Photodynamic therapy for neovascular age-related macular degeneration (Review)

Wormald R, Evans JR, Smeeth LL, Henshaw KS

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2007, Issue 3

http://www.thecochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Photodynamic therapy for neovascular age-related macular degeneration

Richard Wormald[1], Jennifer R Evans[1], Liam L Smeeth[2], Katherine S Henshaw[3]

[1]Cochrane Eyes and Vision Group, ICEH, London School of Hygiene & Tropical Medicine, London, UK. [2]Department of Epidemiology, London School of Hygiene & Tropical Medicine, London, UK. [3]c/o Cochrane Eyes and Vision Group, ICEH, London School of Hygiene & Tropical Medicine, London, UK

Contact address: Richard Wormald, Cochrane Eyes and Vision Group, ICEH, London School of Hygiene & Tropical Medicine, Keppel Street, London, WC1E 7HT, UK. r.wormald@ucl.ac.uk.

Editorial group: Cochrane Eyes and Vision Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 4, 2009.
Review content assessed as up-to-date: 22 April 2009.

Citation: Wormald R, Evans JR, Smeeth LL, Henshaw KS. Photodynamic therapy for neovascular age-related macular degeneration. *Cochrane Database of Systematic Reviews* 2007, Issue 3. Art. No.: CD002030. DOI: 10.1002/14651858.CD002030.pub3.

ABSTRACT

Background

In neovascular age-related macular degeneration (AMD) new vessels grow under the retina distorting vision and leading to scarring. This is exacerbated if the blood vessels leak. Photodynamic therapy (PDT) has been investigated as a way to treat the neovascular membranes without affecting the retina.

Objectives

The aim of this review was to examine the effects of PDT in the treatment of neovascular AMD.

Search methods

We searched CENTRAL (Issue 2, 2009), MEDLINE (1966 to April 2009) and EMBASE (1980 to April 2009). We contacted experts in the field and searched the reference lists of relevant studies.

Selection criteria

We included randomised trials of PDT in people with choroidal neovascularisation due to AMD.

Data collection and analysis

Two authors independently extracted the data. Risk ratios were combined using a random-effects model after testing for heterogeneity.

Main results

Four trials (1429 participants) comparing PDT with verteporfin to PDT with 5% dextrose in water were included in this review. Participants received on average five treatments over two years. The risk ratio of losing 3 or more lines of visual acuity at 24 months comparing the intervention with the control group was 0.80 (95% confidence interval (CI) 0.73 to 0.88). The risk ratio of losing 6 or more lines of visual acuity at 24 months comparing the intervention with the control group was 0.66 (95% CI 0.56 to 0.83). The results at 12 months were similar to those at 24 months. The most serious adverse outcome, severe visual acuity decrease within one week of treatment, occurred in 11 per 1000 patients (95% CI 3 to 48). Infusion related back pain was experienced by 20 per 1000 (95% CI 6 to 70). Two further trials compared different treatment regimens: standard versus delayed light application; retreatment every two months versus every three months. Neither trial demonstrated differences in effectiveness. The overall quality of the evidence included in this review was considered to be high. Five out of the six trials were funded by the manufacturers of verteporfin.

Authors' conclusions

Photodynamic therapy in people with choroidal neovascularisation due to AMD is effective in preventing clinically significant visual loss with a relative risk reduction of approximately 20%. Modified treatment regimens have not convincingly shown increased effectiveness. There was no evidence on quality of life and little on cost.

PLAIN LANGUAGE SUMMARY

Photodynamic therapy for treating age-related macular degeneration

Photodynamic therapy involves injecting a photosensitive chemical (verteporfin) into the blood stream then radiating light onto the affected area of the retina as the chemical flows through the eye. The chemical is activated enough to treat neovascular or "wet" age-related macular degeneration by sealing the new blood vessels at the back of the eye. This review includes four randomised trials involving 1429 participants. All four trials compared verteporfin therapy to 5% dextrose water (placebo treatment). Photodynamic therapy reduces the risk of vision loss caused by "wet" age-related macular degeneration. More people treated with verteporfin also experienced improvements in vision compared to the placebo group, however, the absolute numbers experiencing vision improvement after this treatment was low (80 per 1000). A small number of people may experience acute vision loss within one week after treatment (in approximately 1 in 100 people) and infusion related back pain can occur (in approximately 1 in 50 people).

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

Photodynamic therapy with verteporfin compared to photodynamic therapy with 5% dextrose in water for neovascular age-related macular degeneration

Patient or population: patients with neovascular age-related macular degeneration
Settings: hospital or office
Intervention: photodynamic therapy with verteporfin
Comparison: photodynamic therapy with 5% dextrose in water

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk photodynamic therapy with 5% dextrose in water	Corresponding risk photodynamic therapy with verteporfin				
Loss of 3 or more lines (15 or more letters) visual acuity ETDRS chart Follow-up: 24 months	**609 per 1000**	**487 per 1000** (445 to 536)	**RR 0.8** (0.73 to 0.88)	1381 (4 studies)	⊕⊕⊕⊕ **high**	
Loss of 6 or more lines (30 or more letters) visual acuity ETDRS chart Follow-up: 24 months	**333 per 1000**	**220 per 1000** (176 to 276)	**RR 0.66** (0.53 to 0.83)	1381 (4 studies)	⊕⊕⊕⊕ **high**	
Gain of 3 or more lines (15 or more letters) Follow-up: 24 months	**36 per 1000**	**80 per 1000** (43 to 151)	**RR 2.23** (1.19 to 4.19)	941 (3 studies)	⊕⊕⊕⊕ **high**	
Adverse effects: acute severe visual acuity decrease Follow-up: 7 days	**3 per 1000**	**11 per 1000** (3 to 48)	**RR 3.75** (0.87 to 16.12)	1075 (3 studies)	⊕⊕⊕○ **moderate**[1]	

Adverse effects: infusion-related back pain	**2 per 1000**	**20 per 1000** (6 to 70)	**RR 9.93** (2.82 to 35.02)	1439 (4 studies)	⊕⊕⊕⊕ **high**[2]

*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; **RR:** Risk 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] Serious imprecision: confidence intervals include 1 (no effect).
[2] Not downgraded for imprecision: confidence intervals wide however do not include 1 (no effect).

BACKGROUND

Description of the condition

Age-related macular degeneration (AMD) is a disease affecting the macula, the central area of the retina. The disease is defined as degeneration of the macula in older people (aged over 50) with no other apparent cause for the degeneration.

There are several signs in the retina that are associated with increasing age and increased risk of developing AMD. These signs, known as age-related maculopathy, include the presence of drusen (yellow spots beneath the retina) and pigmentary disturbance. In general age-related maculopathy is not associated with visual loss. Some people with age-related maculopathy will go on to develop AMD.

There are two main types of AMD. In geographic atrophy (dry) AMD, the retinal pigment epithelium is lost completely in localised areas. In neovascular (wet) AMD, sub-retinal neovascular membranes (new blood vessels) develop beneath the retina. These are associated with scarring of the retina that affects vision. The new vessels can leak causing haemorrhage that leads to larger scars or macular oedema and significant loss of vision. This review was concerned with treatment for neovascular AMD.

Sub-retinal neovascular membranes are defined as classic or occult according to their appearance on fluorescein angiography, in which fluorescent dye is injected intravenously and photographed as it passes through the blood vessels of the eye. Classic membranes are clearly delineated and leak fluorescein uniformly. Occult membranes are often hidden or their extent is hard to delineate, and fluorescein leakage is patchy. It is thought that these two angiographic patterns reflect the different extent to which the vessels have penetrated the retinal pigment epithelium, occult vessels lying underneath the retinal pigment epithelium. Some lesions may have both classic and occult components.

Description of the intervention

Trials have shown that early laser photocoagulation of classic extrafoveal membranes (those not directly underneath the fovea at the centre of the macula) could delay the loss of vision in a small number of patients (MPS 1994). However, most patients present with subfoveal membranes, and whilst photocoagulation can limit the extent of the subsequent visual loss, it causes immediate loss of central vision due to the concurrent destruction of the overlying retina.

Photodynamic therapy, originally used in the treatment of cancer, has been investigated as a way to treat the neovascular membranes without affecting the retina. Photoreactive chemicals are injected into the patient and irradiated with light as they pass through the neovascular membranes.

How the intervention might work

When the chemicals are activated, they emit free radicals that seal up the blood vessels. However, this light is not strong enough to cause damage to the overlying retina.

Why it is important to do this review

It is important to do this review to obtain an overall estimate of the effectiveness of this treatment and to assess any harmful effects.

OBJECTIVES

The aim of this review was to examine the effects of PDT in the treatment of neovascular AMD.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs).

Types of participants

We included trials in which participants were people with neovascular AMD as defined by the study investigators.

Types of interventions

We included any study in which PDT was compared to another treatment, placebo or no treatment.

Types of outcome measures

Primary outcomes

The primary outcome for this review was prevention of visual loss. Any well-defined outcome based on visual acuity was used depending on the way in which authors presented trial data. Other validated measures of visual loss, such as contrast sensitivity, were used where available.

Secondary outcomes

The secondary outcomes for this review were:

- new vessel growth;
- quality of life measures - any validated measurement scale which aims to measure the impact of visual function loss on quality of life of participants;
- any adverse outcomes as reported in trials.

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 2, 2009), MEDLINE (January 1950 to April 2009) and EMBASE (January 1980 to April 2009). There were no language or date restrictions in the search for trials. The electronic databases were last searched on 23 April 2009.

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

Searching other resources

We used the Science Citation Index to search for reports that cited relevant study reports. We contacted experts in the field for information about further trials and we searched the reference lists of relevant studies for further trial reports.

Data collection and analysis

Selection of studies

Two authors independently scanned the titles and abstracts resulting from the electronic searches. We obtained full copies of all potentially or definitely relevant articles. Two review authors assessed the full copies according to the 'Criteria for considering studies for this review'. Only articles meeting these criteria were assessed for quality.

Data extraction and management

Two authors independently extracted data using a form developed by the Cochrane Eyes and Vision Group (available from the editorial base). We resolved discrepancies by discussion. Two review authors independently entered data into RevMan and we checked any inconsistencies between the two against the study report.

For updates in Revman 5 both authors extracted data independently. Data were entered into Revman 5 by one author (RW) and checked by another (JE).

Assessment of risk of bias in included studies

For the original review, two authors independently assessed study quality according to methods set out in Section 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2006). The authors were not masked to any trial details during the assessment. Four parameters of quality were considered: allocation concealment and method of allocation to treatment, masking of providers and recipients of care, masking of outcome assessment, and completeness of follow up. Each parameter of trial quality was graded: A (adequate); B (unclear); C (inadequate). Disagreement between the review authors on assessments was resolved by discussion. We contacted the trial authors for clarification on any parameter graded B and we excluded any trial scoring C on allocation concealment.

