Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration

Evans JR

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Abstract

Background
It has been proposed that antioxidants may prevent cellular damage in the retina by reacting with free radicals that are produced in the process of light absorption.

Objective
The objective of this review was to assess the effects of antioxidant vitamin or mineral supplementation on the progression of age-related macular degeneration (AMD).

Search strategy
We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (2007, Issue 3); MEDLINE (1966 to August 2007); EMBASE (1980 to August 2007); NRR (2007, Issue 3); AMED (1985 to January 2006); PubMed (24 January 2006 covering last 60 days) and SIGLE (1980 to March 2005), reference lists of identified reports and the Science Citation Index. We contacted investigators and experts in the field for details of unpublished studies.

Selection criteria
We included randomised trials comparing antioxidant vitamin or mineral supplementation (alone or in combination) to a control intervention in people with AMD.

Data collection and analysis
The author extracted data and assessed trial quality. Where appropriate, data were pooled using a random-effects model unless three or fewer trials were available in which case a fixed-effects model was used.

Main results
Nine trials were included in this review. The majority of people were randomised in one trial (AREDS in the USA) that found a beneficial effect of antioxidant (beta-carotene, vitamin C and vitamin E) and zinc supplementation on progression to advanced AMD (adjusted odds ratio 0.68, 99% confidence interval 0.49 to 0.93). People taking supplements were less likely to lose 15 or more letters of visual acuity (adjusted odds ratio 0.77, 99% confidence interval 0.58 to 1.03). Hospitalisation for genito-urinary problems was more common in people taking zinc and yellowing of skin was more common in people taking antioxidants. The other trials were, in general, small and the results were inconsistent.

Reviewers’ conclusions
The evidence as to the effectiveness of antioxidant vitamin and mineral supplementation in halting the progression of AMD comes mainly from one large trial in the USA. The generalisability of these findings to other populations with different nutritional status is not known. Further large, well-conducted randomised controlled trials in other populations are required. Long-term harm from supplementation cannot be ruled out. Beta-carotene has been found to increase the risk of lung cancer in smokers; vitamin E has been associated with an increased risk of heart failure in people with vascular disease or diabetes.

Synopsis
Antioxidant vitamins and mineral supplements to slow down the progression of age-related macular degeneration
Age-related macular degeneration (AMD) is a condition affecting the central area of the retina (back of the eye). The retina can deteriorate with age and some people get lesions that can lead to loss of central vision. It has been suggested that progression of the disease may be slowed down in people who eat a diet rich in antioxidant vitamins (carotenoids, vitamins C and E) or minerals (selenium and zinc). The author identified nine randomised controlled trials; four trials based in the USA, four in Australia, Austria, Switzerland and the UK and one in China. The review of trials found that supplementation with antioxidants and zinc may be of modest benefit in people with AMD. Long-term harm from these supplements cannot be ruled out. Large well-conducted trials in a range of populations and with different nutritional status are required.

Background

Introduction
Age-related macular degeneration (AMD) is a disease affecting the central area of the retina (macula). In the early stages of the disease lipid material accumulates in deposits underneath the retinal pigment epithelium. These deposits are known as drusen and can be seen as pale yellow spots on the retina. The pigment of the retinal pigment epithelium may become disturbed with areas of hypopigmentation and hyperpigmentation. In the later stages of the disease the retinal pigment epithelium may atrophy completely. This loss can occur in small focal areas or can be widespread (geographic). In some cases new blood vessels grow under the retinal pigment epithelium and occasionally into the subretinal space (exudative or neovascular AMD). Haemorrhage can occur which often results in increased scarring of the retina.

Presentation and epidemiology
The early stages of the disease are in general asymptomatic. In the later stages there may be considerable distortion of vision and complete loss of visual function, particularly in the central area of vision. Population-based studies suggest that in people 75 years and older, approximately 30% have early signs of the disease and 7% have late-stage disease (Klein 1992). It is the most common cause of blindness and visual impairment in industrialised countries. In the UK, for example, over 30,000 people annually are registered as...
Description of studies

Types of outcome measures

Types of participants

Types of intervention

Types of outcome measures

Results

Comparison 01: multivitamin supplement versus placebo
These analyses were restricted to trials of multivitamin and mineral supplements: AREDS (vitamins C, E, beta-carotene and zinc), AMDSG (Ocuguard), Kaiser 1995 (Visaline) and Veterans LAST study (Ocupower). See ‘Characteristics of included studies’ for details of vitamins and minerals included in Ocuguard, Visaline and Ocupower.

