Evidence Review for NHS Surrey Medicines Management Committee

Treatment: Antioxidants and zinc for ocular conditions

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Date: January 2010

1. Purpose of the Review

To review the evidence supporting the clinical effectiveness of nutritional supplements for ocular health – particularly antioxidants and zinc for age-related macular degeneration.

It is not within the scope of this document to provide guidance on diagnosis or the use of all available pharmacological agents in the treatment of macular degeneration.

2. Appropriateness

2.1 The patient: patients with age-related macular degeneration

2.2 The problem:

Age-related macular degeneration (AMD) is a leading cause of visual loss in the Western world; older age, genetic markers and cigarette smoking are risk factors.[1]

Definition: The macula is the central, highly sensitive area of the retina and can be affected by 'dry' or 'wet' degeneration.[1] Dry AMD, which accounts for 90% of cases, has three stages: early, which is associated with the presence of small drusen (yellow deposits) under the retina; intermediate, in which there are many medium, or one or more large drusen; and advanced dry AMD in which there is geographical atrophy of the macula. 'Wet' (neovascular or exudative) AMD is more aggressive and is caused by the growth of abnormal blood vessels in the retina. It is always classed as advanced.[1] The 'dry' form can develop into the 'wet' form.[1]

Effects and prognosis: The early stages of the disease are generally asymptomatic. In the later stages there may be considerable distortion or loss of central vision.[1]

Etiology: The exact aetiology of AMD is unknown; older age, genetic markers and cigarette smoking are the only risk factors consistently reported. Oxidative stress is also thought to be a contributing factor. Certain antioxidants and zinc are found in high concentrations in ocular tissue. The carotenoids lutein and zeaxanthin selectively accumulate in the retina and make up the macular pigment. As well as possessing potent antioxidant properties they filter out harmful blue light. There is some evidence that retinal levels of these substances, and of zinc, can be low in patients with macular disease. This has led to interest in a possible role for antioxidants and for zinc in preventing the onset and progression of AMD. Prevention

of AMD is important as there is no cure, although there are now treatments available that slow the progression of 'wet' AMD and, in some cases, improve vision loss.

2.3 The Intervention:

-Oxidative damage to the retina has also been suggested as a contributing factor leading to the hypothesis that increasing antioxidant (and zinc) intake, through diet or use of nutritional supplements, may protect against the development and/or progression of AMD.[1] This has been tested in a number of observational studies and randomised controlled trials (RCTs) (see review of evidence below).

Care setting: Recommended by ophthalmologists and opticians, prescribed in primary care by GPs. These preparations are prescribable on the NHS however they are classed as a food supplement, not a licensed drug. The prescriber therefore takes full responsibility for its use.

2.4 Alternative treatments:

None. Wet AMD is treated with anti-VEGF drugs (such as ranibizumab) in line with NICE guidance.

3. Effectiveness

3.1 Expected benefits

As stated above, it is hypothesized that nutritional supplements may protect against the development and/or progression of AMD.

3.2 Is there a plausible biological basis for effectiveness?

Possibly.

3.3 Side-effects/complications

These products contain doses that are significantly higher than recommended dietary intakes and their long-term safety is unknown. The benefits and risks of supplementation should be considered on an individual basis.[1]

Of the studies identified and reviewed (see below), only the Age Related Eye Disease Study (AREDS) examined the safety of supplements in any detail.[1,2] It provides some reassurance about the safety of high-dose zinc and antioxidants used for six years. The incidence of adverse effects was not statistically different between groups but patients taking zinc had increased hospital admissions for genitourinary symptoms and patients taking beta-carotene reported yellowing of the skin. [1,2] However, the safety of some of the components of the AREDS supplements has been questioned in other studies.[1,3-6]

A higher incidence of lung carcinoma in smokers taking large doses of beta-carotene has been noted above. Meta-analyses have reported increased risks of all-cause mortality and cardiovascular death with beta-carotene and of all-cause mortality with high doses vitamin E, although some of the included studies used doses considerably higher than those used in AREDS. [1,3,4] High doses of vitamins C and E (twice those used in AREDS) have been associated with worsening disease and an

increase in all-cause mortality in women with pre-existing heart conditions.[1,5] The Heart Outcomes Prevention Evaluation (HOPE) study found a higher risk of heart failure among people with vascular disease or diabetes taking vitamin E 400units daily, the dose taken in AREDS[1,6]. A post-hoc review of data from AREDS found patients in the antioxidant plus zinc group had a 14% relative reduction in mortality risk after an average of 6.5 years compared with those on placebo, and there was no difference in the incidence of congestive heart failure between the two groups.[7] However, AREDS participants were generally healthy and well nourished and may differ from subjects in other trials.

