Laser treatment of drusen to prevent progression to advanced age-related macular degeneration (Review)

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[Intervention Review]

Laser treatment of drusen to prevent progression to advanced age-related macular degeneration

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Editorial group: Cochrane Eyes and Vision Group.
Publication status and date: New, published in Issue 3, 2009.
Review content assessed as up-to-date: 13 November 2008.

Citation: Parodi MB, Virgili G, Evans JR. Laser treatment of drusen to prevent progression to advanced age-related macular degeneration. *Cochrane Database of Systematic Reviews* 2009, Issue 3. Art. No.: CD006537. DOI: 10.1002/14651858.CD006537.pub2.

ABSTRACT

Background

Drusen are amorphous yellowish deposits beneath the sensory retina. People with drusen, particularly large drusen, are at higher risk of developing age-related macular degeneration (AMD). The most common complication in AMD is choroidal neovascularisation (CNV), the growth of new blood vessels in the centre of the macula. The risk of CNV is higher among patients who are already affected by CNV in one eye.

It has been observed clinically that laser photocoagulation of drusen leads to their disappearance and may prevent the occurrence of advanced disease (CNV or geographic atrophy) associated with visual loss.

Objectives

To examine the effectiveness and adverse effects of laser photocoagulation of drusen in AMD.

Search methods

We searched CENTRAL, MEDLINE and EMBASE on 14 November 2008.

Selection criteria

Randomised controlled trials (RCTs) of laser treatment of drusen in AMD in which laser treatment had been compared with no intervention or sham treatment. Two types of trials were included. Some trials studied one eye of each patient (unilateral studies); other studies recruited patients with bilateral drusen and randomised one eye to photocoagulation or control and the fellow eye to the other group.

Data collection and analysis

Two review authors independently selected studies and extracted data. We pooled data from unilateral and bilateral studies using a random-effects model. For the bilateral studies, we estimated the within-patient correlation coefficient from one study and assumed it was valid for the others.

Main results

We found nine studies which randomised 2216 people: four unilateral trials, three bilateral trials and two trials that included both a unilateral and a bilateral study arm.

Overall, the studies were of moderate quality. Only half of the trials reported adequate allocation sequence generation, allocation concealment and masking of visual acuity outcome assessors.

Although two (of the nine) studies reported significant drusen disappearance at two years, photocoagulation did not appear to affect the development of CNV at two years follow up (nine studies, 1767 people followed up, odds ratio (OR) 1.04, 95% CI 0.71 to 1.51) or the loss of three or more lines of visual acuity (six studies, 1628 people followed up, OR 1.17, 95% CI 0.75 to 1.82).

Authors' conclusions

The trials included in this review confirm the clinical observation that laser photocoagulation of drusen leads to their disappearance. However, there is no evidence that this subsequently results in a reduction in the risk of developing CNV, geographic atrophy or visual acuity loss.

PLAIN LANGUAGE SUMMARY

Laser treatment of drusen to prevent progression to advanced age-related macular degeneration

Drusen are amorphous yellowish deposits beneath the sensory retina. People with drusen, particularly extensive large drusen, are at higher risk of developing age-related macular degeneration (AMD). The most common complications in AMD are the growth of new blood vessels in the centre of the macula (choroidal neovascularisation or CNV also known as 'wet AMD') and loss of photoreceptors (geographic atrophy). It has been observed clinically that laser photocoagulation of drusen leads to their disappearance. Laser photocoagulation of drusen has thus been proposed as a way to prevent the development of CNV and geographic atrophy. This review included data from nine trials of moderate quality. These studies confirmed the clinical observation that laser photocoagulation of drusen leads to their disappearance. However, there was no evidence that laser photocoagulation of drusen reduced the risk of developing CNV, geographic atrophy or visual acuity loss.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Outcomes at two years	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	**Photocoagulation**				
Development of CNV	**78 per 1000**	**86 per 1000** (60 to 121)	**OR 1.04** (0.71 to 1.51)	1767 (9)	⊕⊕⊕◯ **moderate**[1]	
	Low risk population (patients with bilateral drusen)					
	50 per 1000	**55 per 1000** (38 to 79)				
	HIgh risk population (patients with CNV in the fellow eye)					
	250 per 1000	**270 per 1000** (202 to 352)				
Development of geographic atrophy	**88 per 1000**	**155 per 1000** (28 to 562)	**OR 1.30** (0.38 to 4.51)	66 (1)	⊕⊕◯◯ **low**[2]	
Visual loss of 2-3+ lines of visual acuity	**142 per 1000**	**110 per 1000** (82 to 147)	**OR 0.88** (0.67 to 1.14)	1628 (6)	⊕⊕⊕◯ **moderate**[3]	
Loss of 0.3 log units or more of contrast sensitivity	**119 per 1000**	**100 per 1000** (26 to 309)	**OR 0.82** (0.20 to 3.31)	82 (1)	⊕⊕ **low**[2]	
Reading speed in words/minute	The mean reading speed in words/minute in the control groups was **100 words/minute**	The mean reading speed in words/minute in the intervention groups was **12.5 lower** (7.2 lower to 32.2 higher)		44 (1)	⊕⊕ **low**[2]	

Drusen reduction	**Medium risk population**		**OR 10.72** (3.84 to 29.97	195 (2)	⊕⊕⊕⊕ **high**[4,5]
	235 per 1000	**767 per 1000** (541 to 902)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; OR: odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Allocation sequence generation and allocation concealment and masking of visual acuity outcome assessors was achieved in half or less of them. Risk of bias from incomplete outcome data was unclear in one study and high in two studies, but sensitivity analyses did not suggest meaningful changes of pooled ORs (see Figure 5 and Figure 6). Other quality items were not a problem.
[2]Small study yielding wide 95% confidence intervals.
[3]Visual acuity examiners were masked in less than half of studies.
[4]The two studies included in this analysis have low risk of bias.
[5]Estimates are heterogenous but they both suggest a strong effect.

BACKGROUND

Description of the condition

Age-related macular degeneration (AMD) is the leading cause of vision loss in industrialised countries (Klein 2004; Vingerling 1996). Early AMD is characterised by focal or diffuse depositing of extracellular material between the retinal pigment epithelium and Bruch's membrane, forming drusen or basal laminar deposits respectively (Bressler 1994; Sarks 1999; Young 1987). This process is associated with progressive degeneration of retinal pigment epithelium and photoreceptor cells (Guidry 2002; Phipps 2003; Young 1987). Advanced AMD is characterised by the development of geographic atrophy (characterising the non-exudative AMD form) or choroidal neovascularisation (characterising the exudative AMD). When the fovea, which represents the centre of vision, is involved by atrophic or exudative manifestations of AMD a severe visual loss results.

Advanced AMD was found to have a prevalence that increases markedly with age (EDPRG; Owen 2003). In the US, advanced AMD prevalence is 3.5% to 4% at 75 to 79 years among white males and females respectively (EDPRG). Based on a systematic review of UK studies, Owen 2003 reported that there were approximately 214,000 people (95% CI 151,000 to 310,000) with visual impairment caused by AMD, and this is estimated to become 239,000 in 2011. In this study, the ratio of neovascular AMD to geographic atrophy was about 2:1, such as in Smith 2001.

Drusen results from deposition of the photoreceptors debris, which are composed of lipofuscin and membranous deposits. Drusen appear when sufficient material has been deposited, clinically characterised by amorphous yellowish deposits beneath the sensory retina. Four main types of drusen can be detected in the retina. Hard drusen are discrete, yellow, nodular deposits, smaller than 50 microns in diameter. Basal laminar drusen are tiny, whitish, multiple deposits with a 'starry night' appearance. Soft drusen are yellowish deposits with poorly defined margins, tending to coalesce, and are usually larger than 50 microns. Crystalline drusen are discrete, calcific, refractile deposits. Drusen characteristics associated with a high risk of progression to exudative AMD (high-risk drusen) include: soft drusen, more than five, larger size (greater than 63 microns), drusen confluence and associated hyperpigmentation.

The cumulative incidence of new exudative or atrophic lesions in eyes initially free of advanced AMD has been estimated as 8.6% at one year, 16.4% at two years and 23.5% at three years (Holz 1994). Focusing on the choroidal neovascularisation (CNV) incidence, the results of a prospective investigation of patients with exudative manifestation in one eye and drusen in the fellow eye has shown that the risk of developing CNV peaks at four years, dissipating thereafter, whereas there is a slightly increased incidence of geographic atrophy in the longer-term (Sarraf 1999). Moreover, the five-year risk of CNV occurrence in the fellow eye of patients who have already experienced CNV in the first eye, varies from 7% to 87% depending on the coexistence of four main risk factors (presence of five or more drusen, focal hyperpigmentation, one or more large drusen and systemic hypertension) (MPSG 1997).

Drusen can spontaneously disappear in patients with AMD, generally leaving atrophic lesions. More specifically, the Waterman study has reported that disappearance of large drusen occurred in 16 (34%) of 47 participants in a five-year longitudinal study (Bressler 1995).

Description of the intervention

Laser treatment is based on the release of a powerful beam of light which, combined with ophthalmic equipment and lenses, can be precisely focused on the retina to treat some diseases. The laser energy causes a certain amount of controlled damage to the tissues in order to obtain the desired effect. Small laser burns are usually employed to obliterate or destroy abnormal blood vessels or other lesions in the eye.

Several observers noted that laser application can lead to drusen being resorbed in the macular area (Cleasby 1979; Gass 1973; Gross-Jendroska 1998; Wetzig 1994). Owing to the risk of vision loss associated with the presence of high-risk drusen, laser application was proposed as an intervention to prevent progression to advanced AMD. Laser burns are applied to the retina, either directly to the drusen or following predefined patterns. Argon, krypton, dye or diode lasers have been used with varying levels of energy (achieving from not visible to faint or intense whitish retinal lesions). The spot size used varies between 100 to 200 microns and number of spots from less than 10 to nearly 300.

How the intervention might work

The mechanisms of laser-induced drusen regression are only speculative. Laser treatment may lead to an increased clearance of debris by choroidal phagocytic cells or macrophages. Alternatively, laser application may improve egress of drusen material through a thinner or more permeable Bruch's membrane, with the consequent reduction of its outflow resistance. Laser effect may manifest by triggering retinal pigment epithelial proliferation leading to the production and release of cytokines and growth factors, which may also act on the drusen remote from the site of the laser energy application (Abdelsalam 1999; Frennesson 1998; Pauleikhoff 1990a; Pauleikhoff 1990b). Histopathologic examinations in animal models have shown that phagocytic cells, probably derived from choriocapillaris pericytes can remove drusenoid material after laser photocoagulation (Duvall 1985). Protrusion of choroidal endothelial cell processes into Bruch's membrane are enhanced by laser photocoagulation and may play a part in the clearance of debris from the Bruch's membrane (Guymer 2001).

Why it is important to do this review

Age-related macular degeneration is a major public health problem in developed economies where the life expectancy is greatest (but of no significance in poorer countries with a life expectancy of under 65). Several investigations about health-related and vision-targeted features have shown that AMD is associated with decreased quality of life (Brown 2006; Chakravarthy 2005; Hassell 2006; Maguire 2004; Mangione 1999).

Although people with drusen experience few visual symptoms, once advanced AMD is present, visual loss is generally irreversible. It has been shown that patients with drusen who take antioxidant supplementation are less likely to lose 15 or more letters of visual acuity over the follow up (AREDS 2001), even though this benefit was considered modest in people with moderate to severe signs of the disease (Evans 2006). Antioxidants have not been shown beneficial in the primary prevention of AMD (Chong 2007). Thus, the identification of a prophylactic treatment able to reduce the complications related to AMD may be highly beneficial.

Laser treatment of drusen appeared to provide positive results in observational studies (Cleasby 1979; Gass 1973; Gross-Jendroska 1998; Sigelman 1991; Wetzig 1994). A systematic review is necessary to ensure that all the evidence on this intervention is considered objectively. People with AMD and their caregivers need to have recommendations as to the possible benefits or harms of this intervention.

OBJECTIVES

The aim of the review is to examine the effectiveness and adverse effects of laser photocoagulation of drusen in AMD.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomised controlled trials (RCTs) of laser treatment of drusen in AMD.

Types of participants

Participants in the trials were people with retinal drusen associated with AMD in one or both eyes.

Types of interventions

We included trials in which laser treatment for retinal drusen was compared with no intervention or sham treatment. A variety of different laser sources and photocoagulation techniques were considered.

Types of outcome measures

Primary outcomes

The primary outcome measure was progression of AMD as measured by the development of CNV or geographic atrophy.

Secondary outcomes

Secondary outcomes included:

- loss of visual acuity (LogMAR values);
- changes in contrast sensitivity;
- drusen reduction;
- changes in reading ability;
- vision-related quality of life.

Visual acuity is generally measured by means of a standard chart, the ETDRS (Early Treatment of Diabetic Retinopathy Study) chart and scored in letters. There are five letters per line in this chart. Both dichotomous outcomes, such as moderate (3 lines or 15 ETDRS letters) and severe (6 lines or 30 ETDRS letters) visual loss and continuous measures (mean visual acuity) were extracted when possible. Whenever no ETDRS values were used, visual acuity was converted to LogMAR (logarithm of the Minimum Angle of Resolution) for pooling data.

Contrast sensitivity is generally measured with the Pelli-Robson chart. Scores are collected in letters or as logarithm of contrast sensitivity. The latter was used for pooling data when feasible. Both continuous and dichotomous measures were extracted if possible. For dichotomous data, the proportion of participants with a change of at least 0.3 or 0.6 log-units, corresponding to a two-fold or a four-fold change respectively, was recorded.

In the protocol, drusen reduction was planned to be evaluated considering the number of eyes showing at least a 50% reduction of drusen area from the baseline aspect. However, data were sparsely reported and therefore we modified the protocol to allow an extraction based on the investigators' definition.

Reading ability measures were converted to LogMAR for reading acuity, whereas reading speed was considered as the logarithm of the number of words read in a minute.

Timing of outcome assessment

We assessed outcomes at 24 months, where data were available.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Group Trials Register) (*The Cochrane Library* Issue 4, 2008), MEDLINE (January 1950 to November 2008) and EMBASE (January 1980 to November 2008). There were no language or date restrictions in the search for trials. The electronic databases were last searched on 14 November 2008.

See Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2) and EMBASE (Appendix 3).

Searching other resources

We searched the reference lists of retrieved articles for details of further relevant studies. We did not handsearch journals or conference proceedings specifically for this review.

Data collection and analysis

Selection of studies

Two authors independently assessed the titles and abstracts resulting from the electronic searches for inclusion. We obtained copies of all relevant or potentially relevant trials and assessed these according to the 'Criteria for considering studies for this review'. The authors were not masked as to the names of authors, institutions, journal of publication or results when making their assessments. We resolved disagreements about whether a trial should be included by discussion and consensus. In cases where additional information was needed before a decision was made whether to include a trial, we obtained this information by contacting the authors.

Data extraction and management

Information about the methods used in the trial was recorded on a form including details of participants, details of intervention, outcomes and other information. Two review authors independently extracted the data for the primary outcomes, secondary outcomes and adverse effects onto paper forms. Since the double-entry facility is no longer available in RevMan 5.0, one review author extracted data and entered them into RevMan 5.0 (RevMan 2008) and another review author checked the entries for errors and inconsistencies.

Assessment of risk of bias in included studies

Two review authors independently assessed the included trials for bias according to the methods described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions 5.0* (Higgins 2008a). With the update of review management software, we assessed risk of bias using the tool set out in the Handbook.

1. Sequence generation: the method used to generate the allocation sequence, to assess whether it should have produced comparable groups.
2. Allocation concealment: the method used to conceal the allocation sequence, to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.
3. Masking of personnel and outcome assessors: the assessments were made for each main class of outcomes (i.e. anatomic versus functional outcomes) and we considered whether all measures used, if any, to mask study personnel from knowledge of which intervention a participant received were adequate.
4. Incomplete outcome data: the assessments were made for each main class of outcomes (i.e. anatomic versus functional outcomes) when possible and were based on the description of the completeness of outcome data, including attrition and exclusions from the analysis and their causes, if they were reported.
5. Selective outcome reporting: the possibility of selective outcome reporting, such as found when some measures were obtained, as declared in the methods section or in protocols, but not reported in the results section.

The following grading was used:

- Low risk of bias: plausible bias unlikely to seriously alter the results.
- Unclear risk of bias: plausible bias that raises some doubt about the results.
- High risk of bias: plausible bias that seriously weakens confidence in the results.

If the information available in the published trial reports was inadequate to assess any of the above items of the risk of bias assessment, we contacted the trial authors for clarification. If they did not respond within a reasonable period of time, we classified the trial based on the available information. When studies did not report any concealment approach, adequacy was considered to be unclear. We also assessed the impact of any assumptions made in this regard in a sensitivity analysis.

We considered a trial to have conducted an intention-to-treat analysis only if it included all participants who were randomised including those randomised but not treated and excluded after randomisation for other reasons.

Measures of treatment effect

We evaluated development of CNV and geographic atrophy on the basis of the percentage of their occurrence over the follow up. We assessed visual acuity loss taking into consideration the loss of 3 or more lines of visual acuity, which corresponds to a doubling of the visual angle if visual acuity is measured using a logMAR chart.