Outcome 1 distance visual acuity: loss of three or more lines

Only AREDS reported visual acuity data in a dichotomous format. People who received antioxidant vitamins plus zinc were less likely to lose 15 or more letters of visual acuity. The odds ratio (OR) adjusted age, sex, race, AMD category and baseline smoking status was 0.77, 95% CI 0.62 to 0.96.

Outcome 2 distance visual acuity: mean

Trials reporting visual acuity in continuous format were smaller and had shorter treatment and follow-up durations (6 months to 18 months) (AMDSG; Kaiser 1995; Veterans LAST study). A total of 69 people were randomised to treatment and 62 to placebo in pooled analyses of all three trials. The results of these trials were consistent I² = 0. Little effect of treatment on visual acuity was seen from these analyses. The pooled standardised mean difference was 0.16 (95% CI -0.19 to 0.51) (Analysis 01.01).

Outcome 3 progression AMD: dichotomous

Only the AREDS trial contributed to this outcome. People taking antioxidant vitamins plus zinc were less likely to progress to advanced AMD. The OR adjusted for age, sex, race, AMD category and baseline smoking status was 0.66, 95% CI 0.53 to 0.87.

Outcome 4 progression AMD: continuous

Only one trial reported the progression of AMD in a continuous format (AMDSG), with 25 people randomised to treatment and 24 to control. There was little evidence of any effect of treatment at 18 months (mean difference -0.06, 95% CI -0.62 to 0.50). The power of the study was low.

Comparison 02: vitamin E versus placebo

There has only been one trial investigating vitamin E alone (VECAT). This trial randomised 587 participants to vitamin E supplementation and 592 to placebo and followed them up for four years on average.

Outcome 1 distance visual acuity: loss of three or more lines

Outcome 2 progression of AMD

There was only limited evidence of any effect of treatment either on visual acuity (OR 1.05, 95% CI 0.70 to 1.57) or progression of AMD (OR 1.11, 95% CI 0.80 to 1.55). Over 80% of participants in this trial did not have signs of ARM or AMD.

Comparison 03: zinc versus placebo

Four trials have investigated the effect of zinc supplementation (AREDS; Holz 1993 (published in abstract form only); Newsome 1988; Stur 1996). In addition there is one unpublished study for which we have no data (France 1998).

Outcome 1 distance visual acuity: loss of three or more lines

Two trials reported visual acuity data in this format (AREDS; Newsome 1988). The pooled analyses include a total of 984 people randomised to zinc supplementation and 974 to placebo. The trials were consistent I² = 0%. There was a modest beneficial effect of treatment on visual acuity (pooled OR 0.81, 95% CI 0.66 to 0.99). (Analysis 02.01)

Outcome 2 distance visual acuity: mean

Two trials provided data for this outcome (Newsome 1988; Stur 1996). A total of 77 people were randomised to zinc supplementation and 78 to placebo in these two trials which had a maximum treatment and follow-up duration of 24 months. The results of these trials were less consistent, I² = 56.6% (Analysis 02.02). Newsome 1988 found that there was more visual acuity loss in the control group than the treatment group although this did not reach statistical significance. Stur 1996 found little difference between the two groups with respect to visual acuity at the end of the study.

In Stur 1996 the primary outcome was incidence of choroidal neovascularisation (CNV) in all patients. During the treatment period, a CNV developed in the study eye in 14 patients (nine in the treatment group, five in the placebo group). People who experienced a CNV were not included in the analyses of visual acuity.