For the update in 2009 we used the Cochrane Collaboration tool for assessing the risk of bias (Higgins 2008).

Measures of treatment effect

Our measure of treatment effect is the risk ratio.

Unit of analysis issues

In all the included trials, people were randomised to treatment and one study eye, that received treatment or placebo, was identified.

Dealing with missing data

Three out of the four trials contributing to the main analyses in this review imputed missing data by using the "last observation carried forward" method. This method can give unpredictable results and is not underpinned by statistical theory (www.missingdata.org.uk, accessed June 23rd 2009). This made it difficult for us to do any further assessment of this issue.

Assessment of heterogeneity

We looked at the forest plots to see the extent to which the confidence intervals of the individual studies overlapped. We also considered the Chi^2 test for heterogeneity and I^2 value.

Assessment of reporting biases

Currently there are not enough trials included in this review to assess publication bias. We did an "outcome reporting grid" to assess the extent to which selective outcome reporting might have occurred.

Data synthesis

We pooled the data from the individual studies using a random-effects model.

Subgroup analysis and investigation of heterogeneity

We did not plan any subgroup analyses in the protocol for this review. However, following on from the subgroup analyses presented in TAP 1999, one key issue is whether the effect of treatment is different depending on the type of choroidal neovascularisation lesion (classic or occult).

Sensitivity analysis

In our protocol we planned to determine the effect of excluding studies at high risk of bias. All studies included in this review were considered to be at low risk of bias.

RESULTS

Description of studies

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

Results of the search

Details of the original searches are found in Appendix 4.

For the current update the search was conducted in April 2009. This search found 94 new references and identified one new trial (Schmidt-Erfurth 2008) for inclusion in the review. One further unpublished trial was identified by a colleague who noticed that its results were available on the European Medicines Agency (EMEA) website (VIO 2007). While trying to locate a current email address for the investigators on PubMed we found the publication for this study which was published in June 2009.

The VER 2004, Valio 2007 and Schmidt-Erfurth 2008 trials were all trials comparing modifications of the TAP treatment protocol to the standard and are included here for completeness. VER 2004 remains in 'Characteristics of studies awaiting classification' until we can retrieve and translate the trial report published in German (Stur 2004). The gist of the findings of this study are available from two published (not peer reviewed) abstracts from Association for Research in Vision and Ophthalmology meetings (Stur 2001 and Stur 2005).

Additional reports from TAP 1999 and VIP 2001 trials were identified (Kaiser 2006; Pieramici 2006) and the report from Japan 2003 study was identified. This was an uncontrolled case series report and therefore not included in the review except as a comment on evidence of effectiveness of PDT in other populations. The additional reports from TAP and VIP provide longer term outcomes at five years for people with predominantly classic lesions who remained in the studies (Kaiser 2006). These constitute a relatively small proportion of the original study populations. There is a report from the placebo arm of the VIP study reporting on the natural history of untreated lesions (Pieramici 2006), occult lesions which evolve into predominantly classic lesions. None of these reports provide additional evidence of effectiveness of PDT which could be included in the review.

Included studies

Below is a summary of the included studies. Details can be found in the 'Characteristics of included studies' table.

TAP 1999 was a multicentre study investigating the safety and effectiveness of verteporfin (Visudyne; CIBA Vision Corp, USA). It was conducted in 22 ophthalmology practices in Europe and North America. Participants were people with subfoveal choroidal neovascularisation (CNV) caused by age-related macular degeneration. The majority of participants were white (98%) with a mean age of 75 years. TAP 1999 was originally devised as two concurrent trials in order to comply with regulatory agency requirements. The study protocols were identical. Ten of the clinical centres were assigned to study A and 12 to study B. As the results of the trials were similar and the investigators analysed and presented the data as one trial, we have also assessed it as one trial.

The VIP 2001 study was very similar to the TAP 1999 study. It was conducted in 28 practices, most of whom had also participated in TAP 1999. As for TAP 1999, the majority of participants were white (98%) with a mean age of 75 years.

In both trials verteporfin (6 mg/m^2 body surface area) was compared to placebo (5% dextrose in water) administered via intravenous infusion of 30 ml over 10 minutes. This was followed after 15 minutes by application of 83 seconds of laser light at 689 nm delivered 50 joules/cm^2 at an intensity of 600 mW/cm^2 using a spot size with a diameter 1000 microns larger than the greatest linear dimension of the CNV lesion.

Participants in TAP 1999 were reviewed every three months when visual acuity was measured and repeat fluorescein angiography performed. If the trial surgeon judged a recurrence of the membrane to be present or a persistence of the previous lesion, then repeat treatment was undertaken. In the phase one and two studies it was concluded that up to five treatments were necessary to stabilise the situation (Miller 1999; Schmidt-Erfurth 1999). In the first year a mean of 3.4 treatments were delivered to the treatment group and 3.7 to the control group. In the second year a mean of 2.2 treatments were delivered to the treatment group and 2.8 to the controls group.

Visual acuity was measured in VIP 2001 at 12 and 24 months. The report of the study did not indicate the mean number of treatments delivered for all participants. However, in the subgroup with occult CNV (76% of all participants) 3.1 treatments were given in the treatment group and 3.5 in the control group. In the second year, 1.8 and 2.4 treatments were given in the verteporfin and control groups respectively.

There are a total of 15 papers published on the TAP and VIP trials which are summarised briefly (Table 1).

The VIM 2005 trial randomised participants with minimally classic subfoveal choroidal neovascularisation due to age-related macular degeneration to verteporfin injections or placebo in a ratio 2:1. All participants were also randomised to two intensities of light illumination after verteporfin injection, either standard fluence equivalent to 50 Joules/cm^2 or reduced fluence of 25 Joules/cm^2. This was based on the idea that a less intense illumination may lead to less tissue damage and as a consequence less inflammation and potential sight loss following the treatments. The placebo treated group received an average of three treatments while the verteporfin treated SF group had an average of 2.9 and the RF group, 3.1 treatments in the first 12 months. In the second 12 month period, some placebo treated participants received treatment with verteporfin because their lesion converted from minimally classic to predominantly classic. This was an ethical requirement of the study design because PDT had been previously shown to be effective for predominantly classic lesions.

While engaged in the latest update (2009), a published report of the VIO 2007 appeared. Though details of the study had been posted on an EMEA website, we lacked the details of the study methodology and there was no evidence of formal peer review. With the details provided in the publication, it was clear to the review authors that it should be included in the review. The trial randomised more than 360 people with occult subretinal neovascularisation to verteporfin or placebo (2:1 ratio) in 43 centres across North America.

The report suggests a similar protocol to the VIP 2001 was used.

The Valio 2007 trial randomised 60 patients 1:1 to either Altered Light treatment using delayed light after Visudyne in Occult AMD or the standard TAP 1999 protocol. There was no placebo arm.

The Schmidt-Erfurth 2008 trial randomised 203 patients with predominantly classic choroidal neovascularization (CNV) due to AMD. During the first six months of treatment, patients received treatment either every two or three months. After six months, both groups underwent retreatment every three months for as long as CNV activity was documented.

The VER 2004 trial had a similar design and randomised 320 people with predominantly classic CNV to early retreatment every 1.5 months or every three months in the first six months of treatment. This study is awaiting classification.

Risk of bias in included studies

Risk of Bias tables are now provided for all included studies. See 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.

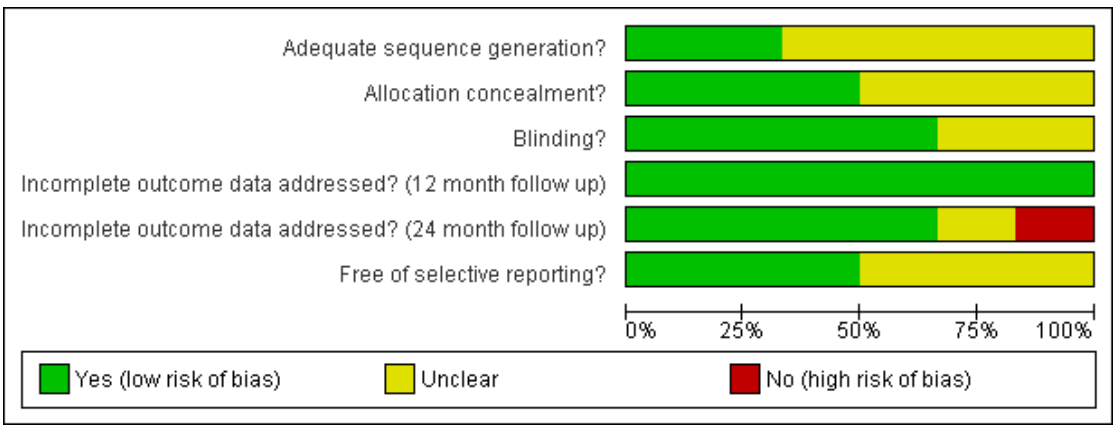
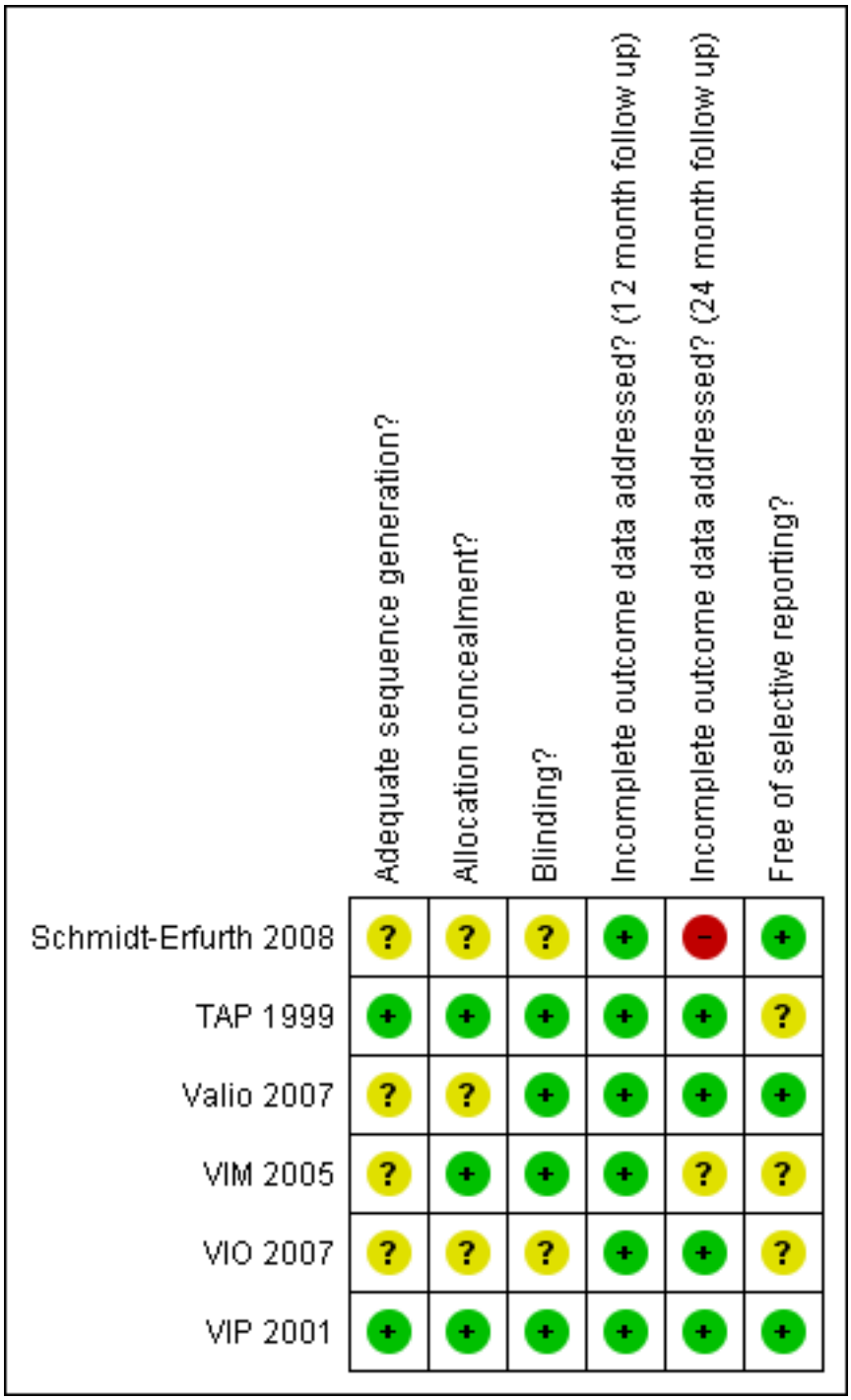