We planned to evaluate drusen reduction considering the number of eyes showing at least a 50% reduction of drusen area from the baseline aspect. However, data were sparsely reported and therefore we modified the protocol to allow an extraction based on the investigators' definition.

Dichotomous data

Dichotomous data included, for example, progression of CNV or geographic atrophy, or loss of 3 or more lines of visual acuity. In the protocol we stated that we would have used the risk ratio or relative risk as our preferred measure of effect since we anticipated that the event rate would be greater than 10%. We actually found that the event rate was lower than this threshold in bilateral studies. Furthermore, to be able to manage data from unilateral and bilateral studies, we had to manipulate them using formulas proposed by Elbourne 2002, which only apply to odds ratios. Little difference is expected between risk ratios and odd ratios in this review, since the crude event rate was less than 10% in bilateral studies and less than 25% in unilateral studies, and also because the pooled odds ratio was close to 1.

Continuous data

Continuous data included, for example, reading speed. We used the weighted mean difference, unless the outcomes were measured on different scales in which case we used the standardised mean difference as the measure of effect.

Unit of analysis issues

Some trials identified a 'study eye' and randomised participants to treatment group. Other trials randomised the eye to treatment and compared with the other eye in the same person. We were careful to consider these trials separately at the data collection and extraction stage.

We did two sets of analyses for the primary outcome 'development of CNV'. Firstly we pooled all the data ignoring the fact that the data from the bilateral studies were not independent. We then did a sensitivity analysis assuming an intra-class correlation coefficient (ICC) of 0.5 for the development of CNV and 0.22 for visual acuity loss. We adjusted the standard errors using the methods of Higgins 2008b and Elbourne 2002. See Appendix 4 for more details.

We used the generic inverse variance facility in RevMan to enter the data for the sensitivity analysis.

Dealing with missing data

In the event that data were missing we contacted the authors of the studies in an attempt to obtain more information. On the basis of the data we could collect, we first did an available case analysis. We recorded the amount of missing data in the included studies as shown in Table 1. At the time the protocol for this review was prepared we planned that if missing data should prove to be a problem in the constituent studies, we would consider doing a sensitivity analysis considering outcome in the people lost to follow up as either 'all OK' or 'all not OK' to see the range within which the true result might lie. This did not prove necessary at this stage. According to further guidance available in section 8 of the current version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008a), missing outcome data is not a problem if loss to follow up is both balanced in the study arms of parallel arm studies and causes of loss are documented and judged to be unrelated to outcome in both study arms. When these conditions are not satisfied a study can still be at low risk of bias if the outcome frequency is around 50% and loss to follow up is below 10% in both arms (Higgins 2008a).

Because our primary outcome was relatively rare in the complete case analysis in this review, and there were missing data of unreported cause, there was potential for bias due to incomplete outcome data in this review. Thus, we used two approaches to deal with missing data as explained in Appendix 5. Both approaches made assumptions regarding informative missing odds ratio (IMOR): one approach was based on an Excel spreadsheet prepared by the authors of this review to assess the risk of bias of each study using a graph and extreme assumptions on *missingness*; the other used the Stata 10.2 (StataCorp, College Station, Tx) users' written function '*metamiss*' to conduct sensitivity analyses on primary outcome meta-analysis results by making different assumptions on IMORs across studies according to White 2008.

Assessment of heterogeneity

Before carrying out a meta-analysis we assessed heterogeneity by examining the characteristics of the study, the forest plot of the results of the studies and the I^2 statistic to assess the presence of statistical heterogeneity.

Assessment of reporting biases

We planned to assess publication bias (using a funnel plot) if there were more than 10 trials. However, currently not enough trials are included in this review to enable this assessment.

Data synthesis

We planned to perform a meta-analysis if there were sufficient trials available without substantial heterogeneity. We used a random-effects model unless there were three or fewer trials in which case

a fixed-effect model was used. We compared fixed and random-effects models to see how robust the results were.

Subgroup analysis and investigation of heterogeneity

If there were sufficient trials, we planned the following subgroup analyses:
1. type of laser treatment;
2. clinically visible burns versus sub-threshold laser treatment.

Sensitivity analysis

We considered the results of between-person and within-person trials separately. We had planned to consider the effect of excluding poor quality studies, if there were sufficient studies. This was not done.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Results of the search

The searches identified 111 reports of studies. We obtained full copies of 31 reports which referred to 10 potentially relevant studies. We excluded two of these trials mainly because the treatment groups were not randomly allocated (see 'Characteristics of excluded studies' table). Overall, nine trials were considered suitable for inclusion in the review (see 'Characteristics of included studies' table). One study was published in abstract form only and the investigators supplied unpublished data for inclusion in this review (Laser to Drusen Study).

Included studies

Types of studies

The study design was different across studies. Three studies included one eye of each patient (Frennesson 1995; Laser to Drusen Study; PTAMD), and will be referred to as 'unilateral' studies. Three studies adopted a paired design whereby both eyes of the participant were included in the study, one eye randomly allocated to photocoagulation or control and the fellow eye to the other group (CAPT; Figueroa 1994; Little 1995) and will be referred to as 'bilateral' studies. Three more studies included both a unilateral and a bilateral arm (CNVPT; DLS; Olk 1999). However, CNVPT did not report results from the bilateral study arm except for the number of patients with a gain of one or more lines of visual acuity at one year in an early report and therefore data on this arm could not be extracted.

Types of participants

The nine trials randomised a total of 2216 people. The studies took place in the USA (CAPT; CNVPT; Laser to Drusen Study; Little 1995; Olk 1999; PTAMD), Sweden (Frennesson 1995), UK (DLS), Germany (DLS), Australia (DLS) and Spain (Figueroa 1994).

The mean age of the patients was approximately 70 years. The majority of participants were women in all studies (range: 54% to 70%).

All studies recruited patients presenting medium (> 63 μm) or large (> 125 μm) drusen with pigmentary changes. CNVPT, DLS and Figueroa 1994 enrolled patients with bilateral macular drusen in the bilateral arm and patients with neovascular AMD in one eye and macular drusen in the fellow eye in a unilateral study. Little 1995, Olk 1999, Frennesson 1995 and CAPT enrolled patients with macular drusen in both eyes.

Types of interventions

Table 2 gives details of the laser treatment employed in the different studies. Five studies employed argon laser, two diode laser and one dye laser. Laser spot size varied from 50 to 200 microns. The duration of each burn ranged from 0.05 second to 0.1 second. The number of laser spots included was between 1 and 60. PTAMD used subthreshold photocoagulation using 810 nm diode laser in all treated patients. Olk 1999 used subthreshold photocoagulation in a random subset of treated eyes.

Primary outcomes

Four bilateral studies or study arms (CAPT; DLS; Little 1995; Olk 1999) and six unilateral studies or study arms (CNVPT; DLS; Frennesson 1995; Laser to Drusen Study; Olk 1999; PTAMD) presented data on the outcome 'development of CNV'.

We stated in the protocol that we aimed to obtain data at two years. However, we used three-year data for two studies that reported the outcome with more detail at this time point (DLS; Frennesson 1995) and Little 1995 used the last visit at a mean of 3.2 years.

CAPT and Olk 1999 did not report crude data at two years, but presented survival curves, from which we extracted graphically the proportion of patients with CNV and atrophy at two years using the number of eyes followed up in each group to compute standard errors. Most bilateral studies provided marginal data only, i.e. a frequency tabulation that ignores the paired nature of data, but we could extract and use a correlation coefficient from DLS as shown in Appendix 4.

Among bilateral studies, we could extract paired data on development of CNV from Little 1995 but we considered that this

was too small a study to estimate the correlation coefficient reliably. Marginal data were available from CAPT, but the P value was obtained from a Cox proportional hazards model, not from a McNemar Chi^2 test, thus we did not use the method shown in Appendix 4.

There was poor reporting of the primary outcome 'development of geographic atrophy'. Data from Laser to Drusen Study were obtained from the authors. Data from survival curves could be estimated from the unilateral arm of CNVPT; cross-tabulations were constructed using the number of complete cases who did not develop CNV because, in the absence of a clear reporting of the total number of eyes at each step of the survival curve, we considered that eyes with a neovascular lesion may have complex fundus changes preventing a precise assessment of geographic atrophy.

Secondary outcomes

Loss of visual acuity was the only secondary outcome which could be extracted for most studies. Particularly, DLS and CAPT presented bilateral data and Olk 1999, DLS, PTAMD and CNVPT presented unilateral data. Most studies provided marginal data, but we could extract a correlation coefficient from Little 1995 and DLS and use it as shown in Appendix 4 to obtain correct standard errors.

Contrast sensitivity and reading ability data were available only in CNVPT.

Drusen reduction was analysed in most studies. It was possible to extract data on this outcome from two unilateral studies. For CNVPT they were extracted graphically from a survival curve using the number of eyes followed up in each group to generate a cross-tabulation of the eyes with a 50% or more drusen area reduction among treated and control eyes. The approximate percentages with apparent drusen reduction was also given in PTAMD at 18 months; we used the number of patients still followed minus those who developed CNV as the total number in each group for generating the 2x2 table. Data on drusen reduction could not be extracted from the other studies. In fact, CAPT and Little 1995 were bilateral studies but reported marginal data only. Olk 1999 provided pooled data only for unilateral and bilateral cases. Frennesson 1995 provided means and standard deviations but used Snellen values to compute them, which is incorrect, and data had a very skewed distribution. Thus, we decided not to use data from this study. DLS did not report this outcome.

Quality of life data were not available in any study.

Other comparisons

Olk 1999 also compared subthreshold, i.e. yielding non-visible laser burns, photocoagulation with observation. Marginal data from the bilateral study arm, but no estimate of the intraindividual correlation, could be obtained, together with data from the unilateral study arm.

Excluded studies

We excluded two studies: Sarks 1999 which was a comparative but non-randomised study and Sigelman 1991 which was a case report.

Sivagnanavel 2004 is as yet unpublished. We are in contact with the trialists and plan to include data from this study at a later date.

Risk of bias in included studies

See 'Risk of bias' tables and Figure 1 and Figure 2.

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies. Quality assessment regarding incomplete outcome data refers to the unilateral study arm only for studies including both unilateral and bilateral arms (DLS; Olk 1999) and to all unilateral studies (CAPT; Frennesson 1995; Laser to Drusen Study). Bias related to incomplete outcome data does not apply to bilateral studies or study arms because both eyes of the patient lost to follow up are commonly lost.

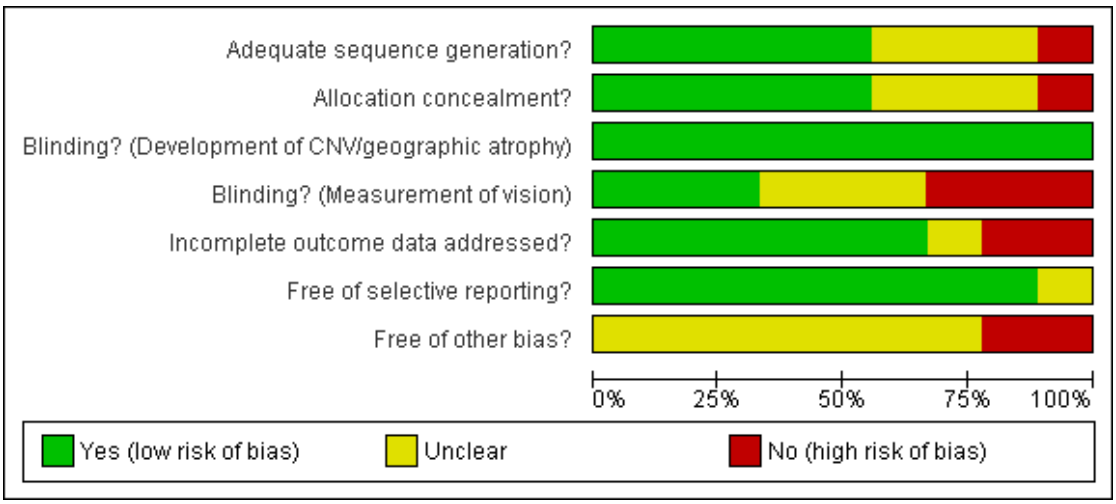
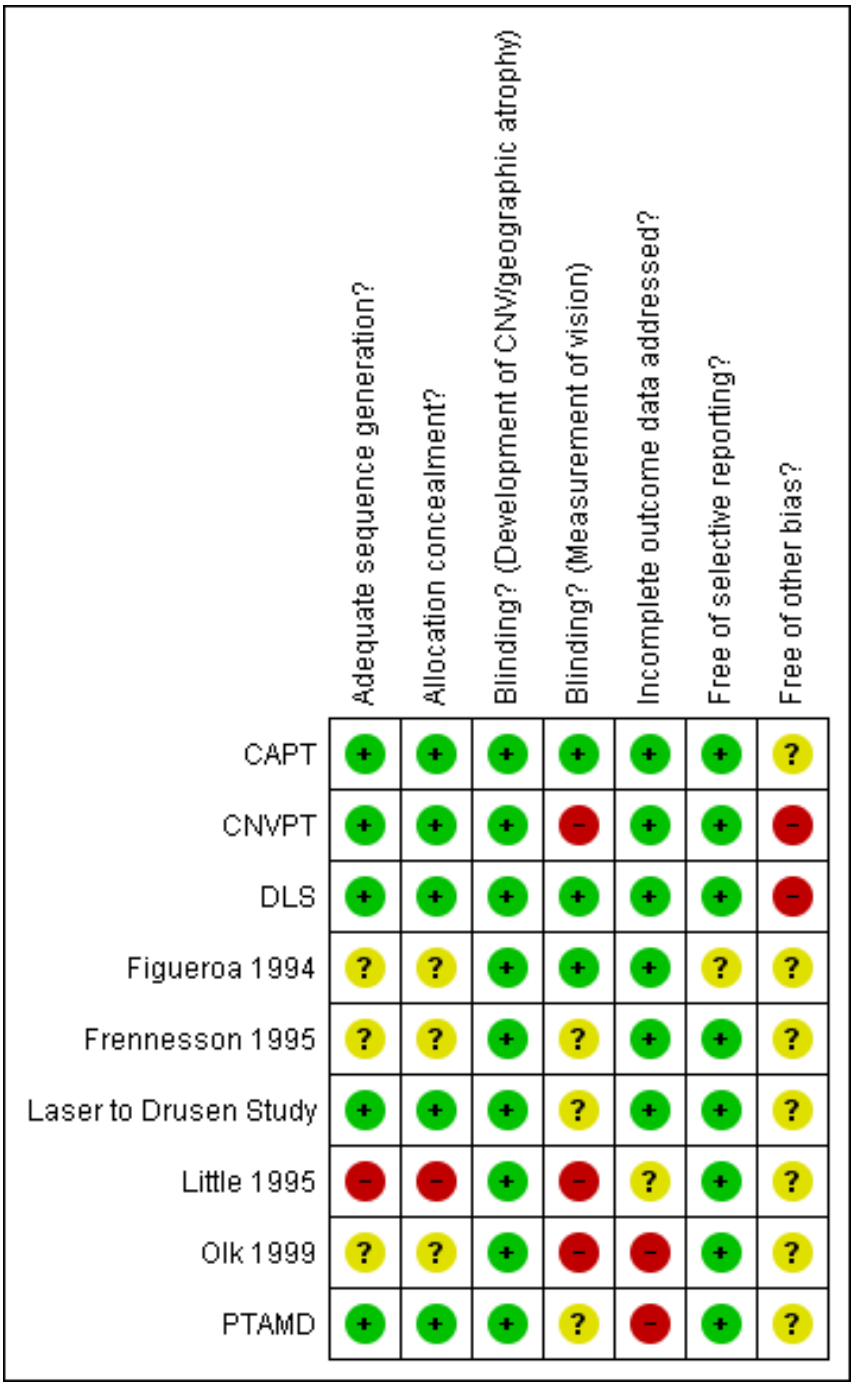


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

Only half of the trials reported adequate methods to generate and conceal the allocation sequence.

Blinding

Patients were not masked (blinded) since a sham procedure was never adopted. We acknowledge that it is not possible to mask outcome assessors to anatomic outcomes because laser scars are visible around the macula. However, masking of functional outcome assessors can be achieved in theory, but was rarely so, or reported as such, in these studies. We think that development of CNV is a sufficiently objective diagnosis to be classified as having low risk of bias despite lack of masking of outcome assessors. On the contrary, vision outcomes such as visual acuity and contrast sensitivity can easily be measured by a masked assessor, and lack of masking can introduce bias because the procedure is operator dependent.