The safety of supplements will be explored further in AREDS 2. [1,8]
This study is enrolling 4,000 subjects with a primary objective of determining whether supplementation with lutein and zeaxanthin, and omega-3 long-chain polyunsaturated fatty acids, will influence development of advanced AMD. [1,8]
The effect of eliminating beta-carotene and reducing the dose of zinc will also be assessed.[1,8]

3.4 Review of evidence (See Appendix 1. for Search Strategy and Summary of Results)

3.4.1 Evidence in Age Related Macular Degeneration
(i) UK Medicines Information Evidence Review - August 2009. Antioxidants and zinc for age-related macular degeneration

Summary:

- To prevent the development of AMD in people who do not have AMD or who have early disease:
  - there is no evidence from RCTs to support the use of nutritional supplements.
  - there is little evidence from epidemiological studies of the benefit of a high dietary intake of individual antioxidants and zinc. However, it seems reasonable to advise people to follow Department of Health dietary guidelines and increase consumption of fruit and vegetables.
- To slow progression in patients with intermediate or advanced AMD in one eye, there is evidence from one study (AREDS) that the specific combination of zinc 80mg, vitamin E 400 units, vitamin C 500mg and beta-carotene 15mg daily may be modestly beneficial.
- Products available in the UK that most closely match this combination are *PreserVision* and *Viteyes Original*. These supplements contain beta-carotene and people who smoke or are recent ex-smokers should not take them. Products that contain substitutes for beta-carotene (e.g. lutein) do not have the same evidence base as the original formulation.
- These products contain doses that are significantly higher than recommended dietary intakes and their long-term safety is unknown. The benefits and risks of supplementation should be considered on an individual basis.

This took into account two systematic reviews and meta-analyses (one Cochrane review).

Evidence Grade 1a (see Appendix 2).

PCT comment: A literature search was conducted to identify any additional study results published since this review was completed. None were identified.

3.4.2 Use of nutritional supplements in other ocular conditions:

(i)Age Related Cataract and Vision Loss:

3 studies identified showed that antioxidants had no effect on the incidence of cataracts (see appendix 1).[9-11]

Evidence Grade 1b (see Appendix 2).

(ii) Diabetic Retinopathy: Royal College of Opthalmologists. Guidelines for Diabetic Retinopathy. 2005.[12]

Section 3.12 ANTIOXIDANTS.

3.12.1. Relationship of antioxidant therapy to diabetic retinopathy

Antioxidants are currently under evaluation for several age related and other diseases such as macular degeneration and cataract. The role of antioxidants in developing retinopathy, and changing existing retinopathy to more aggressive disease has been investigated with observational studies.

There is no evidence of effectiveness.

4. Summary of Key Points for Consideration

4.1 National guidance:

Royal College of Ophthalmologists. Age Related Macular Degeneration – Guidelines for Management. February 2009.[12]

This guideline reaches similar conclusions about the available data supporting antioxidants to the UK Medicines Information review.

They also concluded the following: AREDS revealed a beneficial effect of very high doses of antioxidants (daily dose vitamin C 500mg, vitamin E 400 IU, Beta-carotene 15mg (25,000 IU)) and zinc 80mg (along with 2mg copper to prevent anaemia) in reducing patient's relative risk of progression to advanced AMD by 25%. These supplements may be indicated in patients with advanced AMD in the fellow eye.

4.2 Efficacy

To slow progression in patients with intermediate or advanced AMD in one eye, there is evidence from one study (AREDS) that the specific combination of zinc 80mg, vitamin E 400 units, vitamin C 500mg and beta-carotene 15mg daily may be modestly beneficial. It should be noted however that the ARED trial was published before the routine treatment of wet AMD with Anti-VEGF medications such as ranibizumab.

4.3 Potential Benefits over existing therapy
No equivalent products to compare with.

4.4 Potential disadvantages
Significant costs associated with prescribing these products (see below), with a limited supporting evidence base. Lack of long-term data on adverse effects.

4.5 Budgetary Impact

4.5.1 Cost
Table 1. NHS Surrey prescribing costs for nutritional supplements for ocular health November 2008- October 2009 (from EPACT data).

