<table>
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<tr>
<th>#</th>
<th>Order of importance</th>
<th>Question</th>
<th>Issue, year, Art. No.</th>
<th>DOI</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>Why is there uncertainty?</td>
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<td>2</td>
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<td>What is the cause of age related macular degeneration (AMD)?</td>
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<td>3</td>
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<td>What is the effectiveness of eye injections in the treatment for dry age-related macular degeneration?</td>
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<td>4</td>
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<td>Are there ways of restoring sight loss for people with age related macular degeneration (AMD)?</td>
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<td>5</td>
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<td>Can donor eyes or their components be used to replace ocular components affected by age-related macular degeneration?</td>
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<td>6</td>
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<td>Can dietary factors, nutritional supplements, or complementary therapies or lifestyle changes prevent or slow the progression of early AMD?</td>
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<tr>
<td>7</td>
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<td>Can a treatment to stop dry age related macular degeneration be devised?</td>
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<tr>
<td>8</td>
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<td>What detection methods can be used to envisage age related macular degeneration (AMD)?</td>
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<tr>
<td>9</td>
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<td>Are injections in the eye effective and safe for people with age related macular degeneration (AMD)?</td>
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<tr>
<td>10</td>
<td>1</td>
<td>Can the development of age related macular degeneration be halted?</td>
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Aflibercept for neovascular age-related macular degeneration

Anti-vascular endothelial growth factor for neovascular age-related macular degeneration

Lawrenson JG, Evans JR. Omega 3 fatty acid supplementation for preventing and slowing the progression of age-related macular degeneration. Cochrane Database of Systematic Reviews 2015, Issue 4. Art. No.: CD011977. DOI:10.1002/14651858.CD011977

Implantable miniature telescope (IMT) for vision loss due to age-related macular degeneration

No relevant systematic reviews identified

Reliable up-to-date systematic reviews have not been identified. New research is recommended to determine whether IMT is effective for vision loss due to age-related macular degeneration.

Uncertainties identified in research revealed important continuing uncertainties about treatment effects.

Ranibizumab has been shown to have a significant benefit in patients with AMD to better evaluate whether cataract surgery is necessary or if it can delay the need for surgery in patients with AMD.

Residual confounding from other dietary or lifestyle variables is always a risk of developing AMD or slowing its progression through dietary modification.

Nutritional State and Ethnicity in the Development and Progression of Age-related Macular Degeneration: A Randomised Controlled Trial of Epimacular Brachytherapy Versus Lucentis Only Treatment (MERLOT). A Randomised Controlled Trial of Alternative Treatments to Inhibit the Progression of Age-related Macular Degeneration Treatments Trials: Lucentis-Avastin Trial (CATT). ISRCTN92166560  Comparison of Age-related Macular Degeneration Treatments Trials: Lucentis-Avastin Trial (CATT) (CATT). ISRCTN92166560

FURTHER DETAILS

10.1002/14651858.CD006757.pub3


10.1002/14651858.CD010015


Lawrenson JG, Evans JR. Omega 3 fatty acids for preventing and slowing the progression of age-related macular degeneration. Cochrane Database of Systematic Reviews 2015, Issue 11. Art. No.: CD011346. DOI:10.1002/14651858.CD011346

10.1002/14651858.CD011140


10.1002/14651858.CD011345

Dicker K, Manta Study: Avastin Versus Lucentis in Age Related Macular Degeneration Treatments Trials: Lucentis-Avastin Trial (CATT). ISRCTN92166560

Adverse effects on QoL AMD. An additional primary objective will be to assess the device's impact on improving vision; participants treated with anti-VEGFs showed improved visual outcomes compared to sham and laser treatments. The results of this review will be used to inform future research on the effectiveness and safety of aflibercept in the treatment of neovascular AMD.