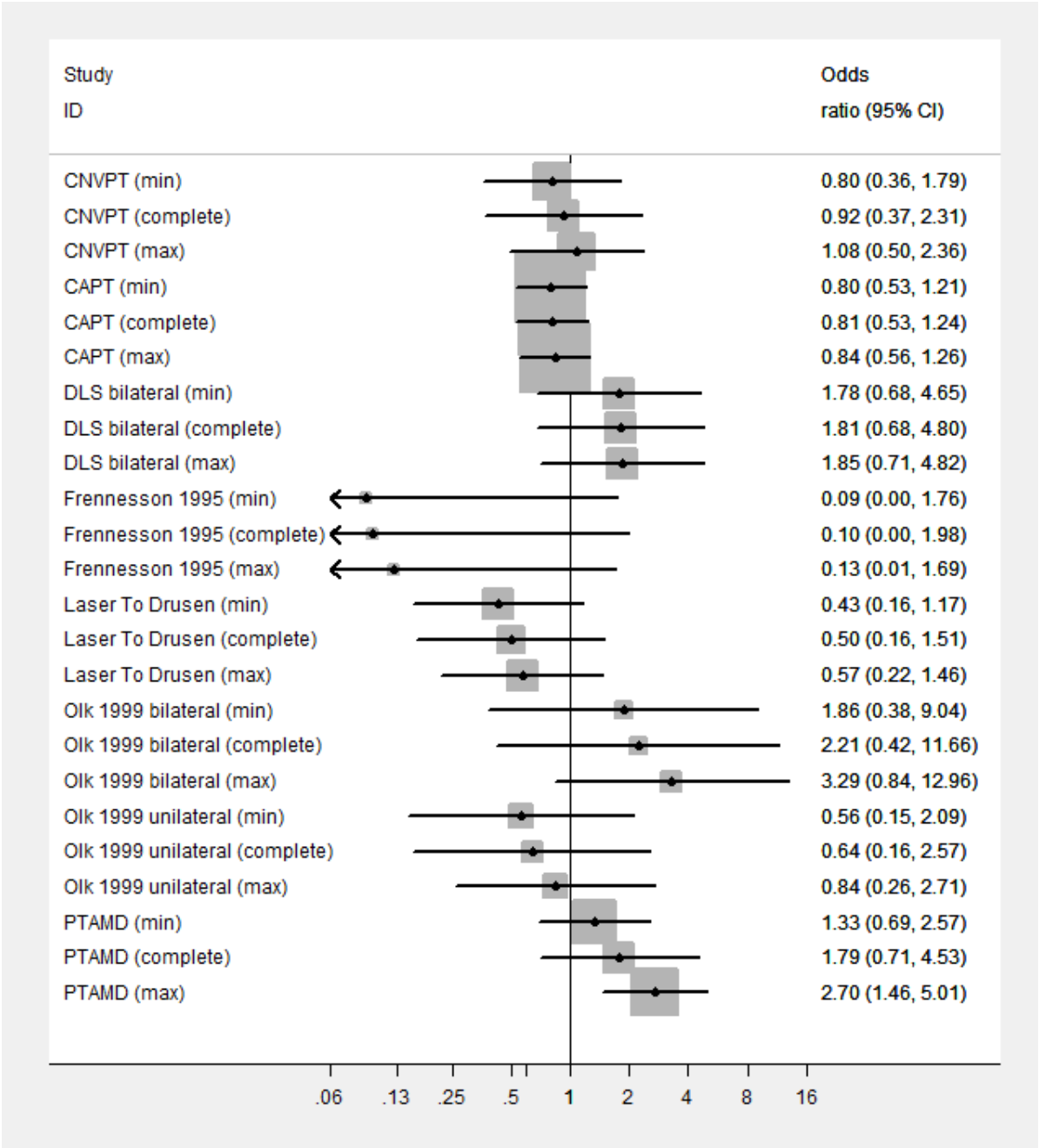
Incomplete outcome data

Table 1 shows events and non-events of complete cases, number of deaths and number of missing patients in the treatment and control arms. These data were used to assess the impact of incomplete outcome data.

Assessment of risk of bias due to incomplete outcome data in each study

(Method 1, see Appendix 5 *and* Figure 3*)*

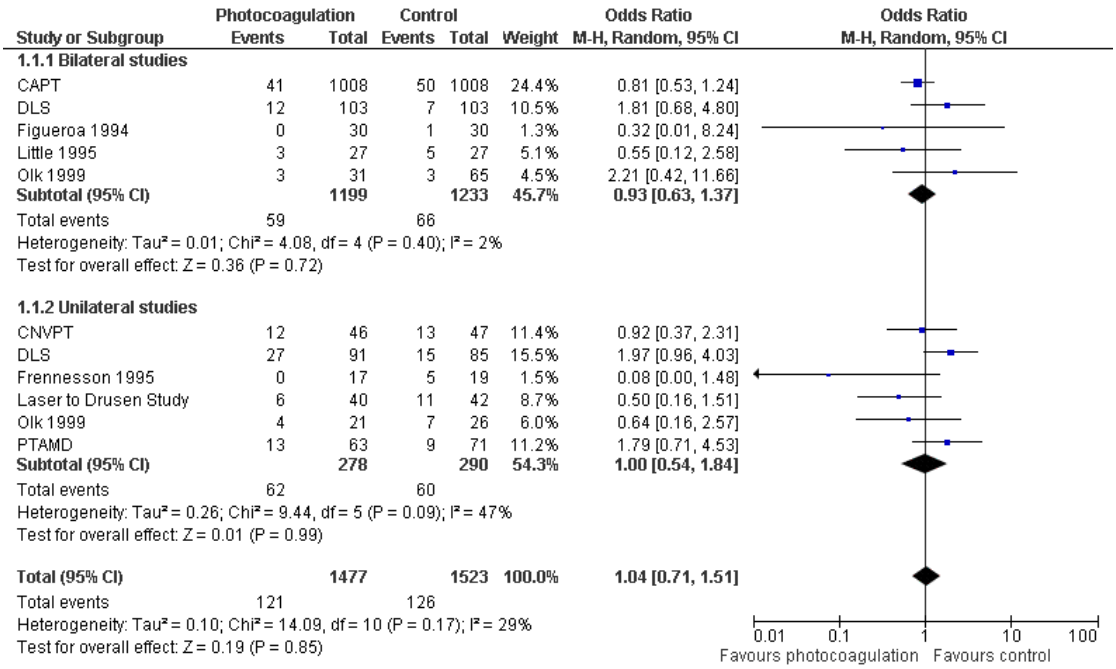
Figure 3. Graphical assessment of the risk of bias due to incomplete outcome data using Method 1 (see Appendix 5). The minimum and maximum OR change, compared to complete or available cases, is assessed graphically and subjectively taking into account its 95% CI. The resulting agreed classification is shown in to classify risk of bias of individual studies regarding the primary outcome of this review.



Besides data on complete and missing participants, Table 1 also shows the judgement on risk of bias due to incomplete outcome data using Method 1, which is also reported in the 'Risk of bias' table. This judgement is based on the examination of Figure 4, which presents the minimum and maximum imputed OR, together with complete case OR obtained from the primary analysis, computed by means of Method 1 (see Appendix 5). The unilateral arm of DLS and Figueroa 1994 had no missing data; thus the risk of bias was low and there was no need of imputation. Little 1995 was classified as unclear since only mean follow up was reported and data were used as such for imputation using Method 2.

For all other studies, except Frennesson 1995, the minimum and maximum imputed OR were obtained assuming twice the odds of CNV among missing patients (OR = 2) and, respectively, values of 0.5 and 2 of the relative OR for treatment effect among missing versus complete cases. Frennesson 1995 had no events among treated patients versus four among controls. Thus, 0.5 was added to all cells of complete cases. The extreme OR values for this study were obtained assuming contemporary extreme values of the two probability modifiers (0.5 - 0.5 and 2 - 2 event occurrence OR and relative treatment OR due to *missingness*).

Figure 4. Forest plot of comparison: 1 Photocoagulation vs. control, outcome: 1.1 Development of CNV



Based on the inspection of additional Figure 4, we classified Olk 1999 and PTAMD as having high risk of bias due to incomplete outcome data, and the other studies with missing data as having low risk of bias. We considered the subjective graphical assessment of both the point estimate and the 95% CI coverage for this classification. We took into account only large changes because these were extreme scenarios, especially regarding the assumption of a two-fold treatment OR modification, considering that complete case meta-analysis yielded a point estimate of 1.04.

Assessment of overall risk of bias in the meta-analysis results using 'metamiss'

(Method 2, see Appendix 5; Figure 5; Figure 6*)*

Figure 5. Sensitivity meta-analysis assuming random uncorrelated opposite IMORs for treatment and controls 1/2 and 2 (prior logIMOR standard deviation 1, uncorrelated IMORs between treatment and control groups (Method 2, see Appendix 5)).

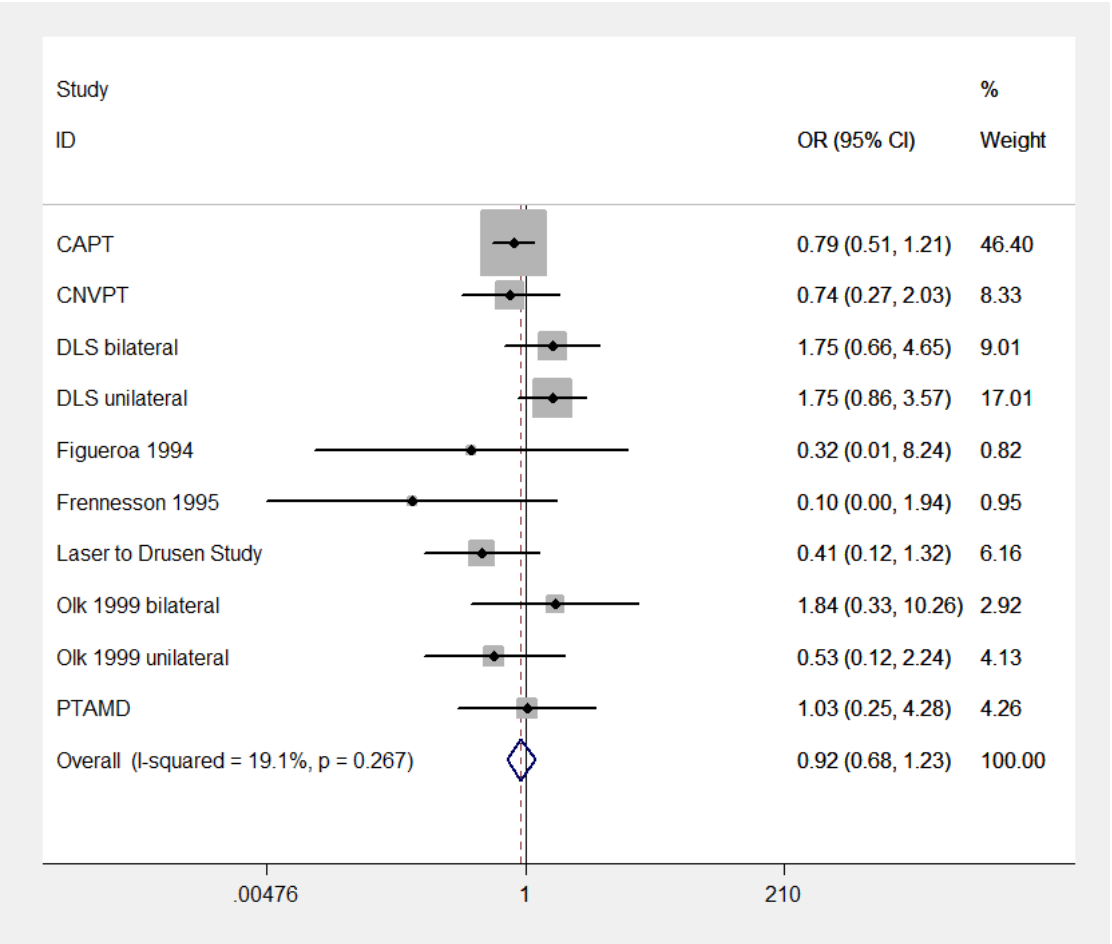
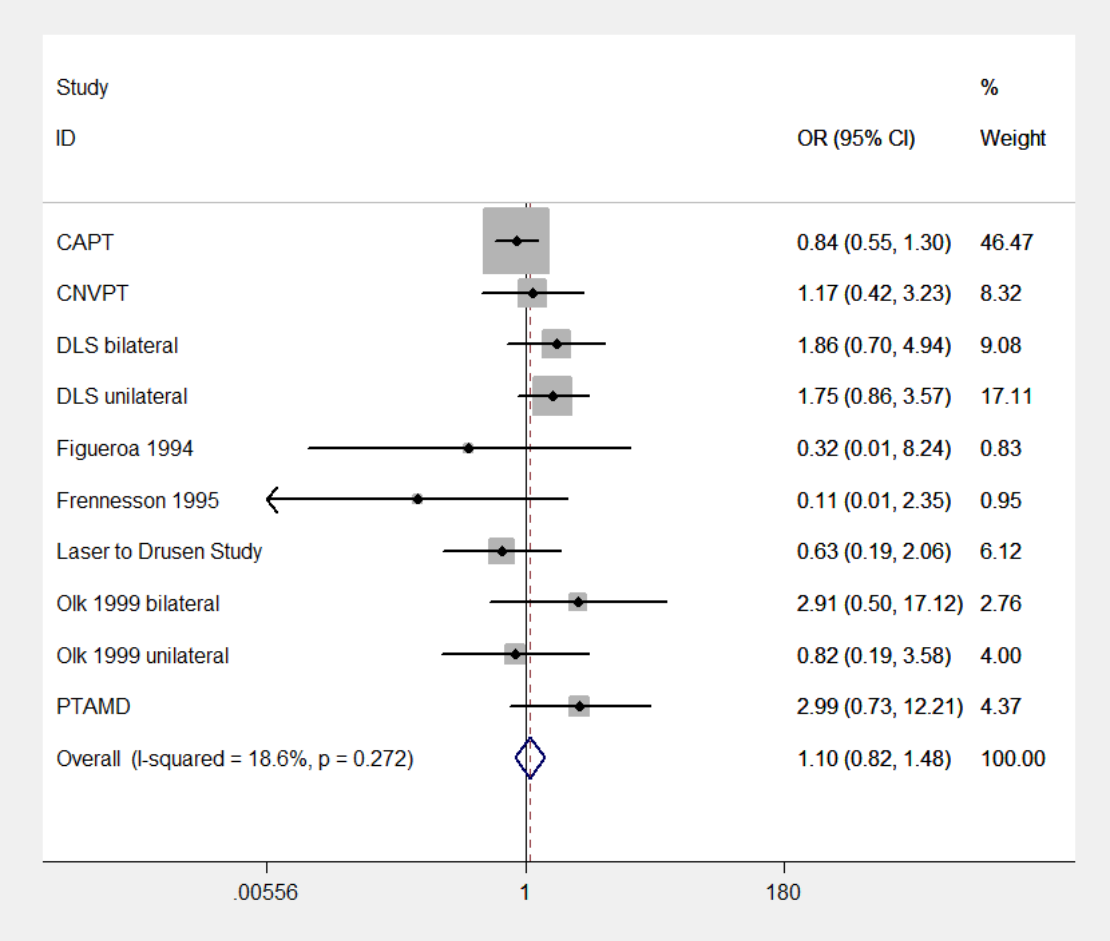


Figure 6. Sensitivity meta-analysis assuming random uncorrelated opposite IMORs for treatment and controls 2 and 1/2, prior logIMOR standard deviation 1, uncorrelated IMORs between treatment and control groups (Method 2, see Appendix 5)



Additional Figure 7 and Figure 8 present sensitivity meta-analyses based on random uncorrelated opposite IMORs for treatment and controls (1/2 and 2; 2 and 1/2): the pooled ORs were 0.92 (95% CI 0.68 to 1.23, I^2 = 19.1%) and 1.10 (95% CI 0.82 to 1.48, I^2 = 18.6%) respectively. Under extreme IMOR assumptions, neither meta-analyses suggests very different estimates compared to our primary analysis. As with Method 1, Olk 1999 and PTAMD showed the larger changes by missing imputation due to a larger number of missing patients.

Figure 7. Forest plot of comparison: 1 Photocoagulation vs. control, outcome: 1.5 Development of CNV: sensitivity analysis assuming moderate correlation (0.5) for bilateral studies.