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Both TAP 1999 and VIP 2001 were high quality studies with a very similar study design.

Allocation of treatment group was by opaque serially-numbered sealed envelopes and was stratified by clinical centre. The baseline characteristics of the participants by treatment group were published. The groups were well balanced with respect to a variety of demographic and clinical variables. Only one eye per person was treated.

Reasonable attempts were made to mask the ophthalmologist, participant, vision examiner and Photograph Reading Center personnel to the treatment assigned. As verteporfin and placebo were different colours (green versus colourless), the solutions and the intravenous tubing were covered with foil. The fundus appearance does not change during treatment to indicate whether verteporfin or placebo had been infused. There is no other physical evidence of treatment as verteporfin dye is excreted in the faeces and does not cause any colour change, and does not alter the colour of the skin or urine. It was therefore unlikely that participants were aware of their treatment status. In TAP 1999 the study investigators reported two instances where the participants were unmasked, and four cases where the ophthalmologists were unmasked, having noted a green solution.

Rates of follow up were high in both studies. In TAP 1999 94% were seen at 12 months and 87% at 24 months. Follow up was similar between the two treatment groups. The analysis was intention-to-treat. Missing data were imputed using the last observation carry forward method. There were a number of subgroup analyses. These were specified in principle in the protocol although it is unclear if the specific details of the subgroups to be considered were specified a priori. In VIP 2001 93% were seen at 12 months and 86% at 24 months. All participants were included in the analyses and missing values were imputed using the method of last observation carried forward.

VIM 2005 also appears to be of high quality though there is not a specific statement about allocation concealment in the study report. It is probable, however, that this was properly done since this was the case in all the other trials conducted by this group. Masking of participants, outcome assessors was maintained. The ophthalmologist applying the laser light could not be masked to the fluence allocation but did not know the verteporfin treatment status.

The VIO 2007 trial is reported as having used a similar protocol to the VIP 2001 although there is no specific information about randomisation methods or allocation concealment.

Lack of detailed reports mean that uncertainty remains about bias in Valio 2007 and Schmidt-Erfurth 2008 (see risk of bias tables).

Effects of interventions

See: **Summary of findings for the main comparison** Photodynamic therapy with verteporfin compared to photodynamic therapy with 5% dextrose in water for neovascular age-related macular degeneration

The realistic aim of PDT is to slow progression of AMD, not to produce normal vision. In the original review, outcomes were therefore expressed as risks of a poor outcome, rather than as improvements in vision. However, for the update in 2009, given the improvements in vision available with other treatments, we felt that data on the outcome "gain in vision" would be useful for consumers in particular to compare the effects of PDT with other available treatments.

Overall analysis (Table 2)

Loss of 3 or more lines of visual acuity

Four trials (1352 participants) provided data on this outcome. At 12 months the pooled risk ratio (RR) of losing 3 or more lines of visual acuity was 0.78 (95% confidence interval (CI) 0.67 to 0.91) (Figure 3). At 24 months the pooled RR was 0.80 (95% CI 0.73 to 0.88) (Figure 4). The results were reasonably consistent. All estimates were in the direction of benefit and confidence intervals overlapped.The Chi^2 test for heterogeneity was P = 0.23 and I^2 was 30%.

Figure 3. Forest plot of comparison: 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO, outcome: 1.1 Loss of 3 or more lines (15 or more letters) visual acuity at 12 months.

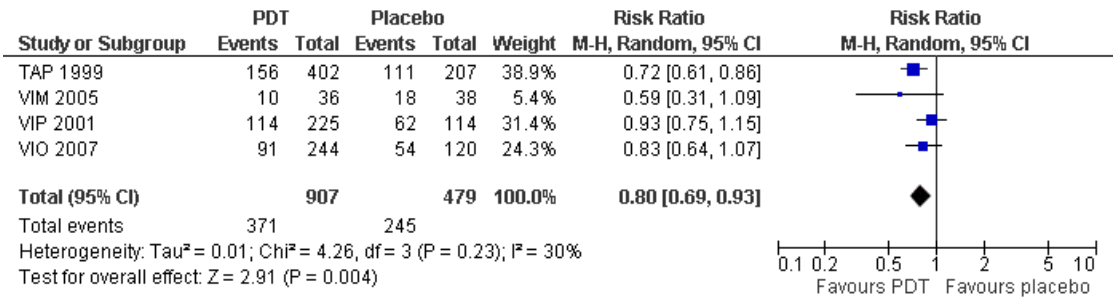
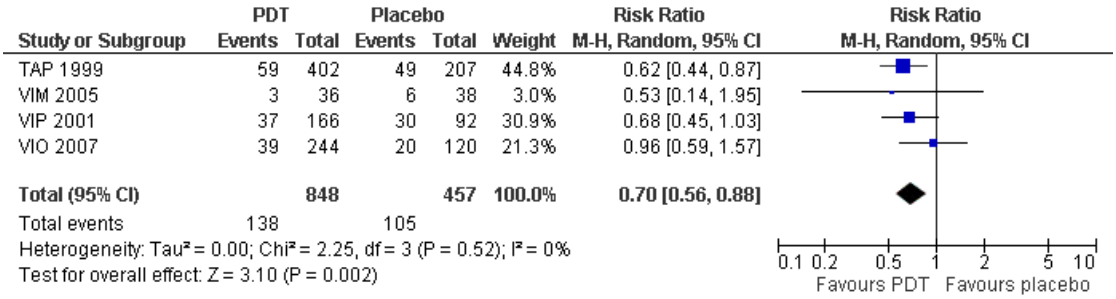


Figure 4. Forest plot of comparison: 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO, outcome: 1.3 Loss of 6 or more lines (30 or more letters) visual acuity at 12 months.



Loss of 6 or more lines of visual acuity

At 12 months the RR of losing 6 or more lines of visual acuity was 0.70 (95% CI 0.56 to 0.88) (Figure 5). At 24 months the pooled RR was 0.66 (95% CI 0.53 to 0.83) (Figure 6). As before the results of the different trials were consistent (Chi^2 P = 0.65, I^2 = 0%).

Figure 5. Forest plot of comparison: 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO, outcome: 1.2 Loss of 3 or more lines (15 or more letters) visual acuity at 24 months.

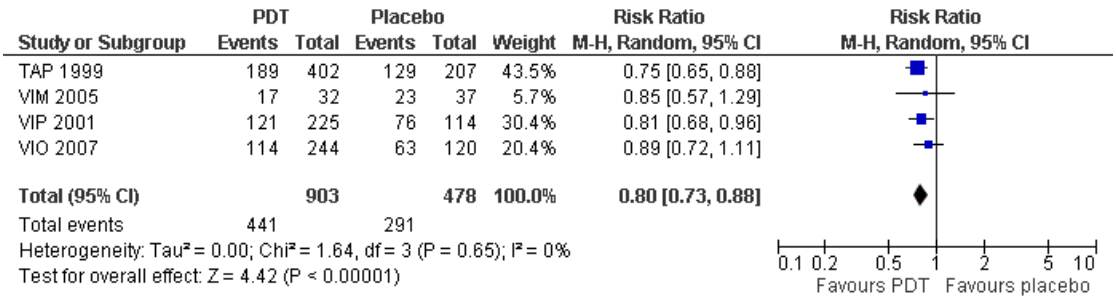
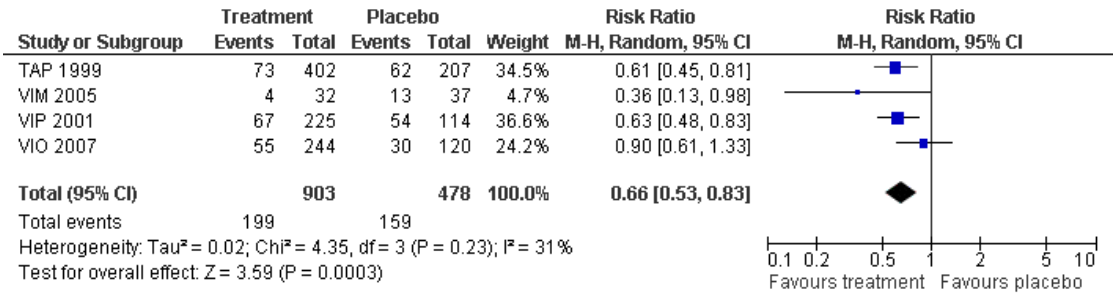


Figure 6. Forest plot of comparison: 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO, outcome: 1.4 Loss of 6 or more lines (30 or more letters) visual acuity at 24 months.



