moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

DESCRIPTION: VIGAMOX® (moxifloxacin HCl ophthalmic solution) 0.5% is a sterile ophthalmic solution. It is an 8-methoxy fluoroquinolone anti-infective for topical ophthalmic use.

CLINICAL PHARMACOLOGY:

Microbiology: The following *in vitro* data are also available, but their clinical significance in ophthalmic infections is unknown. The safety and effectiveness of VIGAMOX® solution in treating ophthalmological infections due to these microorganisms have not been established in adequate and well-controlled trials.

The following organisms are considered susceptible when evaluated using systemic breakpoints. However, a correlation between the *in vitro* systemic breakpoint and ophthalmological efficacy has not been established. The list of organisms is provided as guidance only in assessing the potential treatment of conjunctival infections. Moxifloxacin exhibits *in vitro* minimal inhibitory concentrations (MICs) of 2 µg/ml or less (systemic susceptible breakpoint) against most (≥ 90%) of strains of the following ocular pathogens.

Aerobic Gram-positive microorganisms:

Listeria monocytogenes
Staphylococcus saprophyticus
Streptococcus agalactiae
Streptococcus mitis
Streptococcus pyogenes
Streptococcus Group C, G and F

Aerobic Gram-negative microorganisms:

Acinetobacter baumannii
Acinetobacter calcoaceticus
Citrobacter freundii
Citrobacter koseri
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Klebsiella oxytoca
Klebsiella pneumoniae
Moraxella catarrhalis
Morganella morganii
Neisseria gonorrhoeae
Proteus mirabilis
Proteus vulgaris
Pseudomonas stutzeri

Anaerobic microorganisms:

Clostridium perfringens
Fusobacterium species
Prevotella species
Propionibacterium acnes

Other microorganisms:

Chlamydia pneumoniae
Legionella pneumophila
Mycobacterium avium
Mycobacterium marinum
Mycoplasma pneumoniae

Clinical Studies:

In two randomized, double-masked, multicenter, controlled clinical trials in which patients were dosed 3 times a day for 4 days, VIGAMOX® solution produced clinical cures on day 5-6 in 66% to 69% of patients treated for bacterial conjunctivitis. Microbiological success rates for the eradication of the baseline pathogens ranged from 84% to 94%. Please note that microbiologic eradication does not always correlate with clinical outcome in anti-infective trials.

INDICATIONS AND USAGE: VIGAMOX® solution is indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms:

Aerobic Gram-positive microorganisms:

*Corynebacterium species**
*Micrococcus luteus**
Staphylococcus aureus
Staphylococcus epidermidis
Staphylococcus haemolyticus
Staphylococcus hominis
*Staphylococcus warneri**
Streptococcus pneumoniae
Streptococcus viridans group

Aerobic Gram-negative microorganisms:

Acinetobacter Iwoffi†
Haemophilus influenzae
*Haemophilus parainfluenzae**

Other microorganisms:

Chlamydia trachomatis

*Efficacy for this organism was studied in fewer than 10 infections.

CONTRAINDICATIONS: VIGAMOX® solution is contraindicated in patients with a history of hypersensitivity to moxifloxacin, to other quinolones, or to any of the components in this medication.

WARNINGS:

NOT FOR INJECTION.

VIGAMOX® solution should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.

In patients receiving systemically administered quinolones, including moxifloxacin, serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported, some following the first dose. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial edema), airway obstruction, dyspnea, urticaria, and itching. If an allergic reaction to moxifloxacin occurs, discontinue use of the drug. Serious acute hypersensitivity reactions may require immediate emergency treatment. Oxygen and airway management should be administered as clinically indicated.

PRECAUTIONS:

General: As with other anti-infectives, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue use and institute alternative therapy. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy,

and, where appropriate, fluorescein staining. Patients should be advised not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis.

Information for Patients: Avoid contaminating the applicator tip with material from the eye, fingers or other source.

Systemically administered quinolones including moxifloxacin have been associated with hypersensitivity reactions, even following a single dose. Discontinue use immediately and contact your physician at the first sign of a rash or allergic reaction.