Objectives are as follows: The objectives of this review are to assess the effectiveness and safety of aflibercept with bevacizumab versus ranibizumab for treating neovascular age-related macular degeneration. This is the protocol for a review and there is no abstract. The results will be used to inform future research on the effectiveness and safety of aflibercept in the treatment of neovascular AMD.
Antioxidant multivitamin supplements in malnourished individuals: a systematic review of randomised controlled trials


Omega 3 fatty acids to halt progression of age-related macular degeneration

Intravitreal bevacizumab (Avastin) vs. ranibizumab for neovascular age-related macular degeneration

Dietary antioxidants and primary prevention of age-related macular degeneration

Appropriate duration and optimal treatment regimen of bevacizumab (Avastin) for neovascular age-related macular degeneration

Uncertainties identified in research about the effectiveness of antioxidant vitamin and mineral supplementation in halting the progression of age-related macular degeneration

Authors' conclusions: The evidence as to the effectiveness of antioxidant vitamin and mineral supplementation in halting the progression of age-related macular degeneration 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 associated with a lower risk of AMD, but there is insufficient evidence from the present world literature. This is an intriguing and extremely important question that needs to be addressed in future trials.

Authors' conclusions: The Final appraisal determination from the National Institute for Health and Clinical Excellence (NICE) in August 2008, recommends that people at high risk of AMD should be encouraged to eat a diet rich in fruit, vegetables and fish, particularly oily fish. Care needs to be taken to provide a placebo control that has a similar amount of omega-3 fatty acids (from fish) and other dietary factors, while being nutritionally equivalent. Reliable up-to-date systematic reviews have shown that omega-3 fatty acids may be protective against the disease. We do not know at what stage the use of omega-3 fatty acids will be most effective in relation to the natural history of the disease or diabetes.

Authors' conclusions: In general, beta-carotene and vitamin A supplements are associated with a lower risk of AMD. However, the results of the FRAM study have been inconsistent. The potential for vitamin A supplements to protect against AMD has been explored in a number of randomised controlled trials in other populations. Future trials should be conducted in different populations, including those with different nutritional status. Long-term harm from supplementation cannot be ruled out.

Authors' conclusions: This systematic review and meta-analysis of randomised controlled trials has revealed important continuing uncertainties about the effectiveness of antioxidant vitamin and mineral supplementation in halting the progression of age-related macular degeneration. This would seem to be a cost-effective way forward in research in this area.

Authors' conclusions: The hypothesis that antioxidant micronutrients may protect against the disease is a reasonable one. We do not know at what stage the use of antioxidants will be most effective in relation to the natural history of the disease or diabetes. There is insufficient evidence from randomised controlled trials in other populations that antioxidant supplementation can slow progression of age-related macular degeneration to more severe stages of the disease. The small number of people in our pooled analysis means that the results need to be interpreted with caution.

Authors' conclusions: The UK National Institute for Health and Clinical Excellence (NICE) recommends that the final appraisal determination from its technology appraisal programme in August 2008, is that people at high risk of AMD should be encouraged to eat a diet rich in fruit, vegetables and fish, particularly oily fish. Care needs to be taken to provide a placebo control that has a similar amount of omega-3 fatty acids (from fish) and other dietary factors, while being nutritionally equivalent. Reliable up-to-date systematic reviews have shown that omega-3 fatty acids may be protective against the disease. We do not know at what stage the use of omega-3 fatty acids will be most effective in relation to the natural history of the disease or diabetes.

Uncertainties identified in research about treatment effects revealed important continuing uncertainties. Reliable up-to-date systematic reviews have been conducted; however, one of the main drives for its adoption is its low cost. The data on the safety and efficacy of bevacizumab and no RCTs have yet been submitted by 1 patients, and 1 clinician. Below are the questions thought to be covered by this indicative question: Are injections for wet age-related macular degeneration: a systematic review and economic evaluation. Health Technol Assess 2008;12(16).