Gain of 3 or more lines of visual acuity

Gain in visual acuity was not experienced commonly in the study cohort - approximately 5% of participants at 12 months and 10% at 24 months gained 3 or more lines of visual acuity. However, gain in vision was experienced more often by the treatment group than the control group. The pooled RR at 12 months was 2.19 (95% CI 0.99 to 4.83) (Figure 7) and the pooled RR at 24 months was 2.55 (95% CI 1.31 to 4.99) (Figure 8). The results of the different trials were consistent (I^2 = 0%).

Figure 7. Forest plot of comparison: 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO, outcome: 1.7 Gain of 3 or more lines (15 or more letters) of visual acuity at 12 months.

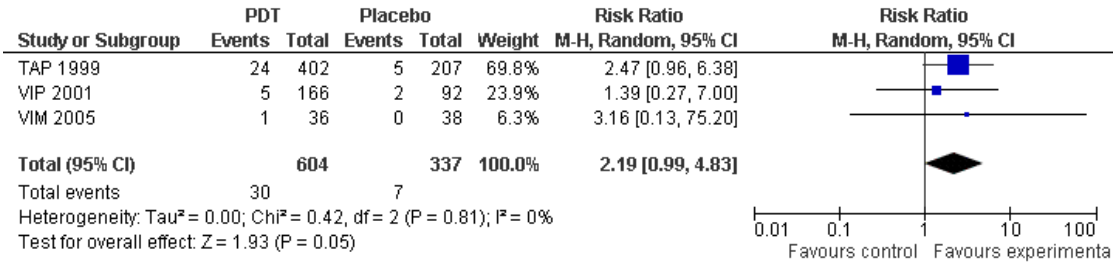
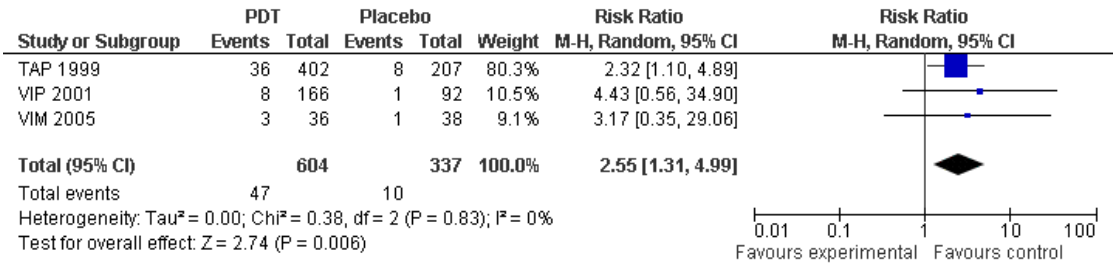


Figure 8. Forest plot of comparison: 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO, outcome: 1.8 Gain of 3 or more lines (15 or more letters) of visual acuity at 24 months.



Mean number of lines lost

Data on visual acuity as a continuous outcome was reported but there were limited data on measures of variability so it was not possible to pool these data. The data available are presented in Table 3 and Table 4.

On average participants in these studies lost vision over 12 and 24 months (Table 3). In all four studies, the verteporfin treated group lost fewer letters of visual acuity and average final visual acuity scores were better in the verteporfin groups (Table 4). The average difference between the groups ranged from two to 10 letters visual acuity.

Subgroup analyses

We did not plan any subgroup analyses in our protocol. However, TAP 1999 found differences in treatment effect depending on how much of the lesion was composed of classic CNV. We therefore have replicated their subgroup analyses using data from other trials (Table 5; Figure 9; Figure 10).

Figure 9. Forest plot of comparison: 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO, outcome: 1.9 Subgroup analysis: lesion area composed of classic CNV. Loss of 3 or more lines at 12 months.

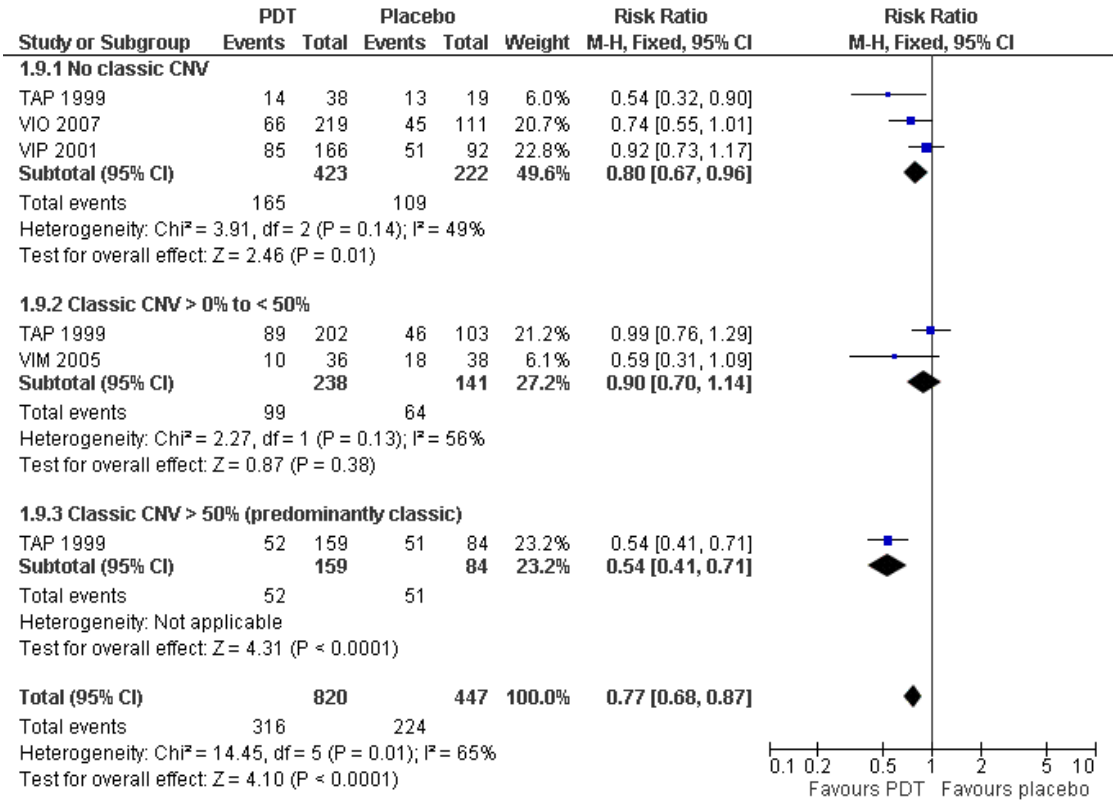
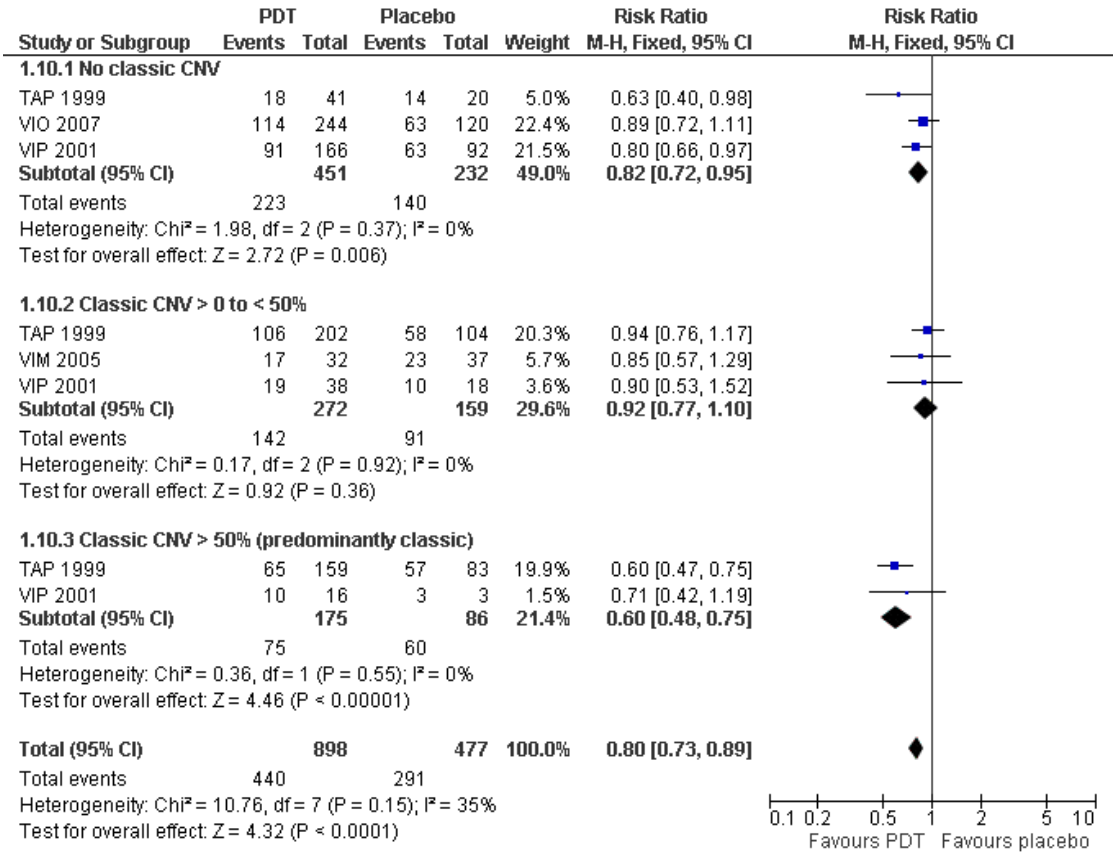


Figure 10. Forest plot of comparison: 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO, outcome: 1.10 Subgroup analysis: lesion area composed of classic CNV. Loss of 3 or more lines at 24 months.



There was some evidence of a stronger treatment effect in people with lesion composed of 50% or more classic CNV "predominantly classic" (pooled RR for loss of 3 or more lines of visual acuity at 12 months 0.54, 95% CI 0.41 to 0.71) (Figure 9). This effect was not significantly different from the effect seen in people who had no evidence of classic CNV (pooled RR at 12 months 0.80, 95% CI 0.67 to 0.96). The least treatment effect seemed to be observed in the middle group with some classic CNV "minimally classic" (pooled RR 0.90, 95% CI 0.70 to 1.14). This was statistically significantly different from the result in the "predominantly classic" group but not the "no classic" group. Similar results were seen at 24 months (Figure 10).

Evidence of occult choroidal neovascularisation

In TAP 1999 the RRs of losing 3 or more lines of visual acuity at 12 months were 0.90 if occult CNV was present (95% CI 0.73 to 1.11) and 0.34 if occult CNV was absent (95% CI 0.22 to 0.51). At 24 months, the RRs were 0.88 (95% CI 0.74 to 1.04) and 0.42 (95% CI 0.30 to 0.60) respectively. The test for effect modification between these two subgroups was significant. Neither the 95% confidence intervals nor the 99% confidence intervals for these two subgroups overlap.