Outcome 3 progression AMD: dichotomous

There was only limited evidence of any effect of treatment on visual acuity (pooled OR 1.05, 95% CI 0.70 to 1.57) or progression of AMD (pooled OR 0.81, 95% CI 0.66 to 0.99). (Analysis 03.01)

Comparison 04: lutein or zeaxanthin versus placebo

Outcome 1 distance visual acuity: mean

There has only been one trial published to date comparing supplementation with lutein versus placebo (Veterans LAST study). The trial was small with 25 people randomised to lutein supplementation and 27 to placebo; the treatment duration and follow up was 12 months. The only outcome of relevance to this review, for which data could be extracted, was mean visual acuity at the end of the study. This showed little evidence of any effect of treatment: mean difference logMAR acuity 0.04 (95% CI -0.15 to 0.23). The power of the study was low.

Comparison 05: any multivitamin or single component antioxidant supplement versus placebo

Outcome 1 distance visual acuity: loss of 15 or more letters

Three trials contributed to this analysis (AREDS; Newsome 1988; VECAT). The trials were reasonably consistent (I² = 27.7%) (Analysis 03.01). Overall there was a small beneficial effect of supplementation (pooled OR fixed-effect model 0.81, 95% CI 0.67 to 0.98, P = 0.03). A random-effects model gave a different result (pooled OR 0.83, 95% CI 0.63 to 1.09, P = 0.18). The difference in these two models reflects the difference in weighting given to the largest trial (AREDS) - 75% in the fixed-effect model versus 63% in the random-effects model.

Outcome 2 distance visual acuity: mean

Not all trials reported visual acuity data in a dichotomous format. Some trials reported average distance visual acuity at the end of the follow-up period or the mean change in visual acuity.

Five trials contributed to this analysis (AREDS; Kaiser 1995; Newsome 1988; Stur 1996; Veterans LAST study). A total of 146 people were randomised to treatment and 140 to control. The results of the different studies were consistent (I² = 0%) (Analysis 03.02). There was little evidence of any benefit of treatment. The pooled standardised mean difference (random-effects model) was 0.02 (95% CI -0.21 to 0.26). A fixed-effect model gave identical results. Duration of treatment and follow up in these trials ranged from 6 to 24 months.

Outcome 3, progression AMD: dichotomous

Data on the progression of AMD was not reported or was reported in such a way as to make it difficult to extract data for this review in three studies (Kaiser 1995; Newsome 1988; Veterans LAST study).

Four trials contributed data on the progression of AMD as a dichotomous outcome (AREDS; Holz 1993; Stur 1996; VECAT) (figure 303). The results of the trials were inconsistent (I² = 64.2%) with the ORs for the individual studies ranging from 0.50 to 2.31. Estimating a pooled OR, therefore, was not of value in this case. Moreover, these trials were quite different in terms of the interventions studied, follow-up period and method of evaluating progression of AMD. (See).

Outcome 4, progression AMD: continuous

One study (AMDSG) reported data on the progression of AMD in a continuous format. There was little evidence for any benefit of treatment (mean difference -0.06, 95% CI -0.62 to 0.50). The number of participants in this analysis was small with 35 in the treatment group and 24 in the control group.

There was limited information from the Chinese trial (Wang 2004), particularly about the definitions of the outcome. However, the
authors reported that supplementation with zinc, vitamin E and vitamin C over 24 months had no effect on the progression of early ARM (chi-squared test $P > 0.05$) but had a beneficial effect on the progression of the disease in people with advanced AMD. 12/124 people receiving supplements who had large drusen, geographic atrophy or neovascularisation in one eye progressed to "advanced AMD" (not defined but perhaps comparable to the AREDS definitions) compared to 36/124 in the placebo group (chi-squared test $P = 0.008$). Participants in the antioxidant arms more frequently reported yellow skin (8.3% versus 6.0%, $P = 0.008$). Participants in the zinc arms reported more anaemia (13.2% versus 10.2%, $P = 0.004$), however, serum haematocrit levels were the same. They found that participants taking zinc had a lower mortality. Later follow-up of the cohort of people taking part in the AREDS study found that there was a significant increase in hospital admissions due to genitourinary diseases in people taking zinc supplements (11.1% versus 7.6% $P = 0.0003$) (Johnson 2007).