Preparation	Number of Items	Total Expenditure per item
ICaps_Tab	3,052	£25,514.84
Ocuvite PreserVision_Tab	804	£8,034.16
Ocuvite_Lutein Cap	504	£3,486.35
Preservision_Lutein Cap	121	£1,494.55
Preservision_Original Cap	123	£1,837.83
Vega_Opticare 20:20 For V/Cap	7	£61.68
Visionace_Tab	30	£163.43
Vitalux Plus_Cap	75	£402.87
Viteyes_Orig For Plus Lutein Cap	41	£855.64
Vivioptal_Cap	23	£157.39
Vivioptal_Plus Cap	1	£15.85
TOTAL	**4981**	**£42024.59**

4.5.2 Precedent setting:
It is estimated that the prevalence of AMD in patients aged ≥65 years is approximately 3.3%. Surrey has a population of approximately 185 000 patients in this age group and it is predicted to rise in the near future. This means that potentially, there are approximately 6100 patients with AMD in Surrey. This could lead to potential expenditure of between £888 000 and £1 320 000 per annum if the two preparations which most closely match the clinical trials (Ocuvite PreserVision and Viteyes Original) are used in all of these patients.

Other PCTs:
-Kent & Medway PCT have considered this at their Area Prescribing Committee:
Summary

1. Kent and Medway APC do not recommend the routine use of antioxidant/mineral supplementation to treat age-related macular degeneration.

2. There are safety concerns about the effect of long-term administration of high dose vitamins and minerals, some of which were evident from the AREDs study.

3. There is a small group (life long non smokers and females with moderate or advanced visual loss) where net patient benefit is more likely (visual acuity gain has to be traded off against other health loss)

4. No antioxidant/mineral supplements are licensed as medicinal products.

5. There is no evidence to show that people with early stages of AMD will benefit from supplementation.

6. Treatments for moderate and advanced AMD have changed since AREDs

7. Smoking cessation and increasing consumption of fruit and vegetables rich in antioxidants are recommended.

NHS Eastern & Coastal Kent has also adopted this position.

5. Conclusions and Recommendations

This review has reached the same conclusions as Kent and Medway PCT detailed above.

Options:

1. NHS Surrey does not recommend the use of antioxidant/ mineral supplementation to treat ocular conditions.

2. NHS Surrey recommends only the use of Ocuvite PreserVision or Viteyes Original in the small subgroup of patients most likely to benefit (non-smokers with intermediate or advanced AMD) – the APC should note however that the ARED trial was published before the routine treatment of wet AMD with Anti-VEGF medications such as ranibizumab. There is the risk that these products may then be prescribed on a wider basis than recommended leading to increased costs, inappropriate use and increased clinical risk to patients.

Appendix 1: Evidence search

Search terms used:

Resource	Used in this review?
National Library for Health (NHL) http://www.library.nhs.uk/Default.aspx A gateway site with access to other resources such as Reviews (Bandolier, Cochrane, CRD etc), Guidelines (e.g. NICE), Clinical Knowledge Summaries (CKS) and Journals including AMED, British Nursing Index, CINAHL, E-books, EMBASE, HMIC, MEDLINE, My Journals, PsycINFO, PubMed, Databases from Dialog.	✓
National Institute of Health and Clinical Excellence (NICE) http://www.nice.org.uk/ NICE produces national guidance in three areas of health:	✓ (through NHL)

1. Public health - guidance on the promotion of good health and the prevention of ill health 2. Health technologies - guidance on the use of new and existing medicines, treatments and procedures within the NHS 3. Clinical practice - guidance on the appropriate treatment and care of people with specific diseases and conditions within the NHS.	
Bandolier http://www.medicine.ox.ac.uk/bandolier/index.html Bandolier is a website about the use of evidence in health, healthcare, and medicine. Information comes from systematic reviews, meta-analyses, randomised trials, and from high quality observational studies.	✓(through NHL)
Centre for Reviews and Dissemination http://www.york.ac.uk/inst/crd/ CRD undertakes high quality systematic reviews that evaluate the effects of health and social care interventions and the delivery and organisation of health care. Databases maintained by CRD include Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA) Database	✓(through NHL)
Scottish Intercollegiate Guidelines Network (SIGN) http://www.sign.ac.uk/ Scottish equivalent of NICE	✓
Medical Services Advisory Committee (Australia) http://www.msac.gov.au/internet/msac/publishing.nsf/Content/home-1 The principal role of the Medical Services Advisory Committee (MSAC) is to advise the Australian Minister for Health and Ageing on evidence relating to the safety, effectiveness and cost-effectiveness of new medical technologies and procedures.	✓
Canadian Agency for Drugs and Technologies in Health (CADTH) http://www.cadth.ca/index.php/en/home The Canadian Agency for Drugs and Technologies in Health (CADTH) is a national body that provides Canada's federal, provincial and territorial health care decision makers with credible, impartial advice and evidence-based information about the effectiveness and efficiency of drugs and other health technologies.	✓