Lesion area composed of classic choroidal neovascularisation

In TAP 1999, the proportion of the lesion comprised of classic CNV was estimated as 0%; greater than 0% but less than 50%; greater than 50%. The proportion was unknown in four participants (three in the treatment group and one in the control group). The subgroup analyses were therefore based on a total of 399 eyes. In VIP 2001, the majority of the participants (76%) had "occult with no classic CNV". An additional 56 eyes had some classic CNV (less than 50% but greater than 0% as above). Only 19 eyes had predominantly classic CNV.

In VIO 2007, all the participants had occult neovascularisation so could be included with the subgroup analyses from TAP 1999 of patients with no classic lesions and the equivalent subgroup in VIP 2001.

The pooled RR for losing 3 or more lines of visual acuity at 12 months for the group with 0% CNV was 0.77 [0.61, 0.97]. Including patients from VIO 2007 greatly reduces the effect estimate by more than 20% from 0.54 if just the TAP 1999 trial patients are included. Results for 3 or more lines lost at 12 months were not reported for the other two subgroups in the VIP 2001 study. We included the participants from VIM 2005 from the placebo and standard fluence intervention arm with TAP 1999 for the minimally classic subgroup (0 to 50% classic). The RRs for losing 3 or more lines of visual acuity at 12 months in people with more than 0% but less than 50% CNV was 0.90 (95% CI 0.70 to 1.14) and 0.54 for greater than 50% CNV - participants from TAP 1999 only - (95% CI 0.41 to 0.71) (*see* Analysis 1.9).

At 24 months the pooled RRs for losing 3 or more lines of visual acuity were 0.77 (95% CI 0.64 to 0.92), 0.93 (95% CI 0.77 to 1.14) and 0.60 (95% CI 0.48 to 0.75) respectively (*see* Analysis 1.10). Adding VIM 2005 to the minimally classic group (standard fluence only) did not materially influence the evidence of ineffectiveness of treatment in this group.

These results suggest there was a reduction in the risk of loss of vision when classic CNV was absent or when greater than 50% of the lesion was comprised of classic CNV. However, there was very little reduction in risk when between 0% and 50% of the lesion was comprised of classic CNV. However, the test for effect modification between these three subgroups was not statistically significant (P = 0.066).

Other primary outcomes

Contrast sensitivity

This outcome from the TAP trial was reported by Rubin 2002. This was measured in participants at baseline and at three-monthly intervals after refraction and measurement of best-corrected visual acuity. Contrast sensitivity was measured using the Pelli Robson chart (no. 7002251 Clement Clarke, Columbus Ohio). The measurements were made using a standard protocol and illumination and outcomes were categorised in terms of more than six or more than 15 letters lost since baseline. A higher proportion of those treated with placebo lost both more than six and 15 letters of contrast sensitivity at 12 and 24 months. The RR of losing 6 lines of contrast sensitivity by 24 months was 0.47 (95% CI 0.37 to 0.60) in the PDT group compared to placebo (*see* Analysis 1.5). For 15 letters the RR was 0.58 (95% CI 0.34 to 0.98) (*see* Analysis 1.6).

Central visual field function

This was reported by Schmidt-Erfurth (Schmidt-Erfurth 2004) for 46 participants of the TAP trial based in Germany. Participants in this centre had various additional investigations reported including Scanning Laser Ophthalmoscopic perimetry of the macular in order to measure the size of the central scotoma in treated and placebo groups. This was reported as mean area in mm^2 The mean area of the absolute scotoma increased in both groups but significantly more the placebo arm (2.5 mm^2 baseline to 7.3 mm^2 at 24 months in the treated group compared to 2.7 mm^2 at baseline to 31.5 mm^2 at 24 months in the placebo group). Similar findings were reported for differences in the increase in size of the relative scotoma between groups. These differences were reported as statistically significant at the level of P < 0.001 though neither standard errors of these means nor 95% confidence intervals are provided.

Secondary outcomes

Neovascular membrane morphology

Schmidt-Erfurth's group also reported on the outcome of Confocal Indocyanine Green Angiography on her subgroup of the TAP trial participants in Germany (Schmidt-Erfurth 2003); in this case outcomes were reported on 60 participants. It is not clear why there is a discrepancy between the 60 participants in this analysis and 46 undergoing measurement of central scotoma as described above. Presumably 14 participants did not have SLO perimetry but did have ICG angiography.

This paper reports outcomes in terms of the mean size of the neovascular membrane in mm^2. Forty eyes received PDT and 20 received placebo. Baseline mean areas of ICG leakage were 3.9 mm^2 for the PDT group and 2.8 mm^2 for the placebo eyes. This reduced to 3.0 mm^2 in the treated group at 24 months compared to a growth to 9.6 mm^2 in placebo eyes. This difference is reported as highly significant by P value (= 0.008) but no standard errors or confidence limits are provided apart from graphically represented error bars which are not specified in the legend.

Quality of life

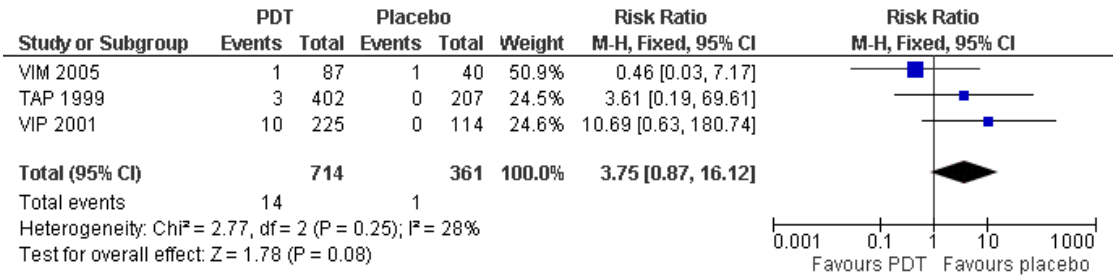
Evidence of efficacy as described above has still not been substantiated by any quality of life outcomes reported from the TAP or VIP trials.

Adverse effects

The risk of severe and profound visual loss became clearer in later reports; two reports from the TAP and VIP investigators (Arnold 2004; Azab 2004) and a large phase 4 open-label study reporting on the outcomes of verteporfin PDT in 4435 patients called the VAM study (Bressler 2004b).

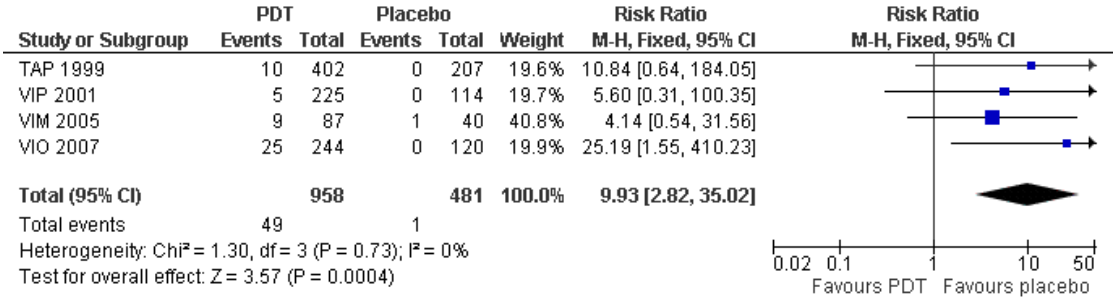
Arnold 2004 focuses on the occurrence of acute severe visual acuity decrease (ASVAD). This was defined as at least a 20 letter loss (equivalent to four lines) within seven days after treatment. Even though this paper reports this outcome from two RCTs they describe the study as an observational case series and a fairly detailed account is given of 15 events in 14 eyes. One of these was later judged as unlikely to be due to PDT. All but two events occurred shortly after the first treatment and only in the treated arm. Three of these events occurred in the TAP trial and ten in the VIP. All 13 events occurred within three days of treatment. The absolute risk difference for both studies is 0.02 (95% confidence interval 0.01 to 0.03) (Figure 11).

Figure 11. Forest plot of comparison: 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO, outcome: 1.11 Adverse effects: acute severe visual acuity decrease.



Azab 2004 provides these data in the context of all other adverse events reported for the two trials. This report is described as a meta-analysis though data are only combined for the two trials for systemic side effects. The authors found that only visual disturbances including ASVAD, injection site reactions, photosensitivity reactions and infusion-related back pain occurred with greater frequency in the treated participants (Figure 12).

Figure 12. Forest plot of comparison: 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO, outcome: 1.14 Adverse effects: infusion-related back pain.



The VAM study (Bressler 2004b reports on outcomes from a larger number of patients recruited from 222 centres in North America (10 times the number in TAP) between September 1999 and June 2000 when the verteporfin became commercially available. Maximum follow up was therefore nine months. About half the study population had six months follow up. This study provides further information on the risk of adverse events outside a RCT setting but as this is an open label study with no comparator group; RRs or risk differences (and hence number needed to harm (NNH)) cannot be calculated. One series from the Wilmer (Do 2004) reports this outcome in 52 patients but unfortunately the denominator was not given (the overall number of persons and eyes receiving PDT). Vision loss can be profound is this group and data from TAP and VIP suggest it may be more likely to occur in people with better initial visual acuity.

Reports of visual disturbance (reports of "abnormal vision", "decreased vision" and visual field defect) occurred in one in every four people taking part in the TAP 1999 and VIP 2001 studies. This is perhaps unsurprising as participants had neovascular AMD. However, people treated with verteporfin were more likely to report visual disturbance (pooled RR 1.61, 95% CI 1.24 to 2.09) (Analysis 1.12). Presumably this visual disturbance must have been reasonably transient as visual outcomes at 12 and 24 months were better in the treatment group. 2.4% of people treated with verteporfin experienced infusion-related back pain and 2.4%

had photosensitivity reactions. Problems with the injection site occurred in 13.1% of people treated with verteporfin compared to 5.6% people in the control group. Few allergic reactions were seen and these were equally likely in treatment and control groups. Adding data from VIM 2005 for adverse outcomes did not materially affect the risk estimates.

The VIM 2005 study findings seem to suggest that the reduced fluence treatment is as or more effective than standard fluence and that both are better than placebo for relatively small minimally classic lesions that were selected for the trial. These smaller lesions were selected for the trial because retrospective analysis (or post hoc) of the 0 to 50% minimally classic group in the TAP and VIP studies suggested smaller lesions had a better outcome to the larger ones. Waiting for minimally classic to become predominantly classic did not appear to improve the outcome and the authors suggest the trial provides evidence for earlier treatment of smaller minimally classic lesions with verteporfin though they are less certain about the benefit of lower fluence and suggest the need for more evidence.

Economic outcomes

No economic analyses have been reported from either TAP, VIP or VIM but a number of separate economic evaluations have now been published.