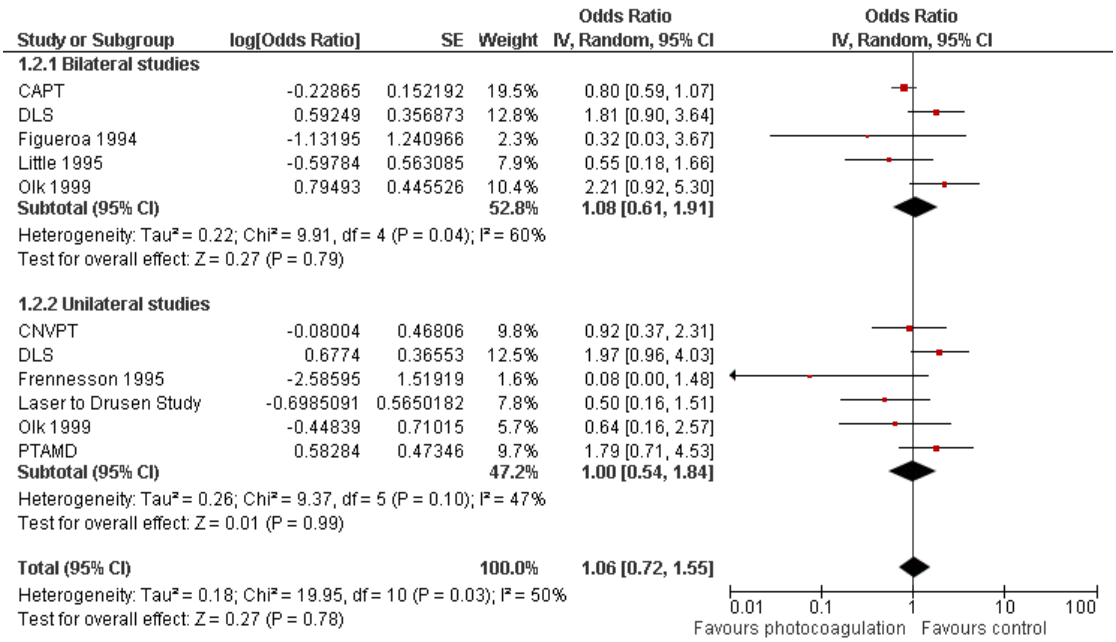
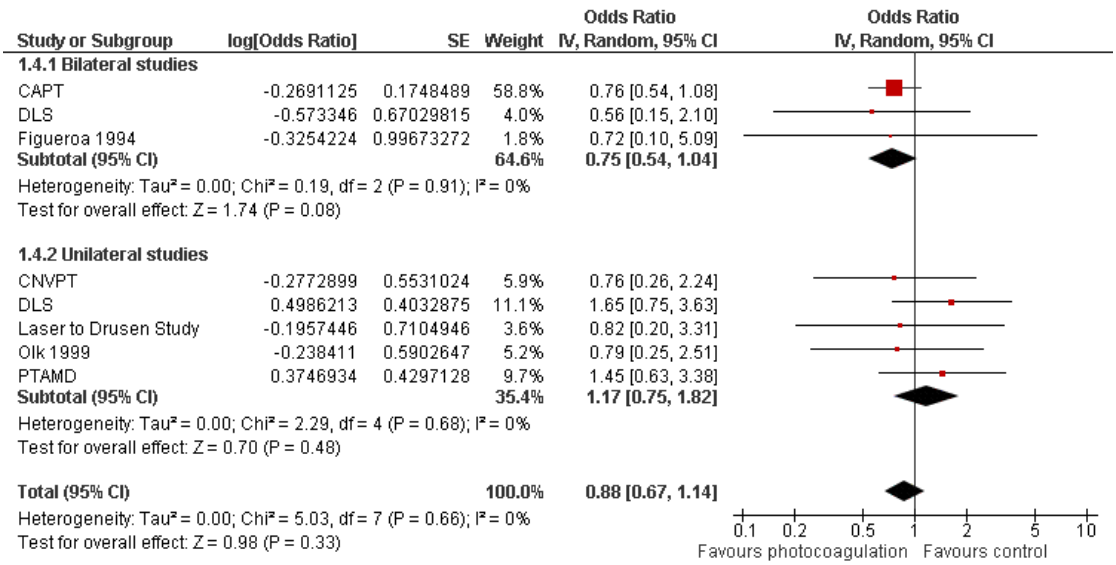


Figure 8. Forest plot of comparison: 1 Photocoagulation vs. control, outcome: 1.2 Visual loss of 2-3+ lines



Selective reporting

Most studies reported the development of CNV and visual acuity which are the key outcomes in this study so selective reporting was not considered to be a problem in this review.

Other potential sources of bias

One trial (DLS) was stopped early because an interim analysis suggested an harmful effect of photocoagulation.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings table: photocoagulation of drusen vs control

Primary outcome: development of choroidal neovascularisation

Pooling the results of five bilateral studies and six unilateral studies, as seen in Figure 4, the development of CNV at two years was not statistically different between photocoagulation and observation but favoured observation (OR 1.04, 95% confidence interval (CI) 0.71 to 1.51).

A sensitivity analysis assuming moderate correlation (0.5) of the outcome within individuals increased the heterogeneity of bilateral studies to an I^2 value of 60%, suggesting that a meta-analysis of these studies may not be appropriate, also given the fact that effect estimates of individual studies were in opposite directions. This is shown in Figure 7 for completeness as well as to show that the conclusions would not change if such a meta-analysis were carried out.

Primary outcome: development of geographic atrophy

As reported above, data on the development of atrophy could be extracted from only two small studies (CNVPT; Laser to Drusen Study). No benefit or harm using photocoagulation could be demonstrated regarding this outcome (OR 1.30, 95% CI 0.38 to 4.51).

One bilateral study presented marginal data on this outcome. Specifically, CAPT reported that 1.9% treated eyes compared to 1.4% control eyes of 1008 individuals developed atrophy at two years, but due to the paired nature we could not extract and analyse these data.

Secondary outcome: visual acuity

Two bilateral studies and five unilateral studies (Figure 8) allowed the extraction of data on the risk of visual loss of 3 or more lines of visual acuity at two years (a value of 2 or more lines was available in Olk 1999). No benefit or harm with photocoagulation could be demonstrated in this analysis (OR 0.88, 95% CI 0.67 to 1.14).

Secondary outcome: contrast sensitivity

Data on contrast threshold were obtained from the authors of the Laser to Drusen Study. There was a large uncertainty of the estimates (Analysis 1.5) and no effect of photocoagulation could be demonstrated.

CAPT also reported on this outcome, but this was a paired study and the data could not be analysed since an estimate of the correlation coefficient was not obtained. The authors reported marginal data at five years, which indicated that 212 (23.9%) of 888 treated eyes and 182 (20.5%) of 887 observed eyes required twice as much contrast (corresponding to a loss of 0.3 log 10 units or more of contrast sensitivity) to read letters.

Secondary outcome: reading ability

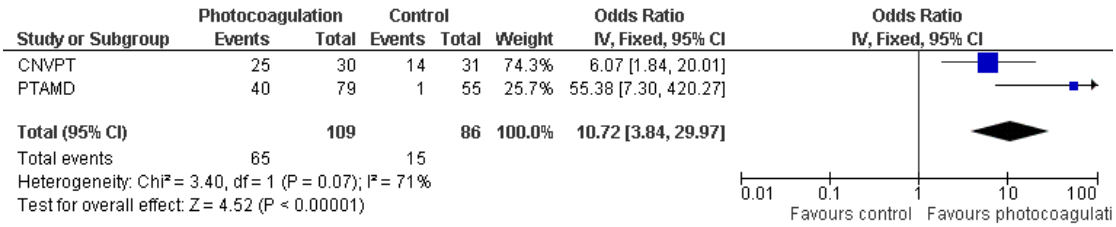
Data on reading speed were obtained by the authors of the Laser to Drusen Study for about 50% of the patients included in this small study. No statistically significant difference between photocoagulation and observation was found (Analysis 1.6).

CAPT also reported marginal data on reading ability expressed as critical print size, i.e. the character prints size below which a patient's reading speed slows down. The authors reported marginal data at five years, which indicated that 260 (29.6%) of 879 treated eyes and 249 (28.4%) of 878 observed eyes required a print size twice as large (3 LogMAR lines) or could not read even the largest print size.

Secondary outcome: drusen reduction

Data on drusen reduction as defined by the investigators could be extracted from two unilateral studies at approximately two years (Figure 9). CNVPT found that 25/30 treated eyes compared to 14/31 control eyes had a 50% or more drusen reduction at 18 months, corresponding to an OR in favour of treatment of 6.07 (95% CI 1.84 to 20.01). PTAMD reported that an apparent drusen reduction was observed in 50% of treated eyes compared to less than 1% of control eyes (we conservatively assumed a risk of 1% among controls); these data generate an OR of 55.38 (95% CI 7.3 to 420.27).These estimates are heterogeneous (I^2 = 71%), possibly due to different outcome definitions, and were not pooled. Nonetheless, they point in the same direction and indicate that drusen area decreases in treated eyes.

Figure 9. Forest plot of comparison: 1 Photocoagulation vs. control, outcome: 1.4 Drusen reduction.



Among bilateral studies, others presented marginal data suggesting that photocoagulation causes drusen resorption, but we could not extract these data since an estimate of the within-patient correlation was not obtained. Specifically, CAPT found that 34.3% treated eyes versus 8.6% control eyes of 1008 individuals had a 50% drusen reduction at two years. Figueroa 1994 reported that 29/30 treated eyes versus 2/30 control eyes were found to have drusen reduction, on average after three months. Little 1995 reported that 17/27 treated eyes had drusen resorption by six months compared to 5/27 observed eyes by one year.

Other studies reported data suggesting drusen disappearance using photocoagulation compared to observation, but data could not be extracted for various reasons (means and standard deviations suggesting skewed data (Frennesson 1995), pooled data from unilateral and bilateral study arms (Olk 1999), or data not available (DLS)).

Other comparisons

Olk 1999 also compared subthreshold photocoagulation with observation at two years. In the unilateral study arm they reported that 4/15 eyes treated with subthreshold photocoagulation versus 7/26 control eyes (OR 1.0, 95% CI 0.2 to 5.0) developed CNV at one year. In the bilateral study arm the corresponding numbers were 0/34 and 3/65, but we could not use these data since we did not have an estimate of within-patient correlation for this outcome in this comparison.

Considering a visual loss of 2 or more lines, 9/15 treated eyes versus 10/25 control eyes developed visual loss in the unilateral study arm (OR 2.2, 95% CI 0.5 to 10.3).

DISCUSSION

Age-related macular degeneration is a disease characterised by an enormous social burden. The availability of a therapeutic approach able to reduce the incidence of the major complications, i.e. CNV and atrophy, would be extremely welcome. Several authors have recorded that in their experience the use of laser can result in reabsorption of macular drusen (Cleasby 1979; Figueroa 1994; Gass 1973; Wetzig 1994). As yet it is unclear whether drusen reduction can lead to clinical benefits, including improvement or stabilisation of visual acuity, delayed or reduced CNV or harms such as the onset of atrophy.

Summary of main results

In preparing this review we identified nine different trials, including one unpublished trial, in which 2216 patients were randomised to laser treatment of drusen or observation. These trials confirmed the clinical observation that laser photocoagulation of drusen was able to cause their disappearance. However, there was no evidence that this loss of drusen resulted in any benefit in terms of the development of CNV or geographic atrophy or prevention of visual acuity loss. The results of the present review do not indicate that the prophylactic laser treatment of drusen is an effective means for delaying the progression of AMD and preventing visual loss. However, a clinically relevant benefit or harm cannot be excluded based on the primary outcomes 95% CI, which were rather wide (OR 0.71 to 1.51). Among the secondary outcomes, the CI of the visual loss outcome tended to exclude important harms (OR upper limit: 1.14 favouring control).

Overall completeness and applicability of evidence

Some of these trials adopted a paired study design, which rendered the analysis of the data difficult. Moreover, only a few studies reported data on secondary outcomes, especially contrast sensitivity and reading ability. Despite these limitations, the studies included in this review were conducted in different countries and follow up length was enough to be able to record long-term effects of this intervention.

Quality of the evidence

Overall, the studies represent moderate quality of evidence because allocation sequence generation and allocation concealment and masking of visual acuity outcome assessors was achieved in half

or less of them. Three studies, accounting for 27% of the weight in the primary analysis, were of unclear or low quality regarding incomplete outcome data. However, missing data imputation in sensitivity meta-analysis did not change our conclusions. Other quality items were not a problem.

Potential biases in the review process

One peculiar source of bias in this review may be the pooling of unilateral and bilateral studies based on assumptions about the statistical correlation of within-patient data. To try to counteract this potential shortcoming we not only used the information available from some studies, suggesting very low correlation for the primary outcome 'occurrence of CNV', but also used an average correlation as a sensitivity analysis.

AUTHORS' CONCLUSIONS

Implications for practice

Even though drusen area reduction can be achieved through laser treatment, this review does not suggest that this intervention is associated with improved outcomes for the patients, based on meta-analyses of studies which, overall, had a moderate risk of bias.

Implications for research

The results of this review do not encourage the conduct of more research on photocoagulation directed to drusen in patients with AMD.

ACKNOWLEDGEMENTS

- Thank you to Barbara S. Hawkins, PhD; Marta M. Gilson, PhD; Susan Vitale, PhD; Neil M. Bressler, MD; and Susan B. Bressler MD for providing unpublished data on the Laser to Drusen Study.

- The Cochrane Eyes and Vision Group created and executed the search strategies.

- We thank José María Ruiz-Moreno and Alicja Rudnicka for their comments on this review and Stephen Gichuhi and Barbara Hawkins for their comments on the protocol for this review.

- We gratefully acknowledge the contribution of David Brandon, Harold Burton, Peter Dyson, Jan Elson and Brenda Rogers of the CEVG AMD Consumer Panel for their comments on the abstract and plain language summary.

REFERENCES

References to studies included in this review

CAPT ***{published data only}***

Alexander J, Elsner KS, Javornik NB, Whittock ER, Brightwell-Arnold M, Duncan JL, et al.CAPT Study Group. Characteristics of exudation in patients with bilateral large drusen. *Investigative Ophthalmology & Visual Science* 2004; **45**:ARVO E-abstract 2989.

* Complications of Age-Related Macular Degeneration Prevention Trial Research Group. Laser treatment in patients with bilateral large drusen: the complications of age-related macular degeneration prevention trial. *Ophthalmology* 2006;**113**(11):1974–86.

Complications of Age-Related Macular Degeneration Prevention Trial Study Group. The Complications of Age-Related Macular Degeneration Prevention Trial (CAPT): rationale, design and methodology. *Clinical Trials* 2004;**1** (1):91–107.

Figueroa M, Schocket LS, DuPont J, Metelitsina TI, Grunwald JE. Effect of laser treatment for dry age related macular degeneration on foveolar choroidal haemodynamics. *British Journal of Ophthalmology* 2004;**88** (6):792–5.

Figueroa M, Schocket LS, DuPont J, Metelitsina TI, Grunwald JE. Long-term effect of laser treatment for dry age-related macular degeneration on choroidal hemodynamics. *American Journal of Ophthalmology* 2006; **141**(5):863–7.

Grunwald JE, Figueroa M, Metelitsina TI, Schocket LS, DuPont JC. Effect of CAPT laser treatment on choroidal hemodynamics in age-related macular degeneration (AMD). *Investigative Ophthalmology & Visual Science* 2004; **45**:ARVO E-abstract 3133.

Maguire M, Complications of Age-Related Macular Degeneration Prevention Trial Research Group. Baseline characteristics, the 25-Item National Eye Institute Visual Functioning Questionnaire, and their associations in the Complications of Age-Related Macular Degeneration Prevention Trial (CAPT). *Ophthalmology* 2004;**111**(7): 1307–16.

Sbarbaro JA, Maguire MG. CAPT Study Group. Annual changes in refractive error over 3 years among eyes with early AMD. *Investigative Ophthalmology & Visual Science* 2004;**45**:ARVO E-abstract 3055.

Stoltz RA, Ying GS, Alexander J. CAPT Study Group. Fundus features of untreated eyes with visual acuity loss in CAPT. *Investigative Ophthalmology & Visual Science* 2004;

45:ARVO E-abstract 1389.
Ying GS, Liu C, Maguire MG. CAPT Research Group. Night-vision symptoms as a risk factor for vision loss and choroidal neovascularization in the Complications of Age-related Macular Degeneration Prevention Trial (CAPT). *Investigative Ophthalmology & Visual Science* 2005;**46**: ARVO E-abstract 204.

CNVPT ***{published data only}***

Anonymous. Choroidal neovascularization in the Choroidal Neovascularization Prevention Trial. The Choroidal Neovascularization Prevention Trial Research Group. *Ophthalmology* 1998;**105**(8):1364–72.
Anonymous. Laser treatment in eyes with large drusen. Short-term effects seen in a pilot randomized clinical trial. Choroidal Neovascularization Prevention Trial Research Group. *Ophthalmology* 1998;**105**(1):11–23.
Choroidal Neovascularization Prevention Trial Research Group. Laser treatment in fellow eyes with large drusen: updated findings from a pilot randomized clinical trial. *Ophthalmology* 2003;**110**(5):971–8.
Fine SL, Maguire MG, Javornik NB, Ho AC. CNVPT Research Group. The choroidal neovascularization prevention trial (CNVPT): 4-year results. *Investigative Ophthalmology & Visual Science* 2001;**42**:ARVO Abstract 676.
Ho AC, Maguire MG, Yoken J, Lee MS, Shin DS, Javornik NB, et al.Laser-induced drusen reduction improves visual function at 1 year. Choroidal Neovascularization Prevention Trial Research Group. *Ophthalmology* 1999;**106**(7): 1367–73.
Ho AC, Yoken J, Lee MS, Shin DS, Javornik NB, Maguire MG, et al.Laser-induced drusen reduction improves visual function at one year. *American Academy of Ophthalmology* 1998:127.
Kaiser RS, Berger JW, Maguire MG, Ho AC, Javornik NB. Choroidal Neovascularization Prevention Trial Study Group. Laser burn intensity and the risk for choroidal neovascularization in the CNVPT Fellow Eye Study. *Archives of Ophthalmology* 2001;**119**(6):826–32.
Prenner JL, Rosenblatt BJ, Tolentino MJ, Ying GS, Javornik NB, Maguire MG, et al. CNVPT Research Group. Risk factors for choroidal neovascularization and vision loss in the fellow eye study of CNVPT. *Retina (Philadelphia, Pa.)* 2003;**23**(3):307–14.
Regillo CD. Laser treatment in fellow eyes with large drusen: updated findings from a pilot randomized clinical trial. *Evidence-Based Eye Care* 2003;**4**(4):204–5.
Rosenbaltt BJ, Prenner JL, Tolentino M, Ying G, Javornik NB, Maguire MG, et al. CNVPT Research Group. Predictors of visual acuity loss in the fellow eye study of the Choroidal Neovascularization Prevention Trial (CNVPT). *Investigative Ophthalmology & Visual Science* 2001;**42**: ARVO Abstract 675.