Evidence retrieved

Guidelines

Brief description of any guidelines found

Reviews:

1.UK Medicines Information. Antioxidants and zinc for age-related macular degeneration. August 2009.[1]

Prevention of AMD

There are two recent systematic reviews of the evidence relating to use of dietary antioxidants and supplements to prevent AMD in healthy people or in those with borderline AMD. One, published in the BMJ [1], focuses on observational studies; the second is a Cochrane review of available RCTs [2].

The BMJ analysis included seven prospective cohort studies involving 149,203 people and 1,878 incident cases of early AMD. In most studies, subjects were ≥49 years of age and follow-up was for between five and 18 years (mean nine years). Three studies were population based and four included volunteers and health professionals. The studies used validated food frequency questionnaires to assess intake of antioxidants. The assessment and definition of AMD varied between studies, but all studies adjusted for age and smoking. Most compared the highest fourth or fifth intake of antioxidants with the lowest fourth or fifth intake [1].

The analysis found no significant association between any of the antioxidants studied and early AMD, with the possible exception of vitamin E, which was of borderline significance. The pooled odds ratio [and 95% confidence intervals] reported for each of antioxidant is given in the table:

Antioxidant	Odds ratio	[95% CI]	Antioxidant/mineral	Odds ratio	[95% CI]
vitamin A	0.98	0.81 to 1.18	beta-carotene	1.04	0.86 to 1.25
vitamin C	1.11	0.84 to 1.46	beta-cryptoxanthin	1.01	0.85 to 1.22
vitamin E	0.83	0.69 to 1.01	lycopene	1.05	0.88 to 1.25
lutein / zeaxanthin	0.98	0.86 to 1.13	zinc	0.91	0.74 to 1.11
alpha-carotene	1.05	0.87 to 1.26			

The review concluded that high antioxidant levels in healthy people do little to prevent the development of early AMD. However, limitations of the review were acknowledged including the inability to evaluate the effect of potential antioxidant synergism. It was noted, for example, that the Rotterdam Eye Study (n=4,170), which was included in the analysis, found an above median dietary intake of combined antioxidants (beta-carotene, vitamins C and E and zinc) was associated with a larger reduced risk of AMD than each of the antioxidants individually.

Since publication of this meta-analysis, updates covering an extended period of follow-up or additional analyses have been published for four of the included studies: the Beaver Dam Eye Study (BDES, n=2,375), the Blue Mountains Eye Study (BMES, n=2,454), the Nurse Health Study (NHS, n=71,494) and the Health Professional Study (HPS, n=41,564). The BDES originally found modest benefits of antioxidants, but the update reported no significant association between supplement use and early AMD [3]. In contrast, BMES which originally reported no benefit of higher antioxidant and zinc intakes over five years, reported data for up to ten years suggesting that there was a reduced risk of early AMD in participants with higher dietary intakes of lutein and zeaxanthin (relative risk 0.66 [0.48 to 0.92]), and of zinc (RR 0.54 [0.30 to 0.97]) [4]. Further analyses of the NHS and HPS studies for up to 18 years of follow-up found that lutein/zeaxanthin intake was not associated with the risk of self-reported early AMD [5].

The Cochrane review included three RCTs involving 23,099 randomised subjects [2]. In the ATBC trial, 1,035 male smokers aged ≥65 years were randomised to alpha-tocopherol 50mg/day, beta-carotene 20mg/day, both alpha-tocopherol and beta-carotene, or placebo, for between five to eight years (median 6.1). In the four-year VECAT study, 1,204 men and women were randomised to vitamin E supplements (500 units/day) or placebo. The third trial was the Physicians' Health Study I (PHS I), in which 22,071 US male physicians were randomised to beta-carotene 50mg or placebo every other day for 12 years.

There was little evidence of any effect of antioxidant supplementation. Overall, there were 583 cases of AMD among those receiving any antioxidant and 419 cases among those on placebo (RR 1.04 [0.92 to 1.18]). Among the 21,589 people in ATBC and PHS I randomised to beta-carotene or placebo, there were 343 cases of AMD in the beta-carotene groups and 327 in the placebo groups (RR 1.03 [0.98 to 1.19]). There was less evidence for alpha-tocopheral alone (1,466 participants randomised to alpha-tocopheral or placebo), but again there was no indication of benefit (RR 1.11 [0.91 to 1.36]).