DISCUSSION

The absence of any effective treatment for neovascular AMD (except for the few in whom laser photocoagulation works) meant that there was intense interest in PDT for the many millions of sufferers of the disease worldwide when it was first made available. With the arrival of the anti vascular endothelial growth factor antibody preparations, the interest in PDT is waning though its use may continue in combination with these and intraocular steroids. Unfortunately PDT, like photocoagulation, can be effective only during the proliferative stage of the disease while the neovascular process is active. It cannot have any effect once sight is lost and the scarring process is complete. Therefore, like so many other degenerative processes of the neuroretina, nothing can be done to restore function once the damage is done. Most sufferers of the condition have established sight loss and, for these, the publicity surrounding the launch of Visudyne (verteporfin) will have raised false hopes just as the new agents now available will do. This review indicates that for people with active neovascular disease photodynamic therapy can prevent vision loss. This is corroborated by additional outcome measures such as contrast sensitivity, size of central scotoma and neovascular membrane dimensions.

A key question is how long the effect of treatment will last and whether repeated treatments would be required in the longer term. This review indicates that treatment benefits last for at least two years. An open-label extension of the TAP 1999 study indicated that vision outcomes remained relatively stable from 24 to 48 months (TAP 2002). Report of five year outcomes suggest it remains stable in those who remained in follow up (Kaiser 2006).

Another important issue is how many presenting patients will benefit from photodynamic therapy. In addition to the problem of accessing specialist services in time, there is the question of the proportion of lesions that will actually be treatable. The evidence reported here suggests that purely classic neovascular membranes do better. Subgroup analysis of the TAP 1999 study suggested that PDT is less effective when occult CNV is present. Occult vessels mean that the extent of the membrane cannot be clearly defined and so it is not surprising that treatment is found to be less effective because the laser cannot be aimed at the entire membrane. However, the VIP 2001 study recruited mostly patients with occult neovascularisation and demonstrated a treatment benefit of photodynamic therapy at 12 and 24 months. However, the VIO 2007 trial also selected patients with occult CNV and did not demonstrate a significant effect of treatment but combining all the patients with occult lesions from TAP, VIP and VIO showed a small significant effect. Pooled analysis of the TAP 1999 and VIP 2001 studies in this review showed no statistically significant difference in treatment effects in subgroups defined by the presence or absence of classic CNV. This observation has been noted by other authors. For example, Meads 2004 casts serious doubt on the validity of the subgroup analyses.

Subsequent reports of exploratory analyses have been published from the TAP trials (Bressler 2002) and from the TAP and VIP trials (Blinder 2003) which find only lesion size (the smaller lesions do better) and poorer presenting acuity (perhaps less vision to lose) were predictors of better outcome. One other report from TAP (Bressler 2004a) examined the natural history of minimally classic lesions which had a poorer outcome in the TAP trial treated group. Of the 207 randomised to the placebo group 98 had minimally classic lesions of which 39 progressed to become predominantly classic (21 of these within three months). The suggestion here is that it might be advisable to wait for minimally classic lesions to progress to become predominantly classic so that potential effectiveness of PDT might be greater. The authors imply that this need not necessarily be at the expense of allowing the lesion to become very large or indeed the vision to deteriorate. A more recent report from the VIP trial comes to similar conclusions (Pieramici 2006).

We are not told in the available reports the extent to which clinicians and indeed the trial Photograph Reading Center personnel were able to agree about the subgroup classification of classic or occult lesions. It is likely that there is much variation in opinion on this. The necessary skill to report on fluorescein angiograms and recognise different lesion types is highly refined. Most experts assert that stereo images are required to be able to locate the position in depth of staining or fluorescein leaks. Stereophotography requires either a dedicated camera equipped to take simultaneous stereo images or a skilled photographer who takes sequential im-

ages slightly laterally displaced from one another, providing a non-simultaneous or pseudo-stereo image. However, the guidelines for reporting angiograms and data on interobserver agreement have now been published for the TAP and VIP trials (Barbazetto 2003). A lot of detail is given on reporting guidelines but the information on agreement is somewhat brief though reported kappa values for the main subgroup criteria were good. This was based on a 10% subsample of graded photographs. Another independent study has reported on agreement within and between 16 different specialists in Germany (Holz 2003) for the same angiographic criteria as for TAP and VIP. Agreement was not quite so good for both intra and interobserver agreement as for the reporting centre for the trials but was acceptable nevertheless.

The natural history of the growth of subretinal membranes varies from individual to individual. They may be aggressive and rapidly growing or indolent. This is the kind of individual factor that will influence the likelihood of a patient being in a position to benefit from this treatment. The trial report does not comment on the proportion of participants presenting to the trial centres that had treatable lesions. The verbal estimate from one trialist was approximately 25% and from another expert between 5% and 7%. This is of crucial importance in estimating the impact of this new treatment on healthcare budgets.

Age-related macular degeneration is a bilateral disease although one eye is usually affected before the other. With a lesion present in one eye, the annual cumulative incidence of a lesion in the second eye is estimated to be about 15%. Clinicians now commonly advise patients with a lesion in one eye to be watchful for the onset of symptoms in the second eye and to present as soon as those symptoms are noticed to improve the chances of catching the lesion in the second eye in time. This often entails the provision of an Amsler grid, a simple chart on which a number of gridlines are printed around a central fixation spot. The patient is instructed to examine the grid and to look for focal distortion of the lines in the grid which would indicate local elevation of the retina as a result of the growth of an underlying membrane. This strategy offers the best hope of saving sight with this new treatment at least in places where access to a qualified ophthalmologist can be slow.

It should also be recalled that this treatment does not restore sight but rather prevents further deterioration. Sustaining numerous assessments which involve relatively invasive treatments may have an adverse effect on the patient. Without patient-orientated outcomes in these trials we cannot comment on the patient's perspective on the experience of Visudyne therapy. It is likely that in most cases, especially where loss of sight of the second eye is threatened, patients will be willing to undergo all the necessary interventions, even when the probability of success is small.

Quality of life outcomes have been independently reported in a cohort of individuals treated with PDT and followed for one year (Armbrecht 2004). There was no comparator group. At 12 months participants were less anxious and more independent than baseline though there was a significant deterioration in more vision-related tasks.

Adverse effects occurred infrequently with the exception of the rather vague "visual disturbance" which affected more people in the verteporfin group compared to the control group. However, this was not reflected in the visual acuity outcomes. Infusion-related back pain occurred in 2.4% which is substantially lower than in some other studies. For example, in a series of 250 people treated with verteporfin 9.6% experienced verteporfin-associated pain, most of which was back pain (Borodoker 2002). It is now clear that acute severe visual acuity decrease is a relatively small but serious risk of poor outcome of treatment.

The trials included in this review appear to have been performed to high standards and were closely supervised by the Food and Drugs Administration of the USA. Both TAP and VIP trials were sponsored by the manufacturers of the drug (CIBA Vision and Novartis Ophthalmics) and declared potential conflicts of interest exist for a number of the trialists who hold interests in the manufacturer of the laser technology. This makes detailed scrutiny of reports of the trial essential. Of concern are the numerous protocol revisions that were registered with the Institutional Review Bodies throughout the study and after completion of follow up. Although we have not yet had access to the main protocol or to the revisions, a CIBA representative has assured us that the changes were not substantive and, in particular, that there were no changes to the a priori determinants of the primary outcomes.

As far as studies on populations other than north American and European, the Japan 2002 study provides evidence albeit uncontrolled that PDT works as well in Japanese people but there is no evidence of effectiveness in other population groups.

New reviews have not drawn any conflicting conclusions or any additional evidence. In particular, the review commissioned by the National Health Service's Research and Development Health Technology Assessment Programme on behalf of the National Institute of Clinical Excellence (NICE) in the UK (accessible at http://www.nice.org.uk) was in accordance with the findings of our review but went on to perform a detailed cost and cost-utility analysis. They concluded through economic modelling that the benefits of PDT with verteporfin at two years were "at best at the margins of what is generally considered to be an efficient use of health care resources".

Another paper from Australia (Hopley 2004) examined cost-utility for PDT for predominantly classic neovascular AMD using data from the TAP trial in two cost-utility models for two case scenarios. They conclude that as the only available treatment for some forms of neovascular AMD, PDT can be considered moderately cost effective for those with reasonable acuity but less so for those with poorer presenting vision. These conclusions depend upon the validity of the subgroup analyses of the TAP trial and there must

be some concern that one of the conclusions of the trialists post hoc analyses that those with poorer presenting vision fare better in terms of numbers of lines of visual acuity lost.

The NICE review concluded that there was still much uncertainty about the effectiveness of this treatment. In the face of enormous pressure to provide something that might work when nothing else is available, provision of service conditional on close monitoring of outcomes is a pragmatic approach, though implementation of this policy is difficult. However a cohort study monitoring the outcomes of PDT (including quality of life) provided by the National Health Service in the UK was commissioned by the NHS HTA. The results of this are not yet available.

AUTHORS' CONCLUSIONS

Implications for practice

This review provides evidence that PDT in people with classic and occult CNV due to AMD is effective in preventing visual loss. On the basis of existing evidence, approximately eight people need to be treated with an average of five treatments over two years to prevent one person losing 3 or more lines of visual acuity. Approximately 1 in every 100 treated patients will have an acute severe loss of vision in the treated eye. For an expensive treatment there are questions about the cost-utility and indeed opportunity cost for health services, especially when resources are limited.

Three out of the four trials included in this review were performed by the same investigators using largely the same clinical centres and funded by manufacturers of verteporfin. As for all new technology, outcomes and potential adverse effects need to be monitored when introduced into clinical practice and this recommendation has been implemented in the UK by the establishment of a national cohort study to monitor outcomes of verteporfin PDT according to NICE guidelines in the NHS. The initial findings of this cohort outcome study should be published within the next year.

There are major implications for health services, both in terms of potential expenditure and organisation, if PDT and indeed other new treatments for AMD are to be introduced. Where referral to an ophthalmologist is through a primary care network, facilities for the recognition of this condition in its early stages are needed. There is potential for an enormous increase in referral of people with early age-related maculopathy for assessment, in case an early treatable lesion is present. This could swamp already overstretched facilities at the secondary care level. Extra resources will be required at the secondary care level to manage increased referrals, for the necessary technology to diagnose treatable lesions and to deliver treatment.

All the above concerns have become less relevant for PDT since its use has been largely replaced by antivascular endothelial growth factor intraocular injections though they remain relevant for this new treatment.

Implications for research

Further independent trials of verteporfin are required to establish that the effects seen in this study are consistent and to examine important issues not yet addressed, particularly relating to quality of life and cost.