Authors' conclusions The evidence as to the effectiveness of antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. NTR1331 http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1331

Evans JR. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. In Issue 1, 2009. DOI: 10.1002/14651858.CD000254.pub2

Evans JR. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. Cochrane Database of Systematic Reviews 2008, Issue 1. DOI: 10.1002/14651858.CD000254.pub2


Effectiveness of treatment; adverse effects; and cost. Included as Research Recommendations

"Age-related macular degeneration" Royal College of Ophthalmologists. Age-related macular degeneration. NCT00710229 http://www.rcophth.ac.uk/docs/publications/AMD_GUIDELINES

Comparison of Age-related Macular Degeneration Treatments with the best available therapy in subjects with choroidal neovascularisation secondary to age-related macular degeneration ISRCTN83325075 [Trial completed, not yet published] The EQUAL study: A randomised trial to study the EQUivalence of three monthly intravitreal injections and additional injections as needed of bevacizumab (Avastin) and ranibizumab (Lucentis) on visual acuity in patients with exudative age-related macular degeneration. NCT00559715  The EQUAL study: A randomised trial to study the EQUivalence of three monthly intravitreal injections and additional injections as needed of bevacizumab (Avastin) and ranibizumab (Lucentis) on visual acuity in patients with exudative age-related macular degeneration. NCT00710229

Evans JR. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. In Issue 1, 2009. DOI: 10.1002/14651858.CD000254.pub2

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Evans JR. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. Cochrane Database of Systematic Reviews 2008, Issue 1. DOI: 10.1002/14651858.CD000254.pub2

Evans JR. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD005139. DOI: 10.1002/14651858.CD005139.pub2

Antioxidant systems and age-related macular degeneration Antioxidant systems and age-related macular degeneration. NCT00345176

Antioxidant systems and age-related macular degeneration Antioxidant systems and age-related macular degeneration. NCT00668213  Age-Related Eye Disease Study 2 (AREDS2) Antioxidant systems and age-related macular degeneration. NCT00345176

Evans JR. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. In Issue 1, 2009. DOI: 10.1002/14651858.CD000254.pub2

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Evans JR. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. Cochrane Database of Systematic Reviews 2008, Issue 1. DOI: 10.1002/14651858.CD000254.pub2

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Evans JR. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD005139. DOI: 10.1002/14651858.CD005139.pub2
Are there any lifestyle changes that can be made to prevent age related macular degeneration (AMD)?

Can dietary measures prevent age related macular degeneration (AMD)?

Can a treatment / cure for macular degeneration be developed?

This is an indicative uncertainty and this question or something like it has been submitted by others. Below are the questions thought to be covered by this indicative question.

Can complementary therapies impact the progression of age related macular degeneration (AMD) to wet age related macular degeneration (wet AMD)?

This is an indicative uncertainty and this question or something like it has been submitted by others. Below are the questions thought to be covered by this indicative question.

Can stem cells treat or retard the progress of age related macular degeneration (wet and dry)?

Might stem cell treatment be used to treat a central ocular scar in wet age-related macular degeneration? Will it ever be possible to regenerate the macula in cases of age-related macular degeneration? Can anything be done to slow the progression of age-related macular degeneration? Can anything be done to reverse the effects of age-related macular degeneration?

This is an indicative uncertainty and this question or something like it has been submitted by 2 carers. Below are the questions thought to be covered by this indicative question.

Can combined Anti-VEGF/steroids/PDT therapies increase chances of longer treatment-free intervals and reduction of number of overall injections for people with age related macular degeneration (AMD)? Can dietary measures and/or the use of nutritional supplements prevent or slow down the development of age-related macular degeneration? What research has been done to evaluate the role of nutrition and nutritional supplements in prevention of age-related macular degeneration?

What is the effectiveness of diet or lifestyle choices in preventing and reducing sight loss due to macular degeneration? What is the role of nutritional supplements in preventing age-related macular degeneration? Does diet have any effect on developing age-related macular degeneration?