### Discussion

The trials contributing to this review fall into two categories. There are two large trials with reasonably long treatment duration and follow-up of four to six years (AREDS; VECAT). The other six trials are smaller (ranging from 20 to 151 participants) and have shorter duration of treatment and follow-up (6 to 24 months).

Many large trials provide reasonably clear answers to different questions. The AREDS trial provides evidence that long-term supplementation with vitamins E, C, beta-carotene and zinc, in people with AMD, reduced the risk of progression of the disease and visual acuity loss. The overall benefit is modest with a risk reduction in the order of 20% to 25%. However, given that treatment options for AMD are limited, and vision loss is rarely recovered, this is of interest to people with AMD.

The VECAT study suggests that the general population should not take vitamin E with a view to preventing the incidence or progression of AMD. However, the study was underpowered to answer the question as to whether people with signs of AMD, such as those participating in the AREDS study, should take vitamin E. Currently VECAT is the only published trial on vitamin E supplementation and AMD.

The other trials of multivitamin preparations, Ocuguard (AMDSG), Ocupower (Veterans LAST study) and Visaline (Kaiser 1995) are too small to provide evidence either way. Pooling results, where possible, did not provide evidence of any benefit of supplementation. However, these trials were of relatively short duration.

A total of five trials investigated zinc supplementation (AREDS; France 1998; Holz 1993; Newsome 1988; Stur 1996). The AREDS study indicated that the beneficial effect of zinc supplementation was of a similar order to that of vitamin supplementation. The other trials provide more conflicting evidence. Newsome 1988 found a reduction in the risk of visual acuity loss with supplementation over 12 to 24 months. However, Stur 1996 found no effect of treatment. Unfortunately Stur 1996, which was planned to recruit 500 participants, was terminated early because the results of the first 40 patients at 24 months indicated no benefit of treatment. The other two trials of zinc supplementation are as yet unpublished, although limited results from Holz 1993 were published in abstract form and are included here. The trials have been contacted with a view to including unpublished data in future versions of this review.

The main evidence that antioxidant vitamin and mineral supplementation is of benefit comes from the AREDS trial. As AREDS is a large well-conducted randomised study, potential biases will have been minimised. The only area where bias may have been introduced is if there were different systemic effects of the antioxidant and zinc supplementation (for example, yellowing of skin or difficulty swallowing tablets) which led the participants to guess which group they were in or alternatively, the retinal fundus photographs might have been different in some way such that the graders response was affected by treatment group. There is little evidence that this was a problem in the study.

AREDS is the only study to examine in detail the question of safety. They found little evidence of harm, however, recent follow-up of the cohort suggests an increased risk of hospital admission due to genitourinary complications in people taking the zinc supplements. The safety of some of the components of the AREDS formulation have been questioned in other studies. Two large randomised controlled trials have indicated that smokers who take beta-carotene may be at increased risk of developing lung cancer (ATBC; Omenn 1996). The Heart Outcomes Prevention Evaluation (HOPE) Study found that, among people with vascular disease or diabetes, vitamin E supplementation was associated with a higher risk of heart failure (HOPE 2005).

### Reviewers' conclusions

#### Implications for practice

People with AMD may experience modest delay in progression of the disease with antioxidant vitamin and mineral supplementation. This finding is drawn from one large trial conducted in a relatively well-nourished American population. Until it is replicated by other large-scale trials in other populations we will not know whether these findings can be applied more generally. Antioxidant vitamin and mineral supplements are readily available for purchase without prescription in many countries. The decision as to whether to take these supplements is at the discretion of the person with AMD. The following benefits and harms need to be considered. People with AMD may delay the progression of their condition if they take antioxidant vitamins and zinc at the levels described in this review. Given that there are few other interventions that offer much in the way of disease prevention or cure this is an important consideration. However, harmful effects associated with long-term vitamin supplementation, particularly in smokers and people with vascular disease, cannot be ruled out. A healthy diet with a variety of fresh fruit and vegetables will have many benefits and is unlikely to be harmful. It may be difficult, however, to consume as part of a normal diet the levels of antioxidants and zinc described in the trials included in this review. For example, one orange provides 80 mg of vitamin C; this is a relatively high amount. However, one would need to eat six to seven oranges daily to obtain 500 mg vitamin C.