A possible reason for the lack of benefit noted in studies so far could be that antioxidants may have been given too late (participants were at least 40 years of age, and many were much older) or for not long enough [2]. The results from several ongoing studies are awaited and may address these issues: the Women's Health Study (WHS) in which 39,876 women are taking vitamin E and/or aspirin; a further Physicians Health Study (PHS II); and the Women's Antioxidant Cardiovascular Study (WACS) of 8,171 female health professionals taking vitamin C, vitamin E, folate, vitamin B6 and vitamin B12 supplements.

Progression of AMD

There is a Cochrane systematic review examining the evidence from RCTs for antioxidant and mineral supplementation on visual acuity and/or progression of the disease in people who already have AMD [6]. There is no systematic review of relevant observational studies. However, in the systematic review of observational studies in primary prevention discussed above, three of the seven studies evaluated the association between antioxidant intake and progression to 'late' AMD [1]. The three studies evaluated different antioxidants so the results could not be pooled. There were few cases of 'late' AMD within the individual studies and the odds ratios had wide confidence intervals. As a consequence, no conclusions can be drawn from these data.

The Cochrane review included eight RCTs of antioxidant vitamin and mineral supplements in people with existing AMD [6]. The majority of randomised subjects included in the review were from one RCT, the Age-Related Eye Disease Study (AREDS, n=3,640).

AREDS reported outcomes for three baseline categories of participants; 1,063 with early or borderline AMD features, 1,621 with intermediate AMD, and 956 subjects with advanced (dry or wet) AMD or reduced visual acuity due to AMD in one eye [7]. Participants were randomised to one of four arms:

- zinc alone (80mg as zinc oxide with 2mg copper daily [prolonged use of zinc can lead to secondary copper deficiency])
- antioxidants alone (vitamin C 500mg, vitamin E 400units and beta-carotene 15mg daily)
- zinc plus antioxidants
- placebo

While AREDS was ongoing, it became evident from other studies that beta-carotene was associated with a higher incidence of lung cancer in smokers. As a consequence, four percent of AREDS participants who were current or former smokers discontinued or changed their study medication.

Follow up was for a mean 6.3 years and the trial had two primary outcomes: progression to advanced AMD and reduction in visual acuity (≥15-letter decrease). Overall, there was a statistically significant odds reduction for the progression to advanced AMD in patients treated with antioxidants plus zinc compared with placebo (OR 0.72 [99% CI 0.52 to 0.98]). The ORs for zinc alone and antioxidants alone were 0.75 [99% CI 0.55 to 1.03] and 0.80 [99% CI 0.59 to 1.09], respectively, and not statistically significant.

In the early AMD group, only 1.3% of patients (12 in the treatment arms and three in the placebo arm) developed advanced AMD by year five. This was a much lower rate than the researchers had expected so they conducted a post-hoc analysis excluding this group. The analysis of subjects with more severe disease showed a greater reduction in risk of progression of AMD, with odds ratios for antioxidants plus zinc and for zinc alone being statistically significant: (antioxidants plus zinc OR 0.66 [99% CI 0.47 to 0.91], zinc alone OR 0.71 [99% CI 0.52 to 0.99], antioxidants alone OR 0.76 [99% CI 0.55 to 1.05]). These results must be interpreted cautiously as the study was not powered for this analysis.

The only statistically significant reduction in rates of visual acuity loss occurred in patients with more severe disease assigned to receive antioxidants plus zinc (OR 0.73 [99% CI 0.54 to 0.99]. Again this analysis was underpowered.

Three other RCTs of multivitamin supplements were included in the Cochrane analysis. They were small and of relatively short duration (six to 18 months) and included patients with intermediate or advanced AMD. One study (AMDSG, n=71) employed a supplement containing vitamins B_2, C and E, beta-carotene, zinc, bioflavonoids and minerals (*Ocuguard)* and another (n=20), a supplement containing vitamins C and E, beta-carotene and buphenine (V*isaline*). The third study, the Lutein Antioxidant Supplementation Trial (LAST, n=90) was conducted following AREDS, and employed the carotenoid, lutein 10mg daily, with or without a multivitamin and mineral preparation (*OcuPower*). In a pooled analysis of these trials there was little effect of treatment on visual acuity, with a standardised mean difference of 0.16 [95% CI -0.19 to 0.51]. Only one trial (AMDSG) reported on progression of AMD and noted little evidence of a treatment effect at 18 months. An analysis of the lutein vs. placebo arms in LAST found no significant effect of lutein on visual acuity. The US Food and Drug Administration concluded in 2006 that there was no credible evidence that lutein or zeaxanthin reduce the risk of AMD [8]. Despite this, these carotenoids are included in an increasing number of ‘ocular health’ products.