A similar recommendation was made by the authors commissioned for NICE for publicly-funded pragmatic trials with economic and vision-related quality of life outcomes over a longer time scale. To our knowledge no such studies are underway. Some commentators argue that technology is progressing at a pace that will render such studies irrelevant. New interventions for AMD, particularly those based on drugs active against Vascular Endothelial Growth Factor, show some promise and there is speculation that the role of PDT-based treatments will be short-lived. It is now unlikely that new studies on PDT alone will be initiated.

Descriptive epidemiology on the population at risk and the numbers likely to benefit from these kinds of interventions remains essential to estimate the impact of these new treatments on health service resources and the well being of the ageing population of more affluent countries with a life-expectancy sufficient to render AMD a significant public health concern. A particular concern remains that people in need of treatment can access it equitably and in time. Health services research of this nature and surveillance for rare but severe adverse effects is required.

ACKNOWLEDGEMENTS

The Cochrane Eyes and Vision Group developed and executed the electronic searches. We would like to thank Neil Bressler, Simon Harding and Javed Bhatti (CIBA Vision) for providing information about the TAP study. Usha Chakravarthy (Queens University, Belfast) and Bob Thompson (Macular Disease Society) provided useful comments on the review.

Many thanks to the following members of the Cochrane Eyes and Vision group Consumer Panel for comments on the plain language summary: Harold Burton, David Brandon, Bill Crowther, Peter Dyson, Diana Fitchett, Esme Green, Oliver Keene, Brenda Rogers, Bob Thomas, David Yule.

REFERENCES

References to studies included in this review

Schmidt-Erfurth 2008 *{published data only}*

Michels S, Wachtlin J, Gamulescu MA, Heimann H, Prünte C, Inhoffen W, et al.Comparison of early retreatment with the standard regimen in verteporfin therapy of neovascular age-related macular degeneration. *Ophthalmology* 2005;**112** (12):2070–5.

* Schmidt-Erfurth U, Sacu S, the Early Retreatment Study Group. Randomized multicenter trial of more intense and standard early verteporfin treatment of neovascular age-related macular degeneration. *Ophthalmology* 2008;**115**(1): 134–40.

TAP 1999 *{published and unpublished data}*

Rubin GS, Bressler NM, the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Effects of verteporfin therapy on contrast sensitivity: results from the treatment of age-related macular degeneration with photodynamic therapy (TAP) investigation - TAP report no. 4. *Retina* 2002;**22**(5): 536–44.

* Treatment of Age-related Macular Degeneration With Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: One-year results of 2 randomized clinical trials - TAP report 1. *Archives of Ophthalmology* 1999;**117**(10):1329–45.

Treatment of Age-related Macular Degeneration With Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: Two-year results of 2 randomized clinical trials - TAP report 2. *Archives of Ophthalmology* 2001;**119**(2):198–207.

Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Verteporfin therapy for subfoveal choroidal neovascularization in age-related macular degeneration: three-year results of an open-label extension of 2 randomized clinical trials - TAP report no 5. *Archives of Ophthalmology* 2002;**120**(10):1307–14.

Valio 2007 *{published data only}*

* Rosenfeld PJ, Boyer DS, Bressler NM, Fish G, Sanderson Grizzard W, Hao Y, et al. The VALIO Study Group. Verteporfin therapy of subfoveal occult choroidal neovascularization in AMD using delayed light application: one-year results of the VALIO Study. *American Journal of Ophthalmology* 2007;**144**(6):970–2.

VIM 2005 *{published data only}*

Azab M, Boyer DS, Bressler NM, Bressler SB, Cihelkova I, Hao Y, et al. Visudyne in Minimally Classic Choroidal Neovascularization Study Group. Verteporfin therapy of subfoveal minimally classic choroidal neovascularization in age-related macular degeneration. *Archives of Ophthalmology* 2005;**123**(4):448–57.

VIO 2007 *{published and unpublished data}*

Altaweel MM, Hiner C, VIO Study Group. Baseline CNV lesion characteristics in the Visudyne in Occult (VIO) trial: comparison between fluorescein angiography and ICG. *Investigative Ophthalmology & Visual Science* 2004;**45**:E-Abstract 3160.

European Medicines Agency (EMEA). Product Name: VISUDYNE Procedure no:EMEA/H/C/000305/II/0053. http://www.emea.europa.eu/humandocs/PDFs/EPAR/Visudyne/H-305-II-53-AR.pdf 5th June 2007.

Kaiser PK, VIO Study Group. Verteporfin In Occult (VIO): the design of a phase III controlled clinical trial of verteporfin therapy for occult with no classic subfoveal CNV secondary to AMD. *Investigative Ophthalmology & Visual Science* 2004;**45**:E abstract 2276.

* Kaiser PK. Visudyne in Occult CNV (VIO) study group. Verteporfin PDT for subfoveal occult CNV in AMD: two-year results of a randomized trial. *Current Medical Research and Opinion* 2009;**25**(8):1853–60.

Retinal Physician. AMD Treatment Choices for Today and Tomorrow. Verteporfin and pegaptanib lead, with a pipeline of new possibilities under investigation. http://www.retinalphysician.com/article.aspx?article=100074 (accessed 22 May 2007).

VIP 2001 *{published data only}*

Bressler NM. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularization - Verteporfin In Photodynamic Therapy Report 2. *American Journal of Ophthalmology* 2002;**133**(1):168–9.

Verteporfin in Photodynamic Therapy (VIP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in pathologic myopia with verteporfin. 1-year results of a randomized clinical trial-VIP report no. 1. *Ophthalmology* 2001;**108**(1):841–52.

* Verteporfin in Photodynamic Therapy Study Group. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularization - Verteporfin in Photodynamic Therapy Report 2. *American Journal of Ophthalmology* 2001;**131**(5):541–60.

References to studies excluded from this review

ADD-V *{published data only (unpublished sought but not used)}*

Southeastern Retina Associates. Currently enrolling clinical trials. www.tennesseeretina.com/news (accessed 22 May 2007).

Japan 2003 *{published data only}*

The Japanese Age-Related Macular Degeneration Trial (JAT) Study Group. Japanese age-related macular degeneration trial: 1-year results of photodynamic therapy with verteporfin in Japanese patients with subfoveal

choroidal neovascularization secondary to age-related macular degeneration. *American Journal of Ophthalmology* 2003;**136**(6):1049–61.

Schmidt-Erfurth 1999 ***{published data only}***
Schmidt-Erfurth U, Miller JW, Sickenberg M, Laqua H, Barbazetto I, Gragoudas ES, et al.Photodynamic therapy with verteporfin for choroidal neovascularisation caused by age-related macular degeneration. Results of retreatment in a phase 1 and 2 study. *Archives of Ophthalmology* 1999;**117**(9):1177–87.

References to studies awaiting assessment

VER 2004 ***{published data only (unpublished sought but not used)}***
Stur M. Verteporfin Early Retreatment (VER) - 12-months results of a phase IIIb controlled clinical trial. *Spektrum Der Augenheilkunde* 2004;**18**(2):108–9.
Stur M, Ergun E, VER Study Group. Verteprofin Early Retreatment (VER) - 24-month results of a phase IIIB controlled clinical trial. The Macula Society. 2005:74.
Stur M, VER Study Group. Rationale for and design of the Visudyne in Early Retreatment (VER) trial. *Investigative Ophthalmology & Visual Science* 2001;**42**:Abstract 2382.
Stur M, VER Study Group. Verteporfin Early Retreatment (VER) - 12-month results of a phase IIIb controlled clinical trial. *Investigative Ophthalmology & Visual Science* 2004;**45**: Abstract 2275.

Additional references

Armbrecht 2004
Armbrecht AM, Aspinall PA, Dhillon B. A prospective study of visual function and quality of life following PDT in patients with wet age related macular degeneration. *British Journal of Ophthalmology* 2004;**88**(10):1270–3.

Arnold 2004
Arnold JJ, Blinder KJ, Bressler NM, Bressler SB, Burdan A, Haynes L, et al.Acute severe visual acuity decrease after photodynamic therapy with verteporfin: case reports from randomized clinical trials-TAP and VIP report no. 3. *American Journal of Ophthalmology* 2004;**137**(4):683–96.

Azab 2004
Azab M, Benchaboune M, Blinder KJ, Bressler NM, Bressler SB, Gragoudas ES, et al.Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: meta-analysis of 2-year safety results in three randomized clinical trials: Treatment Of Age-Related Macular Degeneration With Photodynamic Therapy and Verteporfin In Photodynamic Therapy Study Report no. 4. *Retina* 2004;**24**(1):1–12.

Barbazetto 2003
Barbazetto I, Burdan A, Bressler NM, Bressler SB, Haynes L, Kapetanios AD, et al.Photodynamic therapy of subfoveal choroidal neovascularization with verteporfin: fluorescein angiographic guidelines for evaluation and treatment-TAP and VIP report No. 2. *Archives of Ophthalmology* 2003;**121**(9):1253–68.

Blinder 2003
Blinder KJ, Bradley S, Bressler NM, Bressler SB, Donati G, Hao Y, et al.Effect of lesion size, visual acuity, and lesion composition on visual acuity change with and without verteporfin therapy for choroidal neovascularization secondary to age-related macular degeneration: TAP and VIP report no. 1. *American Journal of Ophthalmology* 2003; **136**(3):407–18.

Borodoker 2002
Borodoker N, Spaide RF, Maranan L, Murray J, Freund KB, Slakter JS, et al.Verteporfin infusion-associated pain. *American Journal of Ophthalmology* 2002;**133**(2):211–4.

Bressler 2002
Bressler NM, Arnold J, Benchaboune M, Blumenkranz MS, Fish GE, Gragoudas ES, et al.Verteporfin therapy of subfoveal choroidal neovascularization in patients with age-related macular degeneration: additional information regarding baseline lesion composition's impact on vision outcomes-TAP report No. 3. *Archives of Ophthalmology* 2002;**120**(11):1443–54.

Bressler 2004a
Bressler SB, Pieramici DJ, Koester JM, Bressler M. Natural history of minimally classic subfoveal choroidal neovascular lesions in the treatment of age-related macular degeneration with photodynamic therapy (TAP) investigation: outcomes potentially relevant to management--TAP report No. 6. *Archives of Ophthalmology* 2004;**122**(3):325–9.

Bressler 2004b
Bressler NM, VAM Study Writing Committee. Verteporfin therapy in age-related macular degeneration (VAM): an open-label multicenter photodynamic therapy study of 4, 435 patients. *Retina* 2004;**24**(4):512–20.

Do 2004
Do DV, Bressler NM, Bressler SB. Large submacular hemorrhages after verteporfin therapy. *American Journal of Ophthalmology* 2004;**137**(3):558–60.

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.