There is currently considerable interest in the potential role of lutein and zeaxanthin supplementation in AMD. This review includes only one small equivocal trial on lutein. Such supplements currently cannot be recommended.

### Implications for research

Trials in other populations, preferably with a variety of nutritional status, are required. These trials should have a large enough sample size to demonstrate effects that are meaningful for people and should also include a component on quality of life. It is likely that AMD develops over many years. Three categories of people may be identified: healthy people at risk because of age or genetic factors; people with early stages of the disease; people with intermediate or late-stage disease. There are likely to be differences in the potential protective effect of antioxidant supplementation depending on the stage of the disease.

### Tables


### Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of allocation: Sponsor prepared coded tablets. Masking: Participant - not clear; Provider - yes; Outcome - yes. Losses to follow up: 4 died (2 treatment, 2 control); 1 adverse effect withdrawn (treatment); 7 lost to follow up (1 treatment, 6 control).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country: USA. Number of participants randomised: 71 veterans. Age: Average age 72 years. Sex: 66 male 5 female. Inclusion criteria: People with a monocular one line drop in Snellen visual acuity not attributable to cataract, amblyopia, systemic or ophthalmic disease AND clinically observable drusen, RPE disruption and loss of macular reflex. Exclusion criteria: Greater than one year use of vitamins; ex-prisoners of war, chronic alcoholics with tobacco/nutritional amblyopia or gastrointestinal absorption disorders.</td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
<td>Treatment: Ocuguard (Twin Lab Inc, Ronkonkoma, NY) broad spectrum antioxidant: beta carotene 20,000 IU, vitamin E 200 IU, vitamin C 750 mg, citrus bioflavonoid complex 125 mg, quercitin (bioflavonoid) 50 mg, bilberry extract (bioflavonoid) 5 mg, rutin (bioflavonoid) 50 mg, zinc picolinate 12.5 mg, selenium 50 mcg, taurine 100 mg, n-acetyl cysteine 100 mg, l-glutathione 5 mg, vitamin B2 25 mg, chromium 100 mcg. Control: Starch placebo. Duration: 18 months.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Snellen acuity with best refraction converted to logMAR units for analysis; Near vision M units with dual sided Bailey-Lovie chart; Contrast sensitivity; Retinal grading score (adapted from Chesapeake Bay Study); Subjective perception of vision; Adverse gastrointestinal reactions.</td>
</tr>
<tr>
<td>Notes</td>
<td>Treatment and placebo may not have been identical. Funders: Twin Laboratories Inc, Ronkokoma NY; Stereo Optical Inc, Chicago, IL; Eye Communications Inc, Upland, CA; Illinois College of Optometry, Chicago, IL; Pacific University College of Optometry, Forest Grove, OR; Ezell Foundation, American Academy of Optometry, Rockville, MD.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of allocation: Coded bottles. Masking: Participant - yes; Provider - yes; Outcome - yes. Losses to follow up: 2.4% balanced across study groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country: USA. Number of participants randomised: 3640. Age: Average age 69 years (range 55 to 80). Sex: 56% female. Inclusion criteria: 20/32 or better in at least one eye; ocular media clear and therefore able to obtain adequate stereoscopic fundus photographs; at least one eye free from eye disease that could complicate assessment of AMD. Exclusion criteria: Illness or disorders that would make long term follow-up or compliance with study protocol unlikely or difficult.</td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
<td>Treatment: Antioxidants (500mg vitamin C, 400IU vitamin E, 15mg beta carotene) zinc (80mg of zinc as zinc oxide and 2mg of copper as cupric oxide). Control: Placebo identical in external appearance and similar in internal appearance and taste. Duration: 7 years.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary outcomes: (1) progression to advanced AMD and (2) 15 letter or more decrease in visual acuity score. AMD assessed using stereoscopic fundus colour photograph; visual acuity measured using EDTRS logMAR chart. Safety outcomes included: reported adverse events; serum levels of haemoglobin; hospitalisations and mortality.</td>
</tr>
<tr>
<td>Notes</td>
<td>2x2 factorial design. 67% participants took additional supplements to RDA levels (Centrum). In 1996 current smokers offered option of discontinuing supplementation; 2% of participants and 18% of smokers did so. A further 2.3% reassigned to no beta-carotene group. Intention to treat analysis maintained.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of allocation: Not known. Masking: Participant - yes; Provider - yes; Outcome - yes. Losses to follow up: Not known.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country: UK. Number of participants randomised: 58. Age: 55 - 82, mean 68.</td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
<td>Treatment: 100mg zinc sulfate twice daily. Control: Placebo. Duration: 12 to 24 months.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Visual acuity; Contrast sensitivity; Dark adaptation; Stereo fundus photographs and fluorescein angiograms.</td>
</tr>
</tbody>
</table>
Notes Data available from abstract only.