In addition, the Cochrane review included two small placebo-controlled trials of 200mg zinc supplement daily, one in patients with early or late AMD and the other in patients with wet AMD in one eye, only the first documented benefit, with subjects in the zinc-treated group less likely to lose vision than controls [6].

Safety

Of the studies discussed above, only AREDS examined the safety of supplements in any detail. It provides some reassurance about the safety of high-dose zinc and antioxidants used for six years [7]. The incidence of adverse effects was not statistically different between groups but patients taking zinc had increased hospital admissions for genitourinary symptoms and patients taking beta-carotene reported yellowing of the skin. However, the safety of some of the components of the AREDS supplements has been questioned in other studies [9-12].

A higher incidence of lung carcinoma in smokers taking large doses of beta-carotene has been noted above. Meta-analyses have reported increased risks of all-cause mortality and cardiovascular death with beta-carotene [9] and of all-cause mortality with high doses vitamin E [10], although some of the included studies used doses considerably higher than those used in AREDS. High doses of vitamins C and E (twice those used in AREDS) have been associated with worsening disease and an increase in all-cause mortality in women with pre-existing heart conditions [11]. The Heart Outcomes Prevention Evaluation (HOPE) study found a higher risk of heart failure among people with vascular disease or diabetes taking vitamin E 400units daily, the dose taken in AREDS [12]. A post-hoc review of data from AREDS found patients in the antioxidant plus zinc group had a 14% relative reduction in mortality risk after an average of 6.5 years compared with those on placebo, and there was no difference in the incidence of congestive heart failure between the two groups [13]. However, AREDS participants were generally healthy and well nourished and may differ from subjects in other trials.

The safety of supplements will be explored further in AREDS 2. This study is enrolling 4,000 subjects with a primary objective of determining whether supplementation with lutein and zeaxanthin, and omega-3 long-chain polyunsaturated fatty acids, will influence development of advanced AMD. The effect of eliminating beta-carotene and reducing the dose of zinc will also be assessed [14].

Antioxidant and zinc preparations

There are a number of products marketed in the UK for the promotion of 'ocular health' (see Appendix 1). These supplements are not licensed and have not undergone regulatory assessment. Two products, *PreserVision* and *Viteyes Original,* closely match the combination of antioxidants and minerals used in the AREDS study. However, as they contain beta-carotene, people who smoke or are recent ex-smokers should not take them. Similar formulations in which beta-carotene has been substituted with lutein (*PreserVision Lutein, Viteyes Smoker's Formula plus Lutein)* lack the evidence base of the original formulation.

These products contain doses that are significantly higher than recommended daily allowances and the safety profile of these products when used long-term is unknown. In view of recent findings of possible harm from high doses of vitamins C and E, the

benefits and risks of supplementation in patients with pre-existing diabetes, heart or vascular conditions should be considered on an individual basis.

Limitations

Data from observational studies are conflicting and there are few RCTs of adequate size or duration to give a robust evidence-based answer.

Trials included in this Review

1. Chong EW-T, Wong TY, Kreis AJ et al. Dietary antioxidants and primary prevention of age related macular degeneration: systematic review and meta-analysis. BMJ 2007; 335: 755-762.
2. Evans JR and Henshaw KS. Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration (Review). Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD000253. DOI:10.1002/14651858.CD000253.pub2.
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4. Tan JSL, Wang JJ, Flood V et al. Dietary antioxidants and the long-term incidence of age-related macular degeneration. The Blue Mountains Eye Study. Ophthalmology 2008; 115: 334-341.
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13. Chew EY and Clemons TE. Heart Outcomes Prevention Evaluation – the ongoing outcomes study, vitamin E, and age-related macular degeneration. Arch Ophthalmol 2006; 124: 1665-1666.
14. Clinical Studies Database. Age-Related Eye Disease Study 2 (AREDS2). Accessed via http://www.nei.nih.gov/neitrials/viewStudyWeb.aspx?id=120 on 19/8/2009.

2.Bandolier review of the AREDS trial. Available from: http://www.medicine.ox.ac.uk/bandolier/booth/older/MDantiox.html. Accessed 19/01/10.