Drug Interactions: Drug-drug interaction studies have not been conducted with VIGAMOX® solution. *In vitro* studies indicate that moxifloxacin does not inhibit CYP3A4, CYP2C8, CYP2C9, CYP2C19, or CYP1A2 indicating that moxifloxacin is unlikely to alter the pharmacokinetics of drugs metabolized by these cytochrome P450 isozymes.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term studies in animals to determine the carcinogenic potential of moxifloxacin have not been performed. However, in an accelerated study with initiators and promoters, moxifloxacin was not carcinogenic in rats following up to 38 weeks of oral dosing at 500 mg/kg/day (approximately 21,700 times the highest recommended total daily human ophthalmic dose for a 50 kg person, on a mg/kg basis).

Moxifloxacin was not mutagenic in four bacterial strains used in the Ames *Salmonella* reversion assay. As with other quinolones, the positive response observed with moxifloxacin in strain TA 102 using the same assay may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay. An equivocal result was obtained in the same assay when v79 cells were used. Moxifloxacin was clastogenic in the v79 chromosome aberration assay, but it did not induce unscheduled DNA synthesis in cultured rat hepatocytes. There was no evidence of genotoxicity *in vivo* in a micronucleus test or a dominant lethal test in mice.

Moxifloxacin had no effect on fertility in male and female rats at oral doses as high as 500 mg/kg/day, approximately 21,700 times the highest recommended total daily human ophthalmic dose. At 500 mg/kg orally there were slight effects on sperm morphology (head-tail separation) in male rats and on the estrous cycle in female rats.

Pregnancy: Teratogenic Effects.

Pregnancy Category C: Moxifloxacin was not teratogenic when administered to pregnant rats during organogenesis at oral doses as high as 500 mg/kg/day (approximately 21,700 times the highest recommended total daily human ophthalmic dose); however, decreased fetal body weights and slightly delayed fetal skeletal development were observed. There was no evidence of teratogenicity when pregnant Cynomolgus monkeys were given oral doses as high as 100 mg/kg/day (approximately 4,300 times the highest recommended total daily human ophthalmic dose). An increased incidence of smaller fetuses was observed at 100 mg/kg/day. Since there are no adequate and well-controlled studies in pregnant women, VIGAMOX® solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Moxifloxacin has not been measured in human milk, although it can be presumed to be excreted in human milk. Caution should be exercised when VIGAMOX® solution is administered to a nursing mother.

Pediatric Use: The safety and effectiveness of VIGAMOX® solution in infants below 1 year of age have not been established.

There is no evidence that the ophthalmic administration of VIGAMOX® solution has any effect on weight bearing joints, even though oral administration of some quinolones has been shown to cause arthropathy in immature animals.

Geriatric Use: No overall differences in safety and effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS:

The most frequently reported ocular adverse events were conjunctivitis, decreased visual acuity, dry eye, keratitis, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, subconjunctival hemorrhage, and tearing. These events occurred in approximately 1-6% of patients.

Nonocular adverse events reported at a rate of 1-4% were fever, increased cough, infection, otitis media, pharyngitis, rash, and rhinitis.

Rx Only

Manufactured by Alcon Laboratories, Inc. Fort Worth, Texas 76134 USA

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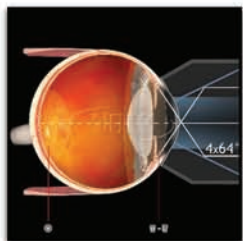
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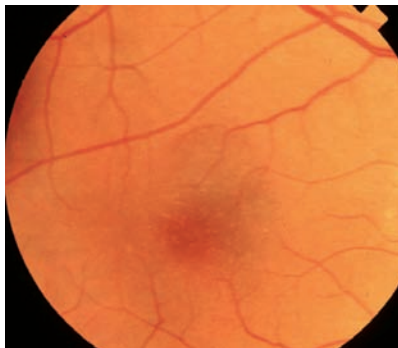


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Research Review



3. This patient shows signs of early AMD associated with drusen and areas of retinal pigment epithelium disruption.

considerably better understanding of age-related macular degeneration.

A growing body of evidence supports the hypothesis that nutritional supplementation may serve as a mainstream preventive management strategy.

As the population ages, the number of patients with AMD will continue to increase. The next research frontier will further advance our complete understanding of AMD and may clarify the true role of nutritional supplements in helping to treat or prevent this disease. ■

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