DLS ***{published data only}***

Kertes PJ. Prophylactic laser treatment hastens choroidal neovascularization in unilateral age-related maculopathy: final results of the drusen laser study - Commentary. *Evidence-Based Ophthalmology* 2006;**7**(3):135–7.
Owens SL, Bunce C, Brannon AJ, Wormald R, Bird AC. Drusen Laser Study Group. Prophylactic laser treatment appears to promote choroidal neovascularisation in high-risk ARM: results of an interim analysis. *Eye (London, England)* 2003;**17**(5):623–7.
Owens SL, Bunce C, Brannon AJ, Xing W, Chisholm IH, Gross M, et al. Drusen Laser Study Group. Prophylactic laser treatment hastens choroidal neovascularization in unilateral age-related maculopathy: final results of the drusen laser study. *American Journal of Ophthalmology* 2006;**141**(2):276–81.
Owens SL, Guymer RH, Gross-Jendroska M, Bird AC. Fluorescein angiographic abnormalities after prophylactic macular photocoagulation for high-risk age-related maculopathy. *American Journal of Ophthalmology* 1999;**127** (6):681–7.

Figueroa 1994 ***{published data only}***

Figueroa MS, Regueras A, Bertrand J. Laser photocoagulation to treat macular soft drusen in age-related macular degeneration. *Retina (Philadelphia, Pa.)* 1994;**14** (5):391–6.
Figueroa MS, Regueras A, Bertrand J, Aparicio MJ, Manrique MG. Laser photocoagulation for macular soft drusen. Updated results. *Retina (Philadelphia, Pa.)* 1997; **17**(5):378–84.

Frennesson 1995 ***{published data only}***

Frennesson C, Nilsson SE. Prophylactic laser treatment in early age related maculopathy reduced the incidence of exudative complications. *British Journal of Ophthalmology* 1998;**82**(10):1169–74.
Frennesson CI. Prophylactic laser treatment in early age-related maculopathy: an 8-year follow-up in a randomized pilot study shows a reduced incidence of exudative complications. *Acta Ophthalmologica Scandinavica* 2003;**81** (5):449–54.
Frennesson IC, Nilsson SE. Effects of argon (green) laser treatment of soft drusen in early age-related maculopathy: a 6 month prospective study. *British Journal of Ophthalmology* 1995;**79**(10):905–9.
Frennesson IC, Nilsson SE. Laser photocoagulation of soft drusen in early age-related maculopathy (ARM). The one-year results of a prospective, randomised trial. *European Journal of Ophthalmology* 1996;**6**(3):307–14.

Laser to Drusen Study ***{unpublished data only}***

Bressler SB, Vitale S, Hawkins BS, Alexander J, Orr PR, Schachat AP, et al.Laser to Drusen Trial: an assessment of short term safety within randomized, prospective, controlled clinical trial. Investigative Ophthalmology & Visual Science. 1995:ARVO abstract 1028.

Little 1995 ***{published data only}***

Little HL, Showman J. A pilot randomized, controlled study on the effect of laser photocoagulation of confluent soft macular drusen. *American Academy of Ophthalmology* 1995:120.
Little HL, Showman JM, Brown BW. A pilot randomized controlled study on the effect of laser photocoagulation of

confluent soft macular drusen. *Ophthalmology* 1997;**104**(4):623–31.

Olk 1999 *{published data only}*
Olk RJ, Friberg TR, Stickney KL, Akduman L, Wong KL, Chen MC, et al.Therapeutic benefits of infrared (810-nm) diode laser macular grid photocoagulation in prophylactic treatment of nonexudative age-related macular degeneration: two-year results of a randomized pilot study. *Ophthalmology* 1999;**106**(11):2082–90.

PTAMD *{published data only}*
Friberg TR, Musch DC, Lim JI, Morse L, Freeman W, Sinclair S. PTAMD Study Group. Prophylactic treatment of age-related macular degeneration Report Number 1: 810-nanometer laser to eyes with drusen. Unilaterally eligible patients. *Ophthalmology* 2006;**113**(4):612–22.
Rodanant N, Friberg TR, Cheng L, Aurora A, Bartsch D, Toyoguchi M, et al.Predictors of drusen reduction after subthreshold infrared (810 nm) diode laser macular grid photocoagulation for nonexudative age-related macular degeneration. *American Journal of Ophthalmology* 2002;**134**(4):577–85.

References to studies excluded from this review

Sarks 1999 *{published data only}*
Sarks SH, Arnold JJ, Killingsworth MC, Sarks JP. Early drusen formation in the normal and aging eye and their relation to age related maculopathy: a clinicopathological study. *British Journal of Ophthalmology* 1999;**83**(3):358–68.

Sigelman 1991 *{published data only}*
Sigelman J. Foveal drusen resorption one year after perifoveal laser photocoagulation. *Ophthalmology* 1991;**98**(9):1379–83.

References to studies awaiting assessment

Sivagnanavel 2004 *{published data only}*
Sivagnanavel V, Chong V. Diffuse laser for drusen reduction in high risk age-related maculopathy. *Investigative Ophthalmology & Visual Science* 2004;**45**:ARVO E-abstract 3097.

Additional references

Abdelsalam 1999
Abdelsalam A, Del Priore L, Zarbin MA. Drusen in age-related macular degeneration: pathogenesis, natural course, and laser photocoagulation-induced regression. *Survey of Ophthalmology* 1999;**44**(1):1–29.

AREDS 2001
Age-Related Eye Disease Study Research Group. 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: AREDS report No. 8. *Archives of Ophthalmology* 2001;**119**(10):1417–36.

Bressler 1994
Bressler NM, Silva JC, Bressler SB, Fine SL, Green WR. Clinicopathologic correlation of drusen and retinal pigment epithelial abnormalities in age-related macular degeneration. *Retina* 1994;**14**(2):130–42.

Bressler 1995
Bressler NM, Munoz B, Maguire MG, Vitale SE, Schein OD, Taylor HR, et al.Five-year incidence and disappearance of drusen and retinal pigment epithelial abnormalities. Waterman study. *Archives of Ophthalmology* 1995;**113**(3):301–8.

Brown 2006
Brown MM, Brown GC, Sharma S, Stein JD, Roth Z, Campanella J, et al.The burden of age-related macular degeneration: a value-based analysis. *Current Opinion in Ophthalmology* 2006;**17**(3):257–66.

Chakravarthy 2005
Chakravarthy U, Stevenson M. Self-reported visual functioning and quality of life in age-related macular degeneration. *Current Opinion in Ophthalmology* 2005;**16**(3):179–83.

Chong 2007
Chong EW, Wong TY, Kreis AJ, Simpson JA, Guymer RH. Dietary antioxidants and primary prevention of age related macular degeneration: systematic review and meta-analysis. *BMJ* 2007;**335**(7623):755.

Cleasby 1979
Cleasby GW, Nakanishi AS, Norris JL. Prophylactic photocoagulation of the fellow eye in exudative senile maculopathy. A preliminary report. *Modern Problems in Ophthalmology* 1979;**20**:141–7.

Duvall 1985
Duvall J, Tso MO. Cellular mechanisms of resolution of drusen after laser coagulation. An experimental study. *Archives of Ophthalmology* 1985;**103**(5):694–703.

EDPRG
Eye Diseases Prevalence Research Group. Prevalence of age-related macular degeneration in the United States. *Archives of Ophthalmology* 2004;**122**:564–72.

Elbourne 2002
Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**(1):140–9.

Evans 2006
Evans JR. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. *Cochrane Database of Systematic Reviews* 2006, Issue 2. [Art. No.: CD000254. DOI: 10.1002/14651858.CD000254.pub2]

Frennesson 1998
Frennesson C, Nilsson SE. Prophylactic laser treatment in early age related maculopathy reduced the incidence of exudative complications. *British Journal of Ophthalmology* 1998;**82**(10):1169–74.

Gass 1973
Gass JD. Drusen and disciform macular detachment and degeneration. *Archives of Ophthalmology* 1973;**90**(3): 206–17.

Glanville 2006
Glanville JM, Lefebvre C, Miles JN, Camosso-Stefinovic J. How to identify randomized controlled trials in MEDLINE: ten years on. *Journal of the Medical Library Association* 2006; **94**(2):130–6.

Gross-Jendroska 1998
Gross-Jendroska M, Owens SL, Flaxel CJ, Guymer RH, Bird AC. Prophylactic laser treatment to fellow eyes of unilateral retinal pigment epithelial tears. *American Journal of Ophthalmology* 1998;**126**(1):77–81.

Guidry 2002
Guidry C, Medeiros NE, Curcio CA. Phenotypic variation of retinal pigment epithelium in age-related macular degeneration. *Investigative Ophthalmology & Visual Science* 2002;**43**(1):267–73.

Guymer 2001
Guymer RH, Hageman GS, Bird AC. Influence of laser photocoagulation on choroidal capillary cytoarchitecture. *British Journal of Ophthalmology* 2001;**85**(1):40–6.

Hassell 2006
Hassell JB, Lamoureux EL, Keeffe JE. Impact of age related macular degeneration on quality of life. *British Journal of Ophthalmology* 2006;**90**(5):593–6.

Higgins 2008a
Higgins JPT, Altman DG (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 (updated February 2008). The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

Higgins 2008b
Higgins JPT, Deeks JJ, Altman DG (editors). Chapter 16: Special topics in statistics. In: Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 (updated February 2008). The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

Holz 1994
Holz FG, Wolfensberger TJ, Piguet B, Gross-Jendroska M, Wells JA, Minassian DC, et al.Bilateral macular drusen in age-related macular degeneration. Prognosis and risk factors. *Ophthalmology* 1994;**101**(9):1522–8.

Klein 2004
Klein R, Peto T, Bird A, Vannewkirk MR. The epidemiology of age-related macular degeneration. *American Journal of Ophthalmology* 2004;**137**(3):486–95.

Maguire 2004
Maguire M, Complications of Age-Related Macular Degeneration Prevention Trial Research Group. Baseline characteristics, the 25-Item National Eye Institute Visual Functioning Questionnaire, and their associations in the Complications of Age-Related Macular Degeneration Prevention Trial (CAPT). *Ophthalmology* 2004;**111**(7): 1307–16.

Mangione 1999
Mangione CM, Gutierrez PR, Lowe G, Orav EJ, Seddon JM. Influence of age-related maculopathy on visual functioning and health-related quality of life. *American Journal of Ophthalmology* 1999;**128**(1):45–53.

MPSG 1997
Macular Photocoagulation Study Group. Risk factors for choroidal neovascularization in the second eye of patients with juxtafoveal or subfoveal choroidal neovascularization secondary to age-related macular degeneration. *Archives of Ophthalmology* 1997;**115**(6):741–7.

Owen 2003
Owen CG, Fletcher AE, Donoghue M, Rudnicka AR. How big is the burden of visual loss caused by age related macular degeneration in the United Kingdom?. *British Journal of Ophthalmology* 2003;**87**:312–7.

Pauleikhoff 1990a
Pauleikhoff D, Harper CA, Marshall J, Bird AC. Aging changes in Bruch's membrane. A histochemical and morphologic study. *Ophthalmology* 1990;**97**(2):171–8.

Pauleikhoff 1990b
Pauleikhoff D, Chen JC, Chisholm IH, Bird AC. Choroidal perfusion abnormality with age-related Bruch's membrane change. *American Journal of Ophthalmology* 1990;**109**(2): 211–7.

Phipps 2003
Phipps JA, Guymer RH, Vingrys AJ. Loss of cone function in age-related maculopathy. *Investigative Ophthalmology & Visual Science* 2003;**44**(5):2277–83.

RevMan 2008
The Nordic Cochrane Centre. The Cochrane Collaboration. Review Manager (RevMan). 5.0. Copenhagen: The Nordic Cochrane Centre. The Cochrane Collaboration, 2008.

Sarraf 1999
Sarraf D, Gin T, Yu F, Brannon A, Owens SL, Bird AC. Long-term drusen study. *Retina* 1999;**19**(6):513–9.

Smith 2001
Smith W, Assink J, Kein R, Mitchell P, Klaver CCW, Klein BEK, et al.Risk factors for age-related macular degeneration. Pooled findings from three continents. *Ophthalmology* 2001;**108**:607–704.

Vingerling 1996
Vingerling JR, Hofman A, Grobbee DE, de Jong PT. Age-related macular degeneration and smoking. The Rotterdam Study. *Archives of Ophthalmology* 1996;**114**(10):1193–6.

Wetzig 1994
Wetzig PC. Photocoagulation of drusen-related macular degeneration: a long-term outcome. *Transactions of the American Ophthalmological Society* 1994;**92**:299–303.

White 2008

White IR, Higgins JPT, Wood AM. Allowing for uncertainty due to missing data in meta-analyses. Part 1: two-stage methods. *Statistics in Medicine* 2008;**27**:711–27.

Young 1987

Young RW. Pathophysiology of age-related macular degeneration. *Survey of Ophthalmology* 1987;**31**(5): 291–306.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

CAPT

Methods	Method of allocation: treatment assignments were generated using a randomly permuted block method, stratified by clinical centre and using a randomly chosen block size. A member of the CAPT Co-ordinating Centre reviewed an eligibility checklist with the local ophthalmologist and clinic co-ordinator during a teleconference before disclosing which of the two eyes was assigned to laser treatment Masking: masked visual acuity examiners. Unclear if patients and care providers were masked. Not reported if anatomic outcomes assessors were masked (i.e. Photograph Reading Centre), but masking is unlikely to be achieved since photocoagulation generates visible scars Exclusions after randomisation: none reported Losses to follow up: through 5 years of follow up, 5891 (97.2%) visits were completed of the 6061 6-month and annual visits scheduled for surviving CAPT participants. This percentage was relatively stable over time Unusual study design: bilateral or paired study, i.e. one eye randomised to treatment or control and the fellow eye to the other study arm
Participants	Country: USA Number randomised: 1052 patients Age: mean 71 Sex: 637 females (60.6%) Inclusion criteria: at least 10 drusen of size 125 micrometres or more within 3000 micrometres of FAZ centre; BCVA: 20/40 or more; 50 year or older Exclusion criteria: CNV or serous retinal pigment epithelial detachment in either eyes; geographic atrophy within 500 micron of FAZ centre; any ocular disease that might affect visual acuity
Interventions	Treatment: 60 burns in a grid pattern using a 100 micrometre spot size, 0.1 second duration and power to achieve a barely visible lesion. The burns were applied within an annulus between 1500 and 2500 micrometres from the FAZ centre. Control: observation
Outcomes	Primary: loss of 15 letters or more Secondary: change in VA; change in contrast sensitivity; change in critical print size; incidence of late AMD (CNV, serous pigment epithelial detachment, geographic atrophy)
Notes	Since 2001 the patients were informed of the AREDS results and were left free to consume antioxidants

Risk of bias

Item	Authors' judgement	Description

CAPT (*Continued*)

Adequate sequence generation?	Yes	Randomly permuted block method used, stratified by clinical centre and using a randomly chosen block size
Allocation concealment?	Yes	Eligibility assessed before randomisation and central allocation by telephone
Blinding? Development of CNV/geographic atrophy	Yes	Unmasked study, but CNV occurrence is sufficiently objective as a diagnosis to be considered unbiased
Blinding? Measurement of vision	Yes	Masked visual acuity examiners, unclear if care providers were masked. Patients cannot be masked since no sham procedure is mentioned
Incomplete outcome data addressed? All outcomes	Yes	See Appendix 5 and Figure 3. Through 5 years of follow up, 5891 (97.2%) visits were completed of the 6061 6-month and annual visits scheduled for surviving CAPT participants. This percentage was relatively stable over time
Free of selective reporting?	Yes	Development of CNV and atrophy, as well as loss of 3 or more lines of visual acuity are well-defined and relevant outcomes
Free of other bias?	Unclear	Unclear