Allocation concealment B - Unclear

Study Kaiser 1995

Methods Method of allocation: Sponsor prepared coded tablets. Masking: Participant - yes; Provider - yes; Outcome - yes. Losses to follow-up: None.

Participants Country: Switzerland. Number of participants randomised: 20. Age: over 50. Average age 72 in treatment group, 74 in control group. Sex: 7 male, 20 female. Inclusion criteria: People with nonserous AMD. All participants had regional atrophy of the pigment epithelium. Corrected visual acuity was between 20/100 and 20/25 with distance correction of less than four dioptres. Exclusion criteria: People with diabetes mellitus, endocrine problems, cardiac dysrhythmia, cardiac infarction or hypotension, other ocular disorders.

Interventions Treatment: Visaline (Novopharma Cham, Switzerland). Each tablet contains 1.5mg buphenine HCl, 10 mg beta-carotene, 10 mg tocopherol acetate, and 50 mg ascorbic acid. Participants took 2 tablets in the morning and at night, daily except for Saturdays and Sundays. Control: Placebo resembling active treatment prepared by sponsor. Duration: 6 months.

Outcomes Only one eye per person was evaluated. In cases of bilateral AMD, the eye with better visual acuity was selected. Distance and near visual acuity; Intraocular pressure; Visual fields; Lens opacity; Retinal visual acuity; Colour vision; Contrast sensitivity.

Notes

Allocation concealment A - Adequate

Study Newsome 1988

Methods Method of allocation: Computer generated table of random numbers. Masking: Participant - yes; Provider - yes; Outcome - yes. Losses to follow up: 23 (10 treatment, 13 placebo).

Participants Country: USA. Number of participants randomised: 174. Age: 42 to 89. Sex: 61 men 113 women. Inclusion criteria: Macular degeneration: clinically visible drusen with varying degrees of pigmentary change with visual acuity in one eye of 20/80 or better. Exclusion criteria: Cataract reducing vision more than one line; other known serious eye disease; diabetes mellitus; other known systematic/metabolic disease or congenital condition which might interfere with results.

Interventions Treatment: Zinc sulfate 100mg twice daily. Control: Identical tablets with lactose and fructose. Duration: 1 to 2 years.

Outcomes Pinhole corrected visual acuity using ETDRS charts; Changes in visible pigment, drusen or atrophy from grading of macular photographs; Adverse effects of zinc including copper deficiency anaemia.

Notes Funders: Research Fund, Department of Veterinary Science, Utah State University, Logan; James L Shupe, DVM; Mary Katherine Peterson Foundation, Houston.

Allocation concealment A - Adequate

Study Stur 1996

Methods Method of allocation: sponsor prepared coded bottles. Masking: Participant - yes; Provider - yes; Outcome - yes. Losses to follow-up: 6 withdrawn due to adverse gastrointestinal effects (4 treatment, 2 control); 14 withdrawn when developed neovascularisation (9 treatment, 5 control); 14 lost to follow up (6 treatment, 8 control).