AREDS. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta-carotene, and zinc for age-related macular degeneration and vision loss. Archives of Ophthalmology 2001 119: 1417-1436.[2]

Study

This large (3,640 patients) study randomised patients with age-related macular degeneration to placebo, antioxidants, zinc, or antioxidants plus zinc for five years. All patients had best-eye visual acuity of 20/32 or better in at least one eye. They had category 2, 3 or 4 disease, meaning that they had to have small drusen to intermediate drusen.

The treatment interventions were identical in appearance. The antioxidants comprised 500 mg vitamin C, 400 IU of vitamin E, and 15 mg beta-carotene, or zinc (80 mg as zinc oxide), or both together. Treatment was for five years.

The main outcome was progression to advanced macular degeneration (AMD event) for a study eye, defined as photocoagulation or other treatment for neovascularisation, or documentation of progression with pre-set criteria. A second outcome was a decrease in best-corrected visual acuity score from baseline of 15 or more letters in a study eye.

Results

Over 90% of patients attended for assessment over the period, and tablet counts suggested that over 70-% of patients took more than 75% of their study tablets.

Progression to an AMD event was more likely for people with more advanced eye disease. For those in category 2, only about 2% had an event by two years. For those with category 3 it was 18%, and for those with category 4 it was 43% (Figure 1). Analysis of the effect of the treatments was very extensive, but the main interest was for those with category 3 and 4 eye disease initially (70% of the patients).

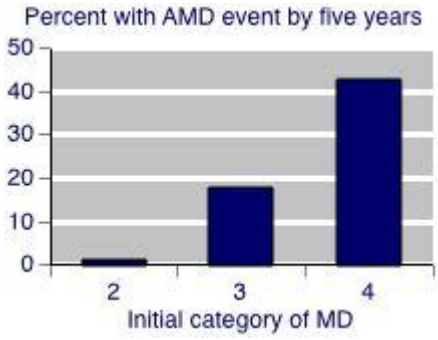

Figure 1: Development of AMD event by initial category of disease

Antioxidants and zinc were associated with lower rates of development of an AMD event or loss of visual acuity. For AMD, the approximate NNT to prevent one event over five years are shown in Table 1. For loss of visual acuity, only patients in category 4 initially had a significantly reduced rate of events compared with placebo. Antioxidants plus zinc was better then either alone.

Table 1: ANMD events in patients with initial category 3 and 4

Treatment	Percent with outcome at five years	Odds ratio (95% CI)	Approximate NNTp
AMD event			
Placebo	28		

Antioxidant	23	0.8 (0.6 to 1.1)	19
Zinc	22	0.7 (0.5 to 1.0)	19
Antioxidant + zinc	20	0.7 (0.5 to 0.9)	13

There were no serious adverse events of note.

3. **Royal College of Ophthalmologists. Age Related Macular Degeneration – Guidelines for Management. February 2009.[12]**

Antioxidant nutrients

The "free-radical" theory of ageing proposes that oxygen radicals damage cells over time.76 It is thought that the retina may be particularly vulnerable to oxidative stress because of a combination of exposure to visible light and high oxygen concentrations.77 Considerable interest has focused on whether foods high in antioxidant micronutrients may be protective for the development of AMD. Carotenoids (in particular beta-carotene, lutein and zeaxanthin), vitamin C, vitamin E and zinc are all common in the diet and have antioxidant properties.

A number of studies have investigated the relationship between dietary intake 78-91 or serum levels92-97 of antioxidant nutrients and risk of AMD with inconsistent results. Difficulties with interpreting these studies include the fact that people with diets rich in antioxidants are different from people with diets that are low in antioxidants. A recent systematic review of prospective studies of dietary intake found no evidence that diets high in antioxidant vitamins protect against AMD. 98 Two systematic reviews of the controlled trials of vitamin supplementation undertaken in this area are available.99, 100 Three large trials provide no evidence to support the hypothesis that supplementation with high dose beta- carotene or high dose vitamin E prevents AMD in the general population.

Eight trials were identified of antioxidant supplementation in people with AMD. The majority of participants were from one trial – the Age-Related Eye Disease Study (AREDS) - which found a reduced risk of progression to advanced AMD in participants with signs of AMD (extensive intermediate size drusen, one or more large drusen, noncentral geographic atrophy in one or both eyes, or advanced AMD or vision loss due to AMD in one eye) who took antioxidant supplements (beta-carotene, vitamin C, vitamin E and high-dose zinc). 101

Although generally regarded as safe, antioxidant supplements can have adverse effects. Two large trials have shown that smokers who take beta-carotene may be at increased risk of lung cancer.102,103 The Heart Outcomes Prevention Evaluation (HOPE) Study found that vitamin E supplementation was associated with an increased risk of heart failure in people with diabetes or vascular disease.104

4.Royal College of Ophthalmologists. Guidelines for Diabetic Retinopathy. 2005.[13]

Section 3.12 ANTIOXIDANTS.
3.12.1. Relationship of antioxidant therapy to diabetic retinopathy
Antioxidants are currently under evaluation for several age related and other diseases such as macular degeneration and cataract. The role of antioxidants in developing retinopathy, and changing existing retinopathy to more aggressive disease has been investigated with observational studies.