CNVPT

Methods	BILATERAL: method of allocation: right eye randomly assigned to either laser treatment or observation. Left eye assigned to alternate treatment UNILATERAL: random allocation to laser treatment or observation Stratified by clinical centre and study (bilateral/unilateral) and blocked using a randomly selected block size. Issued over telephone from central location Masking: participant: no; provider: unclear; outcome: no for fundus features; yes for visual acuity Exclusions after randomisation: not reported. Losses to follow up: among participants alive at 12 months 57/57 were examined in the laser group and 58/61 in the observation group. At 2 years 46/57 (80.7%) treated eyes compared to 47/58 (81%) control eyes were still followed. However, causes of loss to follow up other than death are not reported
Participants	Country: USA 15 clinical centres BILATERAL: number randomised: 156. Age: average 71. Sex: 61% female UNILATERAL: number randomised: 120. Age: average age 73. Sex: 63% female in treatment group; 59% female in control group Inclusion criteria: aged 50 years plus with colour stereo photographs and a fluorescein

	angiogram of both eyes taken within 14 days of enrolment, free of any condition that would preclude 2 years follow up. No exudative AMD. Study eye: > 10 large drusen (> 63 microns) within 3000 microns of the foveal avascular zone with visual acuity of 20/40 or better and no evidence of current or past CNV BILATERAL: no exudative AMD in both eyes UNILATERAL: no evidence of current or past CNV. Exudative AMD in fellow (non-study) eye. Exclusion criteria: evidence of serous pigment epithelial detachment 1 MPS disc area or more, geographic atrophy within 500 microns of the centre of the foveal avascular zone, myopia (>= 8 diopters spherical equivalent), previous laser treatment to the retina, severe non-proliferative or proliferative diabetic retinopathy or diabetic macular oedema, progressive ocular disease
Interventions	Treatment: low-intensity laser treatment. Three different laser treatment protocols: (1) Laser 20: 20 laser burns, 100 microns in diameter, in a pattern of 3 rows placed between the 12 and 6 o'clock positions beyond the temporal perimeter of the foveal avascular zone. The desired intensity of the burns was a grey-white lesion. Direct application of laser burns to drusen to be avoided. Whenever the area of drusen had not been reduced by 50% or more at 6 months of enrolment, a second treatment was applied nasal to the fovea in a mirror image of the first treatment. During the last 6 months of enrolment, a second laser treatment protocol was adopted that specified 24 laser burns, 100 microns in diameter in a circular pattern of 2 rows surrounding the macular drusen Control: observation of fellow eyes
Outcomes	Visual acuity (EDTRS); contrast threshold (Pelli Robson); reading ability (MN Read charts) Development of CNV, development of geographic atrophy, disappearance of drusen (stereoscopic colour photographs of the macular and disc of each eye and fluorescein angiogram)
Notes	Enrolment in these pilot studies was suspended after recommendation by the Data and Safety Monitoring Committee (DSMC) because there was a higher incidence of CNV within 12 months of study enrolment in laser-treated eyes than in observed eyes, predominantly in the Fellow Eye Study Furthermore, data from the bilateral study arm was reported at 12 months but not thereafter

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Stratified by clinical centre and study (bilateral/unilateral) and blocked using a randomly selected block size
Allocation concealment?	Yes	Issued over telephone from central location

CNVPT (*Continued*)

Blinding? Development of CNV/geographic atrophy	Yes	Unmasked study, but CNV occurrence is sufficiently objective as a diagnosis to be considered unbiased
Blinding? Measurement of vision	No	Participant and outcome assessors were not masked, unclear if care providers were masked
Incomplete outcome data addressed? All outcomes	Yes	See Results, Appendix 5 and Figure 3. UNILATERAL: 81% followed at 2 years in both study arms; loss to follow up is balanced but causes of loss are not reported
Free of selective reporting?	Yes	Development of CNV and atrophy, as well as loss of 3 or more lines of visual acuity are well-defined and relevant outcomes
Free of other bias?	No	Enrolment in these pilot studies was suspended under recommendation by the Data and Safety Monitoring Committee (DSMC) because there was a higher incidence of CNV within 12 months of study enrolment in laser-treated eyes than in observed eyes, predominantly in the Fellow Eye Study

DLS

Methods	Method of allocation: randomisation was conducted with a computerised weighted coin method in the Research and Development office.The randomisation assignment was provided by telephone, and the clinic co-ordinator printed the randomisation assignment on the patient's baseline form. The clinical investigator was then informed of the randomisation allocation. All study eyes of eligible patients in the UNILATERAL group were randomised. The study eye was randomised to laser treatment or no laser treatment. All right eyes of eligible patients in the BILATERAL group were randomised to laser treatment or no laser treatment; the fellow eye received the alternate treatment Masking: participant: unclear; provider: unclear, outcome assessor: masked visual acuity examiner Exclusions after randomisation: none reported Losses to follow up: UNITERAL: at 3 years, visual acuity was obtained in 73/92 (80.7%) laser-treated eyes versus 66/85 (77.6%) control eyes. Development of CNV was recorded in 91/92 treated eyes and 85/85 control eyes. BILATERAL: visual acuity obtained in 72/105 patients at 3 years, and CNV development assessed in 103/105 eyes at 3 years Unusual study design: some patients had both eyes randomised (BILATERAL group) and within-patient correlation was taken into account
Participants	Country: UK BILATERAL: number randomised: 105. Age: 70.1 (52 to 100). Sex: 31 males/ 74 females

DLS (*Continued*)

	UNILATERAL: number randomised: 177. Age: 72 (54 to 87). Sex: 80 males/ 97 females Inclusion criteria: drusen with/without focal RPE hyperpigmentation in the study eye and CNV in the fellow eye; BCVA at least 6/12 (20/40); at least 50 years Exclusion criteria: geographic atrophy in either eye; any other eye disease able to influence VA; allergy to fluorescein
Interventions	Treatment: argon green/yellow dye laser with 200 micrometre spot size, 0.2 second duration and the lowest energy to produce a very faint burn; overall 12 burns: 4 burns placed 750 micrometres from FAZ centre (12-3-6-9 o'clock), and 8 burns 1500 micrometres from FAZ centre (12, 1.30, 3, 4.30, 6, 7.30, 9. 10.30, 12 o'clock); drusen treated directly if they were coincident with protocol treatment allocation Control: observation
Outcomes	Proportion of patients who developed CNV; visual acuity
Notes	Protocol of treatment revised after 23 months: 12 burns (0.2 sec to 200 micrometre spot size) placed in circular pattern at 1000 micrometres form FAZ centre

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer generated method
Allocation concealment?	Yes	The clinical investigator was informed of the randomisation allocation by the Co-ordinator by telephone after eligibility was assessed
Blinding? Development of CNV/geographic atrophy	Yes	Unmasked study, but CNV occurrence is sufficiently objective as a diagnosis to be considered unbiased
Blinding? Measurement of vision	Yes	Masked visual acuity examiners. Patients cannot be masked since no sham procedure is mentioned
Incomplete outcome data addressed? All outcomes	Yes	See Results, Appendix 5 and Figure 3. Losses to follow up are balanced but causes are not reported; no risk of bias given the paired study design for the BILATERAL study arm
Free of selective reporting?	Yes	Development of CNV and atrophy, as well as loss of 3 or more lines of visual acuity are well-defined and relevant outcomes

Free of other bias?	No	The trial was stopped early after an interim analysis suggested that laser treatment induced CNV in treated eyes of patients in the unilateral group

Figueroa 1994

Methods	Method of allocation: not reported. One eye of patients with bilateral drusen was assigned to treatment and the other to control Masking: not reported if participants and providers, but patients cannot be masked since there is no sham procedure. Visual acuity examiners were masked Exclusions after randomisation: none reported. Losses to follow up: since they report on results at last examination (mean follow up is 3 years), assessing the impact of loss to follow up is difficult Unusual study design: paired or bilateral study; authors also report on a parallel case series of patients with CNV in one eye who were all treated in the fellow eye
Participants	Country: Spain Number randomised: 30 Age: 69 (range: 62 to 74) Inclusion criteria: AMD with large confluent soft drusen involving the fovea Exclusion criteria: not specified
Interventions	Treatment: green argon laser; 0.1 mW, 0.1 sec, 100 micrometre spot; laser spot on drusen in the temporal fovea, or grid pattern if drusen larger than 300 micrometre Control: observation Duration: 3 years on average (1.5 to 5 years)
Outcomes	Occurrence of CNV, reduction of drusen, visual acuity
Notes	Drusen resolution possible also for drusen located far from the laser application

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? Development of CNV/geographic atrophy	Yes	Unmasked study, but CNV occurrence is sufficiently objective as a diagnosis to be considered unbiased
Blinding? Measurement of vision	Yes	Masked visual examiner

Figueroa 1994 (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	See Results, Appendix 5 and Figure 3. Data at mean follow up are reported. Since 12 out of 30 patients were followed for less than 3 years, it is difficult to assess the impact of this type of reporting
Free of selective reporting?	Unclear	Development of CNV and atrophy, as well as loss of 3 or more lines of visual acuity are well-defined and relevant outcomes
Free of other bias?	Unclear	Unclear

Frennesson 1995

Methods	Method of allocation: not reported; in 5 patients with both eyes eligible the eye with better visual acuity was randomised Masking: participant: unclear; provider: unclear; outcome: unclear Exclusions after randomisation: none reported Losses to follow up: 2/19 patients in the treated group vs. 0/19 in the control group lost to follow up at 3 years Unusual study design
Participants	Country: Sweden Number randomised: 38 Age: 71.6 (6.5 SD) treated patients; 68.5 (6.2 SD) control patients Inclusion criteria: soft drusen; visual acuity at least 0.8 Exclusion criteria: CNV, PED, pigmentary clumping, macular atrophy, haemorrhage, any other eye disorder which could affect VA
Interventions	Treatment: argon green laser with 200 micrometre spot size, 0.05 seconds duration, power to produce a barely visible lesion. Treatment with a temporal horseshoe-shaped area extending to the vascular arcades, with direct treatment of the drusen. Control: observation Duration: 3 to 8 years
Outcomes	Anatomic: mean drusen area, development of CNV. Functional: Snellen visual acuity; colour vision (Farnsworth panel D-15); central visual field (Humphrey 10-2)
Notes	-

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported

Frennesson 1995 (*Continued*)

Blinding? Development of CNV/geographic atrophy	Yes	Unmasked study, but CNV occurrence is sufficiently objective as a diagnosis to be considered unbiased
Blinding? Measurement of vision	Unclear	Not reported. Patients cannot be masked since no sham procedure is mentioned
Incomplete outcome data addressed? All outcomes	Yes	See Results, Appendix 5 and Figure 3. 2/19 (11%) patients in the treated group vs. 0/19 in the control group lost to follow up at 3 years; causes of loss to follow up not reported
Free of selective reporting?	Yes	Development of CNV and atrophy, as well as loss of 3 or more lines of visual acuity are well-defined and relevant outcomes
Free of other bias?	Unclear	Unclear

Laser to Drusen Study

Methods	Method of allocation: computer generated randomisation list with randomly selected block sizes. Allocation groups: observation vs. laser (1:1), laser further divided (1:1) in temporal vs. nasal and temporal treatment Masking: participant: unclear; provider: unclear; outcome: unclear Exclusions after randomisation: none reported Losses to follow up: 7/47 (15%) of treatment group and 10/52 (19%) of control group seen at 2 years
Participants	Country: USA Number randomised: 99 Age: range 55 to 84, mean 74 (6.6 SD) Sex: 69.7% female Inclusion criteria: • Large drusen (> 63 microns in diameter) and focal hyperpigmentation, and no neovascular AMD in one eye only (study eye) • Evidence of neovascular AMD (CNV, disciform scar, laser scar for CNV) in one eye only (fellow eye) • visual acuity 20/40 or better in study eye (other information says 20/50 or better) • no significant coexisting ocular disorder in study eye • age 50 years or older Exclusion criteria: • history of laser surgery or vitreous surgery in study eye • low probability of completing 2-year follow-up schedule (poor health, live far from clinical centre, unwilling to return) • geographic atrophy within 3000 microns of foveal centre • other conditions associated with CNV, including pathologic myopia (spherical equivalent exceeding -8.00 diopters or clinical evidence of lacquer cracks), angioid

	streaks, histo spots, pattern dystrophies of RPE, etc. in study eye • severe non-proliferative or worse diabetic retinopathy or diabetic macular edema in study eye • other progressive ocular disease that could impair visual acuity such as glaucoma in the study eye • lensectomy or intraocular lens implantation within 3 months
Interventions	Laser wavelength: dye yellow laser (577 nm) or infrared diode (very early - was discontinued). Number of burns: various, 2 scatter patterns described below; spot size: 50 microns; duration: 0.1 seconds; intensity: very light grey burn (just visible); no treatment within 500 microns of foveal centre and beyond 3000 microns from foveal centre; scatter burns approximately 2 to 3 burn widths apart, trying to avoid placing burns directly over focal clumps of hyperpigmentation. Do not have to place directly on drusen, but in placing scatter, small placement changes (< 50 microns) should be done to centre spot on drusen Pattern 1) (temporal = 180 degree) - not placed in nasal portion of macula (vertical line intersects foveal centre) Pattern 2) (temporal and nasal = 360 degree) - burns placed in scatter both nasal and temporal portion of macula (exclusive of central macula within 500 microns of foveal centre and not beyond 3000 microns of foveal centre)
Outcomes	Development of CNV, visual acuity; information on other outcomes not available
Notes	Randomisation changed - originally 1:1 (laser vs. observation), then laser group randomised (1:1) infrared diode vs. yellow dye - each colour laser was randomised (1:1) temporal vs. temporal & nasal The red diode laser arm was stopped early (probably December 1995) Pilot study nature - so some clinical centres did not do all tests (reading, contrast) - not all clinical photos graded

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer generated. Randomly selected block size (Marta M Gilson personal communication)
Allocation concealment?	Yes	Serially numbered sealed opaque envelopes. Co-ordinator had to fill out checklist - document eligibility - then open sequentially numbered envelope, record date opened, time opened, patient number, name code, and sign the form, (2 copies - keep one, and fax other to co-ordinating centre within 24 hours of opening. Faxed forms were later mailed to co-ordinating centre (Marta M Gilson personal communication)

Laser to Drusen Study (*Continued*)

Blinding? Development of CNV/geographic atrophy	Yes	Participants: unclear; care providers: ophthalmologists (applying laser) were not masked; care providers - Co-ordinators: unclear; outcome assessors: Photograph Reading Centre graders were to be masked, but it is possible that some of the laser scars may have unmasked the graders (Marta M Gilson personal communication)
Blinding? Measurement of vision	Unclear	Vision acuity examiners: unclear
Incomplete outcome data addressed? All outcomes	Yes	See Results, Appendix 5 and Figure 3. 7/47 (15%) of treatment group and 10/52 (19%) of control group lost at 2 years. No information on reasons for loss to follow up
Free of selective reporting?	Yes	Outcomes selected by review author
Free of other bias?	Unclear	Unclear

Little 1995

Methods	Method of allocation: after patients eligibility was ascertained and patient consent was obtained, one eye was randomised to photocoagulation treatment; the right eye was assigned to treatment if patient's birth date was an odd month, the left if it was an even month Masking: participant: unclear; provider: unclear; outcome assessor: unclear Exclusions after randomisation: Losses to follow up: a minimum 1-year follow up was obtained (mean 3.2 years) Unusual study design (paired study)
Participants	Country: USA Number randomised: 27 Age: mean 69.7 Sex: 9 males/18 females Inclusion criteria: symmetrical drusen; minimum drusen size 100 micrometre; at least 20 drusen or 10 drusen + 2 drusen at least 500 micrometre in diameter; drusen within 500 micrometre from foveola; VA at least 20/60 Exclusion criteria: PED; atrophy; subretinal fluid, haemorrhage, exudate; any other eye disorder which could affect VA
Interventions	Treatment: 577 to 620 wavelength laser with 100 to 200 micrometre spot size, 0.05 to 0.1 seconds duration, 100 to 200 power. Direct treatment of the drusen Control: observation Duration: 1 to 6-year follow up

Outcomes	Snellen VA; colour vision (Farnsworth panel D-15 colour-test); central visual field with Humphrey 10-2
Notes	-

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	No	After patients eligibility was ascertained and patient consent was obtained, one eye was randomised to photocoagulation treatment; the right eye was assigned to treatment if patient's birth date was an odd month, the left if it was an even month
Allocation concealment?	No	See above, the enrolling researcher could have foreseen which eye would have been treated. Nonetheless, this can be irrelevant since both eyes of each patient were included, i.e. there is no risk of confounding
Blinding? Development of CNV/geographic atrophy	Yes	Unmasked study, but CNV occurrence is sufficiently objective as a diagnosis to be considered unbiased
Blinding? Measurement of vision	No	Not reported. Patients cannot be masked since no sham procedure is mentioned
Incomplete outcome data addressed? All outcomes	Unclear	Unclear: only last visit data reported, thus being impossible to reconstruct the pattern of missing data; 4 out of 27 patients were followed for at least 1 year but less than 2 years
Free of selective reporting?	Yes	Development of CNV and atrophy, as well as loss of 3 or more lines of visual acuity are well-defined and relevant outcomes
Free of other bias?	Unclear	Unclear