Participants Country: Austria. Number of participants randomised: 112. Age: 50 plus. Sex: 48 men, 64 women. Inclusion criteria: Exudative AMD in one eye (defined as angiographic evidence of classic or occult choroidal neovascularisation or RPE detachment) and early ARM with visual acuity 20/40 or better in other eye (early ARM: macular drusen with no angiographic evidence of exudative lesion). Exclusion criteria: Dense senile cataract; any other eye disease which could produce significant and permanent loss of visual acuity during follow up; physical status that could prevent follow up; history of serious systemic or metabolic disease.

Interventions Treatment: Zinc sulfate 200 mg once daily. Lemon flavoured effervescent tablet made of citric acid containing saccharine and sorbitol. Control: As treatment but without zinc sulfate. Duration: 24 months.
Outcomes

Best corrected LogMAR visual acuity measured using Bailey-Lovie chart; Contrast sensitivity; Incidence of choroidal neovascularisation; Progression of disease (Wisconsin Age-related Maculopathy Grading System); Copper deficiency anaemia.

Notes

A priori sample size estimate was 500 patients but trial stopped early because interim analysis showed no detectable trend. Funders: Astra, Linz, Austria; Austrian Foundation for the Propagation of Scientific Research.

Allocation concealment

A - Adequate

Study

VECAT

Methods

Method of allocation: Coded bottles. Masking: Participant - yes; Provider - yes; Outcome - yes. Losses to follow up: Not known.

Participants

Country: Australia. Number of participants randomised: 1204. Age: 55 - 80 mean 66. Sex: 56% female. Inclusion criteria: Lens and retina of at least one eye available for documentation. Exclusion criteria: Previous cataract surgery or advanced cataract in both eyes; steroid or anticoagulation use; serious disease; regular use or sensitivity to vitamin E.

Interventions

Vitamin E 500 IU per day: natural vitamin E in soybean oil medium. Control: Placebo identical in sight, taste and smell. Duration: 4 years.

Outcomes

2m logMAR visual acuity; clinical examination; colour stereoscopic fundus photographs graded using International Grading Scheme.

Notes

Worse eye used as the study eye. Methodology published but results available from abstract only.

Allocation concealment

A - Adequate

Study

Veterans LAST study

Methods

Method of allocation: Coded bottles. Masking: Participant - yes; Provider - yes; Outcome - yes. Losses to follow up: 7 withdrew, 4 lost to follow-up, 3 died. Slightly lower % follow up in group 2 (lutein/antioxidant) 80% compared to other 2 group (lutein alone 86% placebo 87%).

Participants

Country: USA. Number of participants randomised: 90. Approximate average age 75 years. Sex: 86/90 male. Inclusion criteria: Atrophic AMD diagnosed by ophthalmoscopy and at least one visual abnormality: reduced contrast sensitivity, photo-stress glare recovery deficit or deficit on Amsler grid. Clear ocular media, free of any other ocular/systemic disease that could affect central or parafoveal macular visual function. Exclusion criteria: Cataract or retinal surgery within 6 months, photosensitizing drugs, taken lutein supplements within the previous six months.

Interventions

Treatment: Group 1 L: Lutein 10mg non-esterified lutein (FloraGlo from Kemin Foods International, Des Moines, Iowa); Group 2 L/A: Lutein plus additional antioxidants and nutrients (OcuPower (see below) from Nutraceutical Sciences Institute (NSI), Boynton Beach, Florida) Group 3 P: maltodextrin. Duration: 12 months. Ocupower had a range of nutrients including lutein, vitamin A, betacarotene, vitamins C, D3, E, B1, B2, B3, B5, B6, B12, folc acid, biotin, calcium, magnesium, iodide, zinc copper, manganese, selenium, chromium, molybdenum, lycopene, bilberry extract, alpha lipoic acid, N-acetyl cysteine, quercitin, rutin, citrus bioflavonoids, plant enzymes, black pepper extract, malic acid, taurine, L-glutathione, boron.

Outcomes

The following clinical measurements were made: Lens opacity; retinal images; Macular Pigment Optical Density (MPOD); visual acuity (Snellen) distance and near; glare testing; glare recovery; contrast sensitivity; VFQ-14 (activities of daily living, night driving, glare recovery symptoms); Amsler grid; self-reported vision.