This is an indicative uncertainty and this question or something like it has been submitted by 3 patients, and 2 clinicians. Below are the questions thought to be covered by this indicative question.

Are any effective treatments available for age-related macular degeneration (AMD)?

Can a treatment / cure effective for all be developed for dry age related macular degeneration (AMD)?

Can a stem cell treatment for age related macular degeneration (AMD) be developed?

Can diagnostic tests for age related macular degeneration (AMD) be developed? Do diagnostic tests increase chances of longer treatment-free intervals and reduction of number of overall injections for people with age related macular degeneration (AMD)?

Reliable up-to-date systematic reviews have revealed important continuing uncertainties about treatment effects and acceptability to the patient; and cost.

Evans JR. Ginkgo biloba extract for age-related macular degeneration. Cochrane Database of Systematic Reviews 2012, Issue 11. Art. No.: CD000254. DOI: 10.1002/14651858.CD000254.pub3


Can dietary supplements help slow the progression of age-related macular degeneration (AMD)?

Can nutritional supplements prevent age-related macular degeneration (AMD)?

Can laser eye surgery trigger the progression of age-related macular degeneration (AMD)?

Change in symptoms; adverse effects or complications; acceptability to the patient; and cost

Can Macushield help prevent age-related macular degeneration (AMD)?

Can Lutein help prevent age-related macular degeneration (AMD)?

Could vision be improved by the use of glasses (or with appropriate vision correction)?

Can drusen be prevented?

This is an indicative uncertainty and this question or something like it has been submitted by 1 Patients, and 2 clinicians. Clinicians. Below are the questions thought to be covered by this indicative question:

- What is the effectiveness of Macushield capsules in preventing the progression of dry age-related macular degeneration?
- What is the effectiveness of Visionace, Lutein, Beta-Carotenet tablets and Blueberry that the use of vitamins and food supplements, such as lutein and zeaxanthin, is advisable as a preventative for age-related macular degeneration? What is the effectiveness of tablets Macushield for macular degeneration? What is a safe amount of Lutein/Zeaxanathin to eat fruit and green vegetables daily? What are the most effective tablets covered by this indicative question: Is a dietary supplement containing lutein and zeaxanthin, or macular degeneration? What is the effectiveness of food supplements for patients with macular degeneration? What is the effectiveness of Macushield capsules for patients with dry age-related macular degeneration (AMD)? What is the effectiveness of nutritional supplements for patients with macular degeneration? What is the effectiveness of food supplements for preventing age-related macular degeneration?