Olk 1999

Methods	Method of allocation: not reported; BILATERAL: 1 eye was assigned to treatment and 1 eye to observation. UNILATERAL: 1 eye eligible that eye was assigned to either treatment or observation. BILATERAL/UNILATERAL: eyes assigned to treatment were further randomised to either 'visible' or 'subthreshold' treatment Masking: participant: unclear; provider: unclear; outcome: unclear Exclusions after randomisation: 25/152 patients (35 eyes) were enrolled initially in the pilot study but subsequently determined to be ineligible for various reasons, mainly violation of inclusion criteria Losses to follow up: at 24 months, 33 eyes had missed visits: 9 eyes (4 observation, 2 visible, 3 subthreshold) were in deceased patients, 14 eyes were in the observation group, and 10 eyes were in the treatment group (5 eyes, visible; 5 eyes, subthreshold) Unusual study design: some eyes
Participants	Country: USA Number randomised: BILATERAL: 77 patients (154 eyes) with both eyes eligible UNILATERAL: 75 patients (75 eyes) with 1 eye eligible (unilateral study arm), that eye was assigned to either treatment or observation Sex: of 152 patients enrolled; 57 males, 95 females Age: mean 74.5, range of 54 to 88 years Inclusion criteria: age older than 50 years; diagnosis of AMD with at least 5 large (63 µm or more), soft drusen within 2250 µm of the centre of the foveal avascular zone in both eyes (bilateral study arm) or in one eye (unilateral study arm) if the fellow eye had evidence of exudative AMD; and VA of 20/63 or greater on the ETDRS chart in all eligible eyes Exclusion criteria: exudative macular degeneration in either eye for bilateral patients and in both eyes for unilateral patients; other ocular diseases
Interventions	Eyes were treated with a slit-lamp integrated diode photocoagulator using 810-nm wavelength (IRIS Medical OcuLight SLx; IRIDEX Corp., Mt. View, CA). 48 diode laser lesions of 125 mm were applied in 4 concentric circles outside the FAZ in a scatter or grid pattern between 750 mm and 2250 mm from the centre of the fovea. Test spot laser lesions were applied to the retina nasal to the optic nerve using 200-msec duration, and the power was increased to produce a mild grey lesion (visible burn). For eyes assigned to visible treatment, this intensity was then applied in a grid pattern as described above. For eyes assigned to subthreshold treatment, the energy needed for the visible test burn was kept constant, but the duration was halved to 100 msec and treatment then carried out. Only one laser treatment was applied to each eye throughout the duration of the study
Outcomes	Anatomic: reduction of drusen, development of CNV. Functional: visual acuity
Notes	Within-patient correlation of outcomes in the bilateral arm not analysed and reported

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not reported

Olk 1999 (*Continued*)

Allocation concealment?	Unclear	Not reported
Blinding? Development of CNV/geographic atrophy	Yes	Unmasked study, but CNV occurrence is sufficiently objective as a diagnosis to be considered unbiased
Blinding? Measurement of vision	No	Not reported. Patients cannot be masked since no sham procedure is mentioned
Incomplete outcome data addressed? All outcomes	No	See Results, Appendix 5 and Figure 3. Losses to follow up: at 24 months, 33 eyes had missed visits: 9 eyes (4 observation, 2 visible, 3 subthreshold) were in deceased patients, 14 eyes were in the observation group, and 10 eyes were in the treatment group (5 eyes, visible; 5 eyes, subthreshold). Causes of loss to follow up other than death are not reported
Free of selective reporting?	Yes	Development of CNV and atrophy, as well as loss of 3 or more lines of visual acuity are well-defined and relevant outcomes
Free of other bias?	Unclear	Unclear

PTAMD

Methods	Method of allocation: study eyes were assigned randomly to either treatment or observation by a computer-generated, centre-specific, variable block size randomisation at a 1:1 ratio. These random assignments were concealed in opaque envelopes that were opened only upon enrolment of an eligible patient who gave consent Masking: participant: unclear; provider: unclear; outcome: unclear Exclusions after randomisation: not reported Losses to follow up: at 1 year 184/244 (75%) patients followed (5 deaths), 92 treated eyes and 99 control eyes followed. At 3 years 124/244 (51%) patients followed (20 deaths), 64 treated eyes and 55 control eyes followed Unusual study design: another arm of the study included patients with both eyes eligible, but this report deals with unilateral patients only
Participants	Country: USA Number randomised: 244 Age: mean 75.4 treated patients, 75.1 observed patients Gender: (% female) 59.3 treated patients, 61.5 observed patients Inclusion criteria: age 50 or more. Eligible eye must have BCVA of at least 20/63 on the ETDRS chart; AMD with at least 5 drusen that are 63 μm in diameter and are located within 2250 μm of the centre of the fovea; unilateral participants must have one eye ineligible due to vision loss that is attributed to advanced AMD Exclusion criteria: other ocular disease causing visual loss

Interventions	Eyes randomised to treatment received a single-session treatment of a grid of 48 diode laser lesions of 125 micrometre in diameter. Laser treatment was applied in an annular grid that extended from 0.5 (750 micrometre) to 2.0 (3000 micrometre) disc diameters from the centre of the foveal avascular zone. A slit lamp-based diode laser photocoagulation system (IRIS Medical, Mountain View, CA) emitting energy at 810 nm was used to deliver the laser treatment. Laser lesions were placed in a subthreshold manner by first delivering test spot(s) of 200-millisecond duration placed outside of the macula at a low power (e.g. 200 mW) and then incrementally increasing the power in small (50 mW) increments until a faint grey (threshold) lesion could be detected visually through the treatment lens. While the power setting was left unchanged, the pulse duration was reduced to a 100-millisecond interval to achieve an invisible subthreshold lesion. Laser lesions were then scattered within the annular grid as defined above, beginning by placing 12 spots in a given quadrant and then proceeding to adjacent quadrants to complete the treatment pattern. The drusen were not targeted specifically or preferentially. If a visible lesion was produced while the annular grid treatment was performed, the power setting was reduced to achieve subthreshold lesions with the remainder
Outcomes	Anatomic: drusen reduction, development of CNV. Functional: visual acuity
Notes	-

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer generated, centre-specific, variable block size randomisation
Allocation concealment?	Yes	Random assignments were concealed in opaque envelopes that were opened only upon enrolment of an eligible patient who gave consent
Blinding? Development of CNV/geographic atrophy	Yes	Unmasked study, but CNV occurrence is sufficiently objective as a diagnosis to be considered unbiased
Blinding? Measurement of vision	Unclear	Not reported, masking of care providers and photograph graders might be achieved since subthreshold photocoagulation should not generate visible scars. Patients cannot be masked since no sham procedure is mentioned
Incomplete outcome data addressed? All outcomes	No	See Results, Appendix 5 and Figure 3. Survival analysis used. Losses to follow up: at 1 year 184/244 (75%) patients followed (5 deaths), 92 treated eyes and 99 control eyes followed. At 3 years 124/244 (51%) pa-

PTAMD (*Continued*)

		tients followed (20 deaths), 64 treated eyes and 55 control eyes followed. Causes of loss other than death are not reported
Free of selective reporting?	Yes	Development of CNV and atrophy, as well as loss of 3 or more lines of visual acuity are well-defined and relevant outcomes
Free of other bias?	Unclear	Unclear

AMD: age-related macular degeneration
AREDS: Age-related Eye Disease Study
BCVA: best-corrected visual acuity
CNV: choroidal neovascularisation
ETDRS: Early Treatment Diabetic Retinopathy Study
FAZ: foveal avascular zone
MPS: Macular Photocoagulation Study
PED: pigment epithelial detachment
RPE: retinal pigment epithelial
VA: visual acuity
vs.: versus

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Sarks 1999	Comparative study but no randomisation
Sigelman 1991	Case report

Characteristics of studies awaiting assessment *[ordered by study ID]*

Sivagnanavel 2004

Methods	Prospective, double masked, randomised controlled trial at King's College Hospital, London
Participants	Patients with subfoveal choroidal neovascularisation (CNV) from age-related macular degeneration (AMD) in one eye and significant drusen (> 5 large drusen or > 20 small drusen) in the fellow eye
Interventions	Drusen photocoagulation by means of diode laser using large spot size, low energy and long duration (4200 microns x 400 mw x 60 s); control group received sham treatment (laser with no energy)

Sivagnanavel 2004 (*Continued*)

Outcomes	Fundus changes measured with photography, visual acuity, contrast sensitivity and colour contrast sensitivity recorded every 3 months
Notes	-

DATA AND ANALYSES

Comparison 1. Photocoagulation versus control

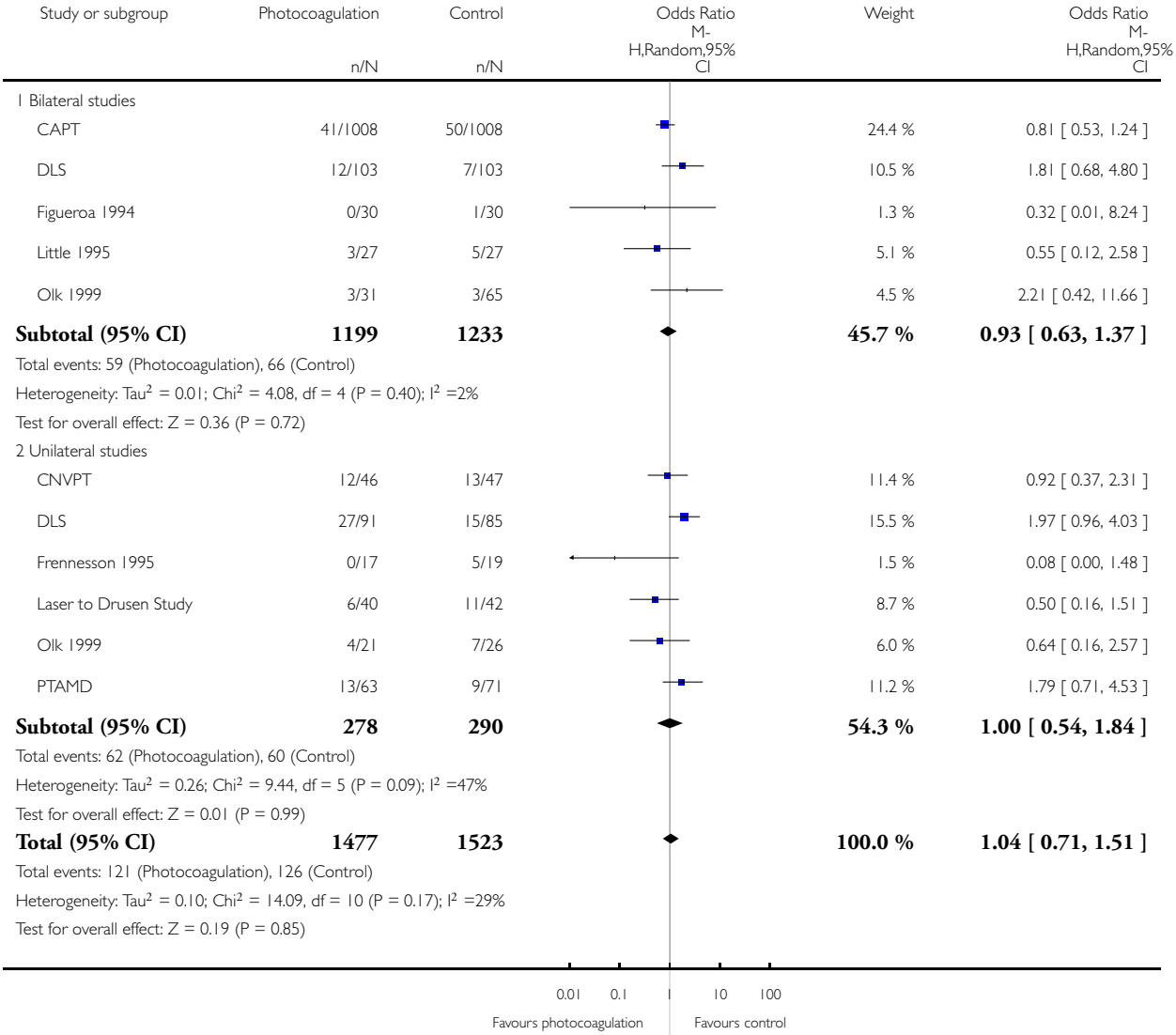
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Development of CNV	9	3000	Odds Ratio (M-H, Random, 95% CI)	1.04 [0.71, 1.51]
1.1 Bilateral studies	5	2432	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.63, 1.37]
1.2 Unilateral studies	6	568	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.54, 1.84]
2 Development of CNV: sensitivity analysis assuming moderate correlation (0.5) for bilateral studies	9		Odds Ratio (Random, 95% CI)	1.06 [0.72, 1.55]
2.1 Bilateral studies	5		Odds Ratio (Random, 95% CI)	1.08 [0.61, 1.91]
2.2 Unilateral studies	6		Odds Ratio (Random, 95% CI)	1.00 [0.54, 1.84]
3 Development of geographic atrophy	2	148	Odds Ratio (M-H, Fixed, 95% CI)	1.30 [0.38, 4.51]
4 Visual loss of 2 to 3+ lines	7		Odds Ratio (Random, 95% CI)	0.88 [0.67, 1.14]
4.1 Bilateral studies	3		Odds Ratio (Random, 95% CI)	0.75 [0.54, 1.04]
4.2 Unilateral studies	5		Odds Ratio (Random, 95% CI)	1.17 [0.75, 1.82]
5 Loss of 0.3 or more log units of contrast sensitivity at 2 years	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6 Reading speed (words/minute)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7 Drusen reduction	2	195	Odds Ratio (IV, Fixed, 95% CI)	10.72 [3.84, 29.97]

Analysis 1.1. Comparison 1 Photocoagulation versus control, Outcome 1 Development of CNV.

Review: Laser treatment of drusen to prevent progression to advanced age-related macular degeneration

Comparison: 1 Photocoagulation versus control

Outcome: 1 Development of CNV



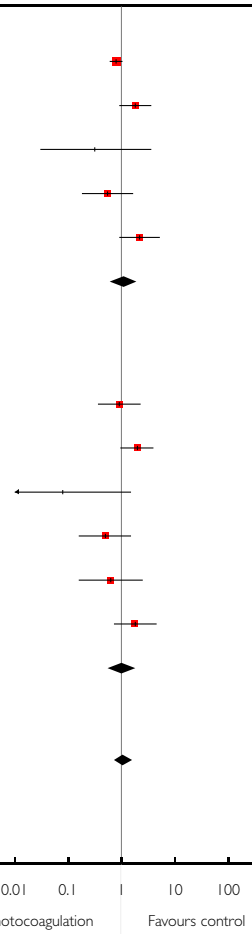
Analysis 1.2. Comparison 1 Photocoagulation versus control, Outcome 2 Development of CNV: sensitivity analysis assuming moderate correlation (0.5) for bilateral studies.

Review: Laser treatment of drusen to prevent progression to advanced age-related macular degeneration

Comparison: 1 Photocoagulation versus control

Outcome: 2 Development of CNV: sensitivity analysis assuming moderate correlation (0.5) for bilateral studies

Study or subgroup	log [Odds Ratio] (SE)	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
1 Bilateral studies				
CAPT	-0.22865 (0.152192)		19.5 %	0.80 [0.59, 1.07]
DLS	0.59249 (0.356873)		12.8 %	1.81 [0.90, 3.64]
Figueroa 1994	-1.13195 (1.240966)		2.3 %	0.32 [0.03, 3.67]
Little 1995	-0.59784 (0.563085)		7.9 %	0.55 [0.18, 1.66]
Olk 1999	0.79493 (0.445526)		10.4 %	2.21 [0.92, 5.30]
Subtotal (95% CI)			**52.8 %**	**1.08 [0.61, 1.91]**
Heterogeneity: Tau^2 = 0.22; Chi^2 = 9.91, df = 4 (P = 0.04); I^2 =60%				
Test for overall effect: Z = 0.27 (P = 0.79)				
2 Unilateral studies				
CNVPT	-0.08004 (0.46806)		9.8 %	0.92 [0.37, 2.31]
DLS	0.6774 (0.36553)		12.5 %	1.97 [0.96, 4.03]
Frennesson 1995	-2.58595 (1.51919)		1.6 %	0.08 [0.00, 1.48]
Laser to Drusen Study	-0.6985091 (0.5650182)		7.8 %	0.50 [0.16, 1.51]
Olk 1999	-0.44839 (0.71015)		5.7 %	0.64 [0.16, 2.57]
PTAMD	0.58284 (0.47346)		9.7 %	1.79 [0.71, 4.53]
Subtotal (95% CI)			**47.2 %**	**1.00 [0.54, 1.84]**
Heterogeneity: Tau^2 = 0.26; Chi^2 = 9.37, df = 5 (P = 0.10); I^2 =47%				
Test for overall effect: Z = 0.01 (P = 0.99)				
Total (95% CI)			**100.0 %**	**1.06 [0.72, 1.55]**
Heterogeneity: Tau^2 = 0.18; Chi^2 = 19.95, df = 10 (P = 0.03); I^2 =50%				
Test for overall effect: Z = 0.27 (P = 0.78)				



Analysis 1.3. Comparison 1 Photocoagulation versus control, Outcome 3 Development of geographic atrophy.