There is no evidence of effectiveness.

Journals

Brief description of any further published studies found outside those already covered in any reviews described above. E.g. if a review only covered a certain time period, the journals could be searched to find studies published outside these dates. Briefly describe in table below.

Study	Design	Number of participants	Results
Title: 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. **Citation:** Archives of Opthalmology. 2001; Oct 19. p1439. **Author(s):** Age-Related Eye Disease Study Research Group	Randomised Double-blind placebo controlled trial. Participants were randomly assigned to receive daily oral tablets containing either antioxidants (vitamin C, 500 mg; vitamin E, 400 IU; and beta carotene, 15 mg) or no antioxidants. Participants with more than a few small drusen were also randomly assigned to receive tablets with or without zinc (80 mg of zinc as zinc oxide) and copper (2 mg of copper as cupric oxide) as part of the age-related macular degeneration trial. Baseline and annual (starting at year 2) lens photographs were graded at a reading center for the severity of lens opacities using the AREDS cataract grading scale.	Of 4757 participants enrolled, 4629 who were aged from 55 to 80 years had at least 1 natural lens present and were followed up for an average of 6.3 years.	**Main Outcome Measures:** Primary outcomes were (1) an increase from baseline in nuclear, cortical, or posterior subcapsular opacity grades or cataract surgery, and (2) at least moderate visual acuity loss from baseline (≥15 letters) No statistically significant effect of the antioxidant formulation was seen on the development or progression of age-related lens opacities (odds ratio=0.97, *P*=.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. For the 1117 participants with no age-related macular degeneration at baseline, no statistically significant difference was noted between treatment groups for at least moderate visual acuity loss. No statistically significant serious adverse effect was associated with treatment.

Title: The Antioxidants in Prevention of Cataracts Study: effects of antioxidant supplements on cataract progression in South India. **Citation:** The British journal of ophthalmology, July 2006, vol./is. 90/7(847-51), 0007-1161 **Author(s):** Gritz D, et al.	5 year, randomised, triple masked, placebo controlled, field based clinical trial to assess the ability of interventional antioxidant supplements to slow cataract progression.	798 patients	There was no significant difference between placebo and active treatment groups for either the primary or secondary outcome variables. **CONCLUSION:** Antioxidant supplementation with beta carotene, vitamins C and E did not affect cataract progression in a population with a high prevalence of cataract whose diet is generally deficient in antioxidants.
Title: Supplements and age-related eye conditions the beaver dam eye study. **Citation:** Ophthalmology. 2008 Jul;115(7):1203-8. **Author(s):** Klein B, et al.	METHODS: Use of all medications and supplements were collected from study participants at each of 4 examinations.	Subjects were participants in the Beaver Dam Eye Study who contributed data in 1988 to 1990 (n = 4926), 1993 to 1995 (n = 3722), 1998 to 2000 (n = 2962), and 2003 to 2005 (n = 2375).	MAIN OUTCOME MEASURES: Incidence of age-related cataracts, macular degeneration (AMD), and high IOP for one set of analyses and incidence of supplement use for the second set of analyses. RESULTS: **There was little evidence of any significant associations between supplement use and incident ocular outcomes except for a small protective effect for cortical cataracts by vitamins A and D, zinc, and multivitamins and increased odds of late AMD**. Late AMD was associated with incident use of vitamins A, C, and E and zinc. CONCLUSIONS: Age-related macular degeneration seems to precede use of vitamins A, C, and E and zinc. This may reflect advice by family, friends, and health care providers about the benefits of Age-Related Eye

Appendix 2: Grading of evidence

- Ia: systematic review or meta-analysis of randomised controlled trials
- Ib: at least one randomised controlled trial
- IIa: at least one well-designed controlled study without randomisation
- IIb: at least one well-designed quasi-experimental study, such as a cohort study
- III: well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, case–control studies and case series
- IV: expert committee reports, opinions and/or clinical experience of respected authorities

Appendix 3: References

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