No relevant systematic reviews identified

Existing relevant systematic reviews are not up-to-date about treatment effects

Reliable up-to-date systematic reviews have been published in the Cochrane Library, which contains only systematic reviews of healthcare interventions. Data were added to the second and third editions of the Cochrane Databases of Systematic Reviews and the Cochrane Library in 2004 and 2012, respectively. Data for the systematic review are up-to-date as of 10 March 2016. Data for the economic model were added to the second and third editions of the Cochrane Databases of Systematic Reviews and the Cochrane Library in 2004 and 2012, respectively. Data for the economic model were up-to-date as of 10 March 2016. Data for the economic model were up-to-date as of 10 March 2016.
Does the use of modern technology increase the risk of long-term blue light exposure leading to retinal damage in cases of dry age-related macular degeneration? Does surgery for cataracts prove to be successful for people with age-related macular degeneration? Is there anything that can be done to prevent the development of wet age-related macular degeneration following cataract extraction? Would the use of UV protective glasses / sunglasses / contact lenses reduce its presentation? What impact do reliable up-to-date systematic reviews have on the provision of age-related macular degeneration care? How do we ensure early diagnosis of age-related macular degeneration? What detection methods can be used for alerting to early stages of macular degeneration and guiding of treatment for neovascular age-related macular degeneration? How can we prevent wet age-related macular degeneration? How can we prevent dry age-related macular degeneration? Can we ensure early diagnosis of age-related macular degeneration? What can be done to prevent risk of developing wet age-related macular degeneration? How effective is Lucentis age-related macular degeneration treatment at different stages of age-related macular degeneration proving to be successful? What is the impact of modern technologies such as coherence tomography (OCT) for the diagnosis, monitoring and guiding of treatment for neovascular age-related macular degeneration? What is the impact of modern technologies such as OCT for the diagnosis, monitoring and guiding of treatment for neovascular age-related macular degeneration? What can be done to improve early diagnosis in age-related macular degeneration? What detection methods can be used for alerting to wet and dry age-related macular degeneration? What detection methods can be used for alerting to an early diagnosis of age-related macular degeneration? What detection methods can be used for early alerting to age-related macular degeneration? What detection methods can be used for alerting to early stages of macular degeneration? How can we ensure early diagnosis of age-related macular degeneration more likely? What can be done to detect age-related macular degeneration more likely? Is there anything that can be done to prevent age-related macular degeneration more likely? How can we ensure early diagnosis of age-related macular degeneration following cataract extraction? Would the use of UV protective glasses / sunglasses / contact lenses reduce its presentation? What impact do reliable up-to-date systematic reviews have on the provision of age-related macular degeneration care? How do we ensure early diagnosis of age-related macular degeneration? What detection methods can be used for alerting to early stages of macular degeneration and guiding of treatment for neovascular age-related macular degeneration?
Is 'cold laser' treatment a possible treatment for drusen?

Diagnostic
Change in symptoms; adverse effects or complications; acceptability

What are the prospects for developing widely available cataracts?

Nutrition
Progression of macular degeneration together with haemorrhage and optic nerve following a stroke?

Genetic testing for the commonest forms of macular degeneration?

Relevant reliable up-to-date systematic reviews have revealed important continuing uncertainties about treatment effects.

Reliable up-to-date systematic reviews have not addressed continuing uncertainties about treatment effects.

No relevant systematic reviews identified about treatment effects revealed important continuing uncertainties.
What is the most effective treatment for age-related macular degeneration?

Uncertainties identified from patients' questions

No relevant systematic reviews identified

Change in symptoms: adverse effects or complications; acceptability to patients; and cost

What is the most effective treatment for dry age-related macular degeneration?

Uncertainties identified from clinicians' questions

No relevant systematic reviews identified

Change in symptoms: adverse effects or complications; acceptability to patients; and cost

What is the most effective treatment for macular degeneration complicated by sub-macular haemorrhage?

Uncertainties identified from carers' questions

No relevant systematic reviews identified

Change in symptoms; adverse effects or complications; acceptability to the patient; and cost

What is the most effective treatment for macular degeneration in younger people?

Uncertainties identified from clinicians' questions

No relevant systematic reviews identified

Change in symptoms; adverse effects or complications; acceptability to the patient; and cost

What is the most effective treatment for pigment epithelial detachment in age-related macular degeneration (AMD)?

Uncertainties identified from carers' questions

No relevant systematic reviews identified

Change in symptoms; adverse effects or complications; acceptability to the patient; and cost

What things can be avoided by the individual to prevent worsening of Charles Bonnet Syndrome?

Uncertainties identified from clinicians' questions

No relevant systematic reviews identified

Change in symptoms: adverse effects or complications; acceptability to patients; and cost

With age-related macular degeneration, is there any evidence as to whether the use of a particular type of sunglasses might stop damaging blue light from entering the eyes?

Uncertainties identified from clinicians' questions

No relevant systematic reviews identified

Change in symptoms; adverse effects or complications; acceptability to the patient; and cost

Would photochromic glasses worn from a young age for all reduce the onset of age-related macular degeneration?

Uncertainties identified from carers' questions

No relevant systematic reviews identified

Change in symptoms; adverse effects or complications; acceptability to the patient; and cost