Review: Laser treatment of drusen to prevent progression to advanced age-related macular degeneration

Comparison: 1 Photocoagulation versus control

Outcome: 3 Development of geographic atrophy

Study or subgroup	Photocoagulation n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
CNVPT	5/32	3/34		56.3 %	1.91 [0.42, 8.76]
Laser to Drusen Study	1/40	2/42		43.7 %	0.51 [0.04, 5.89]
Total (95% CI)	**72**	**76**		**100.0 %**	**1.30 [0.38, 4.51]**

Total events: 6 (Photocoagulation), 5 (Control)

Heterogeneity: Chi^2 = 0.81, df = 1 (P = 0.37); I^2 =0.0%

Test for overall effect: Z = 0.42 (P = 0.68)

Test for subgroup differences: Not applicable

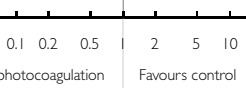
Analysis 1.4. Comparison 1 Photocoagulation versus control, Outcome 4 Visual loss of 2 to 3+ lines.

Review: Laser treatment of drusen to prevent progression to advanced age-related macular degeneration

Comparison: 1 Photocoagulation versus control

Outcome: 4 Visual loss of 2 to 3+ lines

Study or subgroup	log [Odds Ratio] (SE)	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
1 Bilateral studies				
CAPT	-0.2691125 (0.1748489)		58.8 %	0.76 [0.54, 1.08]
DLS	-0.573346 (0.67029815)		4.0 %	0.56 [0.15, 2.10]
Figueroa 1994	-0.3254224 (0.99673272)		1.8 %	0.72 [0.10, 5.09]
Subtotal (95% CI)			**64.6 %**	**0.75 [0.54, 1.04]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.19$, df = 2 (P = 0.91); $I^2 = 0.0\%$				
Test for overall effect: Z = 1.74 (P = 0.083)				
2 Unilateral studies				
CNVPT	-0.2772899 (0.5531024)		5.9 %	0.76 [0.26, 2.24]
DLS	0.4986213 (0.4032875)		11.1 %	1.65 [0.75, 3.63]
Laser to Drusen Study	-0.1957446 (0.7104946)		3.6 %	0.82 [0.20, 3.31]
Olk 1999	-0.238411 (0.5902647)		5.2 %	0.79 [0.25, 2.51]
PTAMD	0.3746934 (0.4297128)		9.7 %	1.45 [0.63, 3.38]
Subtotal (95% CI)			**35.4 %**	**1.17 [0.75, 1.82]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.29$, df = 4 (P = 0.68); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.70 (P = 0.48)				
Total (95% CI)			**100.0 %**	**0.88 [0.67, 1.14]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 5.03$, df = 7 (P = 0.66); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.98 (P = 0.33)				



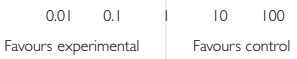
Analysis 1.5. Comparison 1 Photocoagulation versus control, Outcome 5 Loss of 0.3 or more log units of contrast sensitivity at 2 years.

Review: Laser treatment of drusen to prevent progression to advanced age-related macular degeneration

Comparison: 1 Photocoagulation versus control

Outcome: 5 Loss of 0.3 or more log units of contrast sensitivity at 2 years

Study or subgroup	Photocoagulation n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Laser to Drusen Study	4/40	5/42			0.82 [0.20, 3.31]
Subtotal (95% CI)	**0**	**0**			**0.0 [0.0, 0.0]**
Total events: 4 (Photocoagulation), 5 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					



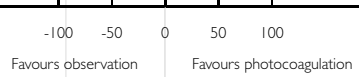
Analysis 1.6. Comparison 1 Photocoagulation versus control, Outcome 6 Reading speed (words/minute).

Review: Laser treatment of drusen to prevent progression to advanced age-related macular degeneration

Comparison: 1 Photocoagulation versus control

Outcome: 6 Reading speed (words/minute)

Study or subgroup	Photocoagulation N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Laser to Drusen Study	20	112.2 (28.8)	24	99.7 (37.8)			12.50 [-7.20, 32.20]
Subtotal (95% CI)	**0**		**0**				**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P < 0.00001)							

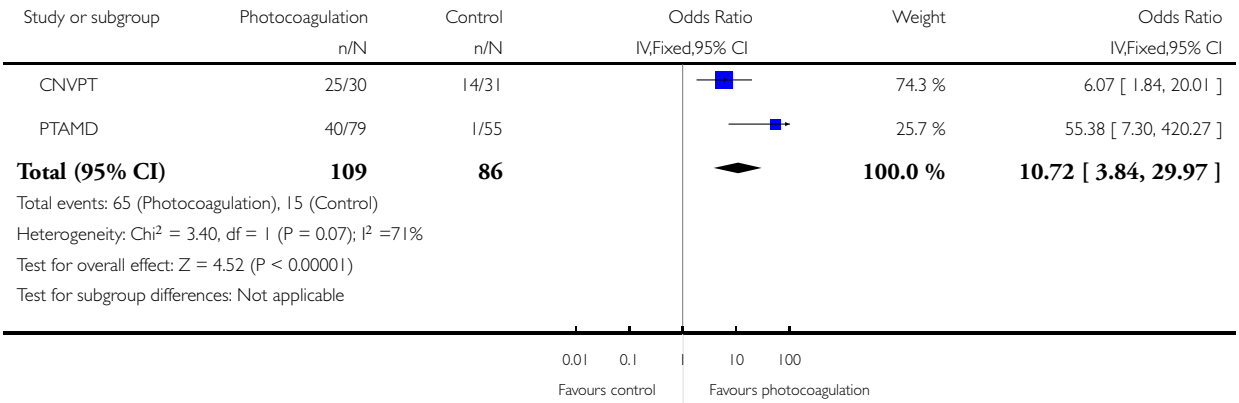


Analysis 1.7. Comparison 1 Photocoagulation versus control, Outcome 7 Drusen reduction.

Review: Laser treatment of drusen to prevent progression to advanced age-related macular degeneration

Comparison: 1 Photocoagulation versus control

Outcome: 7 Drusen reduction



ADDITIONAL TABLES

Table 1. Primary analysis data including deaths and missing cases

Study	Photocoagulation				Observation				Risk of bias due to incomplete outcome data
	F	S	D	M	F	S	D	M	
CAPT	41	967	25	19	50	958	25	19	Low
CNVPT	12	34	2	11	13	34	3	11	Low
DLS bilateral	12	91	0	2	7	96	0	2	Low
DLS unilateral	27	72	0	0	15	70	0	0	Low
Figueroa 1994	0	30	0	0	1	29	0	0	Low
Frennesson 1995	0	17	0	2	4	15	0	0	Low

Table 1. Primary analysis data including deaths and missing cases (*Continued*)

Laser to Drusen Study	6	34	0	7	11	31	0	10	Low
Little 1995 [1]	3	24	NA	NA	5	22	NA	NA	Unclear
Olk 1999 bilateral	3	28	2	10	3	62	4	5	High
Olk 1999 unilateral[2]	4	17	NA	6	7	19	NA	4	High
PTAMD[3]	13	50	5.5	55.5	9	62	5.5	43.5	High

The assessment of the risk of bias due to incomplete outcome data is based on the graphical presentation in Figure 3 based on the methods described in Appendix 5.

F: failures (CNV development), S: successes, D: deaths, M: missing of unknown cause, NA: not available.

[1]Only last visit follow up available and no information on when CV developed in cases with event.

[2]Deaths are not reported and all missing data were coded as missing of unknown cause.

[3]Deaths were provided overall (n = 11 at 2 years) and were equally split between assignment groups. Data at 1 or 3 years are available and midpoints were used.

Table 2. Characteristics of the intervention and control in each study

Study ID	Laser type	Parameters	Control
PTAMD	Diode	125 μm spot size/0.1 sec/grid of 48 lesions	Observation
DLS	Argon green/yellow dye	200 μm spot size/0.2 sec/12 burns	Observation
Little 1995	Dye 577 to 620 nm	100 to 200 μm spot size/ 0.05 to 0.1 sec	Observation
Olk 1999	Diode	125 μm spot size/0.2 sec/grid of 48 burns	Observation
CNVPT	Argon	100 μm spot size/0.1 sec/ laser-20 protocol in 85% of cases	Observation
Frennesson 1995	Argon	200 μm spot size/0.05 sec/temporal horseshoe-shaped area	Observation
Figueroa 1994	Argon	100 μm spot size/0.1 sec/ temporal fovea or grid pattern	Observation

Table 2. Characteristics of the intervention and control in each study (*Continued*)

CAPT	Argon	100 μm spot size/0.1 sec/60 burns	Observation
Laser to Drusen Study	Yellow dye	50 μm spot size/0.1 sec/variable number	Observation

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Retinal Drusen
#2 drusen*
#3 (#1 OR #2)
#4 MeSH descriptor Lasers
#5 laser*
#6 MeSH descriptor Laser Coagulation
#7 photocoagulat*
#8 (#4 OR #5 OR #6 OR #7)
#9 (#3 AND #8)

Appendix 2. MEDLINE search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp retinal drusen/
14. drusen$.tw.
15. or/13-14
16. exp lasers/
17. laser$.tw.
18. exp laser coagulation/
19. photocoagulat$.tw.
20. or/16-19
21. 13 and 20
22. 12 and 21

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville et al (Glanville 2006).

Appendix 3. EMBASE search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin$ adj3 trial$).tw.
14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15. exp placebo/
16. placebo$.tw.
17. random$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control$ or prospectiv$ or volunteer$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp drusen/
34. drusen$.tw.
35. or/33-34
36. exp laser/
37. laser$.tw.
38. exp laser coagulation/
39. photocoagulat$.tw.
40. or/36-39
41. 35 and 40
42. 32 and 41

Appendix 4. Estimate of the correlation coefficient of the measurements within patients in bilateral studies

Elbourne 2002 provides a method for conducting meta-analyses of studies using paired data, such as cross-over studies or studies on paired organs. In this appendix we show how we adjusted the marginal measurements, i.e. with eyes as the unit of analysis extracted from bilateral studies by the intraindividual correlation coefficient extracted from other studies in order to obtain correct standard errors of the odds ratio.

We found both marginal and paired analyses in DLS. Data were limited to the primary outcome 'development of CNV' and to the secondary outcome 'loss of visual acuity'. In particular, Table 4 in DLS presented marginal data on CNV occurrence, our primary outcome - and visual loss while displaying P values obtained with the McNemar test, which is based on the Chi^2 distribution and is adequate for paired data. In particular, 12/103 laser-treated eyes and 7/103 fellow eyes developed CNV and the McNemar P value was 0.2253. The marginal P value using the Chi^2 test would have been 0.2286. We considered that the ratio of the z-values corresponding to these paired and marginal P values (1.2039 and 1.1907, respectively) could be used to adjust the standard errors of the marginal logOR of CNV occurrence for laser-treated eyes compared to controls. The inverse ratio of these two z-values is 0.9782, implying that no adjustment of the marginal logOR standard error is needed for the DLS data. Because the marginal logOR variance is 0.4976, its value adjusted for the correlation between eyes is 0.4867, the difference between the two being twice the covariance (which is 0.0054). From these data the correlation coefficient can be calculated to be only 0.0451 (i.e. 0.0054*square root(12*7*96*91)/103), using the method shown in Elbourne 2002). An issue concerning this correlation coefficient imputation is whether the coverage achieved by the McNemar test is acceptable given the possibility of cells with counts close to nil in paired 2x2 tables from medium size studies such as this when events are not common.

Given the negligible effect of the correlation between eyes of the same patient for the CNV development outcome in DLS, we used marginal data from bilateral studies as if eyes were independent units.

Using the same method for visual acuity loss, the ratio of the marginal and paired logOR standard errors is 0.8143, resulting in a correlation coefficient of 0.2290. Therefore, for this outcome we decided to use the inverse variance method and adjust the marginal logOR standard error by 1.2280 (the reciprocal of the previous ratio).

A different estimate of the correlation between eyes for the CNV outcome was obtained from Little 1995. Using the formulas provided by Elbourne 2002 the correlation coefficient was 0.69 in this small dataset using the last follow up examination to assess the risk of CNV occurrence. Using Elbourne 2002 notations, the number to calculate this value would be: s = 23, t = 2, u = 0, v = 2, hence a = 25, b = 23, c = 2, d = 4. However, this was a very small study and is expected to estimate correlation imprecisely and also to be affected by approximations due to low cell counts, for which common formulas for 2x2 tables do not hold. Thus, we did not use this type of estimate of the correlation coefficient.

Finally, we decided to conduct a sensitivity analysis for the outcome 'development of CNV' using a moderate correlation between eyes of 0.5 to correct standard errors of the marginal OR.

Appendix 5. Methods used to deal with incomplete outcome data

We used the following approaches to take into account the impact of missing data. We conducted and reported these calculations on the odds scale because this was the association measure used in this review, which pooled parallel arm and paired studies.

Method 1

This method aimed at assessing the risk of bias in each study using a forest plot of complete case versus imputed treatment ORs under extreme, but controlled, assumptions. We considered that the missing condition might act as a modifier of the control event rate and/or the treatment effect. Modelling these dimensions implies a response to the following questions:

1. Is the control event rate different for missing versus complete patients? As an example, people at larger or smaller risk of CNV may have been loss to follow up. In this case the OR of event among missing versus complete controls is modelled.
2. Is the control event rate modification different for missing versus complete cases? A relative OR as a multiplier of the observed OR of treatment for observed patients is modelled and applied to the imputed control event odds.

These methods were applied both to unilateral and bilateral studies, since in our primary analysis we estimated a negligible correlation within patient (Appendix 4).

We imputed the dataset using the nine combinations obtained from the crossing of 0.5, 1 and 2 for each of the two modifying ORs. Then we plotted the minimum and maximum OR estimate in a forest plot together with the complete case OR estimate. The resulting

OR change is assessed graphically and subjectively taking into account its 95% CI to discuss the risk of bias in the primary analysis of this review, i.e. considering the main conclusion (in this case equivalence of treatment and observation)
Finally, we considered that deaths were unrelated to treatment and we applied the complete case 2x2 probabilities, after dividing the number of dead patients in each arm by 2, since the a reasonable assumption is that the average observation time before death was the midpoint of the follow up. Because death was rare in this study we expected very little impact of death on missing imputation. We also suggest that any other reported cause of *missingness* believed to be unrelated to treatment may be treated like death, i.e. using the same probability distribution of the complete cases (however using the entire number of unrelated missing patients for imputation as they are presumed to be alive). However, there were no cases with reported and unrelated causes of *missingness* in this review.
As a final comment to Method 1, we observe that no uncertainty is taken into account with respect to more formal methods implemented in '*metamiss*' as used in Method 2. However, we observe that the assumptions on the Informative Missing Odds Ratio (IMOR), which are subjective or motivated by context knowledge, are the key determinant of these analyses. Method 1 may be complementary because it generates graphs for subjective assessment of risk of bias in each study without use of statistical software packages.

Method 2

We used Stata 10.2 software (StataCorp, College Station, Tx) users' written function '*metamiss*'assuming random uncorrelated opposite IMORs for treatment and controls (1/2 and 2; 2 and 1/2), which is not far from what was assumed in Method 1. We assumed additional uncertainty about log(IMOR) by setting its prior standard deviation at 1, which will result in larger 95% CIs and, finally, in less weight on studies with a lot of missing data. Finally, we assumed uncorrelated IMORs of treatment and control groups when setting the '*metamiss*' command. The underlying theory and a link to download '*metamiss*' are provided in White 2008.
The results of these sensitivity meta-analyses on the primary analysis occurrence of CNV are shown and discussed.

HISTORY

Protocol first published: Issue 2, 2007

Review first published: Issue 3, 2009

Date	Event	Description
9 March 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Conceiving the review: JE

Designing the review: MBP, JE, GV

Co-ordinating the review: GV, MBP, JE

Data collection for the review

- Designing search strategies: Cochrane Eyes and Vision Group

- Undertaking searches: Cochrane Eyes and Vision Group

- Screening search results: MBP, JE

- Organising retrieval of papers: Cochrane Eyes and Vision Group

- Screening retrieved papers against inclusion criteria: MBP, JE

- Appraising quality of papers: MBP, JE, GV

- Extracting data from papers: GV, MBP

- Writing to authors of papers for additional information: JE, GV

- Obtaining and screening data on unpublished studies: JE

Data management for the review

- Entering data into RevMan: GV

Analysis of data: GV, JE, MBP

Interpretation of data

- Providing a methodological perspective: GV, JE, MBP

- Providing a clinical perspective: MBP, GV

- Providing a policy perspective: JE, MBP

- Providing a consumer perspective: AMD Consumer Panel

Writing the review: GV, MBP, JE

DECLARATIONS OF INTEREST

None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol we planned to use the risk ratio as the main effect measure but in fact we used the odds ratio because this made it easier to adjust for within-patient correlation. See section 'Measures of treatment effect'.

INDEX TERMS

Medical Subject Headings (MeSH)

Laser Coagulation [methods]; Macular Degeneration [*prevention & control]; Randomized Controlled Trials as Topic; Retinal Drusen [complications; *surgery]

MeSH check words

Humans