Notes

It was difficult to extract data on outcomes of relevance to this review: i.e. visual acuity and progression of AMD.

Allocation concealment

A - Adequate

Study

Wang 2004

Methods

Method of allocation: Unknown. Masking: Participant - unknown; Provider - unknown; Outcome - unknown. Losses to follow up: unknown

Participants

Country: China. Number of participants randomised: 400188 men / 212 women aged 52 to 76, average age 65

Interventions

Treatment: zinc oxide 80mg daily, vitamin C, vitamin E. Control: placebo Duration 24 to 32 months.
Outcomes: visual acuity

Notes: Limited information available on this trial. AMD patients were stratified in early and late stage disease

Allocation concealment: B - Unclear

Additional tables

Supplementary information on trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of AMD</th>
<th>Treatment</th>
<th>Treatment duration</th>
<th>Follow up</th>
<th>Visual acuity</th>
<th>Progression AMD</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMDSG</td>
<td>Early ARM</td>
<td>Ocuguard</td>
<td>18 months</td>
<td>18 months</td>
<td>Snellen</td>
<td>Based on Chesapeake Bay grading but using indirect ophthalmoscopy: expressed as an average grade</td>
<td></td>
</tr>
<tr>
<td>AREDS</td>
<td>ARM &amp; VA 20/32 or better in one eye. 95%/3640 had AMD.</td>
<td>Vitamin C, E, beta-carotene, zinc. Factorial design</td>
<td>Average duration 6.3 years</td>
<td>Average follow-up 6.3 years, 2.4% lost to follow up</td>
<td>Loss of 3 or more lines VA (equivalent to doubling visual angle)</td>
<td>Progression to advanced AMD: photocoagulation or other treatment for CNV; GA involving center of the macula, RPE detachment, hemorrhage under the retina, subretinal fibrosis. Color fundus photography</td>
<td></td>
</tr>
<tr>
<td>Holz 1993</td>
<td>People with drusen</td>
<td>Zinc</td>
<td>Not stated but assume same as follow-up duration</td>
<td>12-24</td>
<td>Not reported</td>
<td>&quot;Incidence of new exudative or dry macula lesions&quot;</td>
<td></td>
</tr>
<tr>
<td>Kaiser 1995</td>
<td>&quot;Nonserous AMD&quot;</td>
<td>Visaline</td>
<td>6</td>
<td>6</td>
<td>Average Snellen score reported, converted to logMAR for this review</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Newsome 1988</td>
<td>Drusen and/or pigmentary change, VA 20/80 or better</td>
<td>Zinc</td>
<td>12-24</td>
<td>12-24</td>
<td>Number of letters lost on logMAR chart, converted to logMAR score for this review.</td>
<td>Difficult to extract data on this. Reported number with increased pigment, drusen and atrophy for two observers. In general found results favouring the zinc treated group</td>
<td></td>
</tr>
<tr>
<td>Neovascular AMD in one eye, VA better than 20/40 in other eye.</td>
<td>Zinc</td>
<td>24</td>
<td>24</td>
<td>Mean logMAR score NOTE: patients with neovascular event excluded from this outcome</td>
<td>Incidence of neovascular lesion in study eye</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stur 1996</td>
<td>Early AMD (18%) Late AMD (0.5%). Rest presumably had no signs of ARM.</td>
<td>Vitamin E</td>
<td>48</td>
<td>48</td>
<td>Loss of more than 9 letters on logMAR chart (two lines)</td>
<td>Investigators defined six stages of AMD progression and defined progression as movement from a lower stage to a higher stage in their worst eye</td>
<td></td>
</tr>
<tr>
<td>VECAT</td>
<td>Atrophic AMD and reduced vision</td>
<td>Lutein and/or Ocupower</td>
<td>12</td>
<td>12</td>
<td>Change in logMAR score</td>
<td>Data not reported</td>
<td></td>
</tr>
</tbody>
</table>

References

References to studies included in this review

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**Holz** *(published data only)*


**Bone** *(published data only)*

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**Benzie** *(published data only)*


**Wang** *(published data only)*


* indicates the major publication for the study

**Veterans LAST study** *(published data only)*


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