Higgins 2006
Higgins JPT, Green S, editors. Assessment of study quality. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]; Section 6. In: The Cochrane Library, Issue 4, 2006. Chichester, UK: John Wiley & Sons, Ltd.

Higgins 2008
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 5.0.1 [updated September 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

Holz 2003

Holz FG, Jorzik J, Schutt F, Flach U, Unnebrink K. Agreement among ophthalmologists in evaluating fluorescein angiograms in patients with neovascular age-related macular degeneration for photodynamic therapy eligibility (FLAP-study). *Ophthalmology* 2003;**110**(2): 400–5.

Hopley 2004

Hopley C, Salkeld G, Mitchell P. Cost utility of photodynamic therapy for predominantly classic neovascular age related macular degeneration. *British Journal of Ophthalmology* 2004;**88**(8):982–7.

Kaiser 2006

Kaiser PK. Verteporfin therapy of subfoveal choroidal neovascularization in age related macular degeneration: 5-year results of two randomized clincal trials with an open label extension. TAP report No. 8. *Graefe's Archive of Clinical and Experimental Ophthalmology* 2006;**244**(9): 1132–42.

Meads 2004

Meads C, Hyde C. Photodynamic therapy with verteporfin is effective, but how big is its effect? Results of a systematic review. *British Journal of Ophthalmology* 2004;**88**(2):212–7.

Miller 1999

Miller JW, Schmidt-Erfurth U, Sickenberg M, Pournaras CJ, Laqua H, Barbazetto I, et al.Photodynamic therapy with verteporfin for choroidal neovascularisation caused by age-related macular degeneration. Results of a single treatment in a phase 1 and 2 study. *Archives of Ophthalmology* 1999; **117**(9):1161–73.

MPS 1994

Macular photocoagulation study group. Laser photocoagulation for juxtafoveal choroidal neovascularization: five year results from randomized clinical trials. *Archives of Ophthalmology* 1994;**112**(4): 500–9.

Pieramici 2006

Writing committee for the VIP Study Group. Occult with no classic subfoveal choroidal neovascular lesions in age-related macular degeneration. VIP report no. 4. *Archives of Ophthalmology* 2006;**124**(5):660–4.

Schmidt-Erfurth 2003

Schmidt-Erfurth UM, Michels S. Changes in confocal indocyanine green angiography through two years after photodynamic therapy with verteporfin. *Ophthalmology* 2003;**110**(7):1306–14.

Schmidt-Erfurth 2004

Schmidt-Erfurth UM, Elsner H, Terai N, Benecke A, Dahmen G, Michels SM. Effects of verteporfin therapy on central visual field function. *Ophthalmology* 2004;**111**(5): 931–9.

Woodburn 2002

Woodburn KW, Engelman CJ, Blumenkranz MS. Photodynamic therapy for choroidal neovascularization: a review. *Retina* 2002;**22**(4):391–405.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Schmidt-Erfurth 2008

Methods	Prospective, randomized, multicenter clinical trial.
Participants	Two hundred three patients with predominantly classic CNV secondary to AMD
Interventions	During the first 6 months of VT, patients underwent retreatment every 2 (group A) or 3 (group B) months. After 6 months, both groups underwent retreatment every 3 months for as long as CNV activity was documented
Outcomes	The primary outcome of the study was best-corrected mean visual acuity as measured using the Early Treatment Diabetic Retinopathy Study protocol. The secondary outcomes were percentage of patients losing at least 3 lines of vision, percentage of patients gaining at least 1 line of vision, and lesion size based on the greatest linear dimension (GLD) documented by fluorescein angiography, impact of initial lesion size, and retreatment rate as well as safety
Notes	Published as two separate reports of 12 and 24 month outcomes

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No information on how the allocation sequence was generated.
Allocation concealment?	Unclear	No information on allocation concealment provided.
Blinding? All outcomes	Unclear	No information provided on whether observers of primary outcome measures were masked to treatment status
Incomplete outcome data addressed? 12 month follow up	Yes	"In both treatment groups, at least 90% of patients completed the 12-month follow-up." Therefore incomplete outcome data unlikely to have introduced bias at 12 months
Incomplete outcome data addressed? 24 month follow up	No	"Fifty-three percent of patients in group A and 59% in group B completed the 2-year follow-up." Such a large loss to follow up must lead to serious doubts about the validity of the study findings at 2 years even without serious imbalance between the two groups

Free of selective reporting?	Yes	Primary and secondary outcomes clearly and consistently reported in both study papers

TAP 1999

Methods	Randomised controlled trial: one eye per patient was randomised in a 2:1 (treatment: control) ratio
Participants	609 people with subfoveal CNV lesions caused by AMD with evidence of classic CNV and best corrected acuity of approximately 20/40 to 20/200
Interventions	Photodynamic therapy following verteporfin injection versus photodynamic therapy following intravenous 5% dextrose
Outcomes	Visual acuity at 12 and 24 months.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	"Random assignments were prepared by the statistical department of CIBA Vision Corp. Sealed envelopes with random assignments were prepared by the Quality Assurance Department within QLT PhotoTherapeutics Inc (Vancouver, British Columbia), which maintained independence from any other function of the trials." TAP report 1, page 1331
Allocation concealment?	Yes	"The allocation of verteporfin therapy or placebo was recorded on a randomization log that was stored in a locked cabinet with both opened and unopened randomization envelopes at each clinical center." TAP report 1, page 1331
Blinding? All outcomes	Yes	"The study coordinator aware of the treatment assignment and anyone else who might assist in the setup of verteporfin or placebo solutions were trained to make every reasonable attempt to maintain masking

		of the ophthalmologist, patient, vision examiner, and Photograph Reading Center personnel. The verteporfin and placebo solutions were different colors (green vs colorless). All verteporfin and placebo solutions as well as the intravenous tubing were covered entirely with foil so that the patient and treating ophthalmologist were masked during the infusion. The ophthalmologist remained masked while administering the light since the fundus appearance during treatment does not change in any way to indicate verteporfin or placebo treatment. On the materials submitted to them, the Photograph Reading Center graders did not have any information to indicate that verteporfin or placebo was administered. The marked hypofluorescence within a treated area noted within 1 week after verteporfin therapy in phase 1 and 2 studies is not readily apparent 3 months after treatment. Therefore, this hypofluorescence was not judged to be a likely source of potential unmasking of the graders evaluating photographs obtained at least 3 months after verteporfin therapy. Clinic monitors also had no access to information that would indicate treatment assignment. There were no known instances of unmasking of the vision examiners or Photograph Reading Center graders. Only 2 patients who noted a green solution following extravasation of drug were likely unmasked. Treating ophthalmologists, but not the patients, were unmasked in 4 additional cases. In 2 of these cases, fluorescein angiography was obtained within 1 week after treatment to evaluate severe visual acuity decrease and showed hypofluorescence typical for verteporfin therapy. In another case the ophthalmologist noted the green verteporfin leaking onto the cover over the intravenous solution, and in 1 additional case, the ophthalmologist became unmasked prior to a vitrectomy for a subretinal hemorrhage; the patient had been assigned to placebo." TAP report 1, page 1331

TAP 1999 (*Continued*)

Incomplete outcome data addressed? 12 month follow up	Yes	Follow-up good and equal between both groups. 94% of patients within each group completed the month 12 follow-up examination. 379/402 in verteporfin group and 194/207 in placebo group.TAP report 1, figure 1, page 1335
Incomplete outcome data addressed? 24 month follow up	Yes	Follow-up equal between both groups. 351/402 (87%) of patients PDT group completed the month 24 follow-up examination compared to 178/207 (86%) of placebo group. TAP report 2, figure 1, page 201
Free of selective reporting?	Unclear	Unlikely for primary analysis of treatment versus control but possible for subgoup analyses by lesion type. No mention of proposed subgroup analyses in power statement and discussion suggests exploratory analysis of data eg. "To explore these subgroup findings further, visual acuity distributions (Figure 9), mean change in contrast sensitivity (Table 6), and angiographic outcomes (Table 6) at the month 12 examination were evaluated, based on lesion components noted at baseline. The lesion components at baseline affected the magnitude of the treatment benefit with respect to the visual acuity distributions." TAP report 1, page 1340 The protocol for this study was not independently published prior to this first report of results but contact with the communicating author provided an assertion that subgoup analyses were planned a priori

Valio 2007

Methods	Altered light treatment using delayed light after Visudyne in occult AMD
Participants	60 patients enrolled at 7 centres in the USA.
Interventions	Participants randomised 1:1 to receive verteporfin injection followed by delayed or standard light application. The assigned treatment was repeated every three months if fluorescein leakage was detected
Outcomes	Visual acuity at least 6 months.

Notes	Published as a short report in the American Journal of Ophthalmology with additional details on line

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Patients were "randomised" but no information on how the sequence generation is provided in the protocol details available at AJO.COM
Allocation concealment?	Unclear	No information on allocation concealment provided online as above at AJO.COM
Blinding? All outcomes	Yes	"All outcome assessors, including vision examiners, photographers, treating ophthalmologists, DARC (reading centre) graders, and clinic monitors, were masked to the treatment assignment. The ophthalmologist was asked to leave the room for at least 30 minutes before treatment and did not return for the light application until notified by the study coordinator." "During the trial, investigators were not unmasked to the treatment assignment for any patient. The success of masking was not evaluated formally."
Incomplete outcome data addressed? 12 month follow up	Yes	A CONSORT flow chart is provided at AJO.COM which shows 82% 12 month follow up in the standard light arm and 81% in the delayed light arm
Incomplete outcome data addressed? 24 month follow up	Yes	Not relevant
Free of selective reporting?	Yes	Unlikely since the insignificant primary outcome measure is clearly stated

VIM 2005

Methods	Randomised controlled trial: One eye of each patient was enrolled. No information on allocation concealment is provided but double masking is described. Participant were randomised to Verteporfin or placebo in a 2:1. Patients were also randomised 1:1 into two groups of fluence, reduced and standard in which the reduced group had less intense illumination of the photodynamic dye as it passed through the neovascular membrane
Participants	117 patients with minimally classic CNV due to AMD.
Interventions	Photodynamic therapy following verteporfin injection versus photodynamic therapy following intravenous 5% dextrose. Participants in the placebo and treatment groups were also randomised to Standard Fluence (SF) intensity of illumination equivalent to a light dose of 50 Joules per square centimetre amd a Reduced Fluence (RF) equivalent to 25 Joules per square centimetre
Outcomes	Visual acuity at 12 and 24 months. Acute severe visual acuity loss.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	"Patients were randomly assigned to 1 of 2 fluence groups; at the same time, patients were randomly assigned to received verteporfin therapy or placebo." Main report published Archives of Ophthalmology 2005, page 450
Allocation concealment?	Yes	Allocation concealment not specifically mentioned but probably adequate as was well dealt with in all the other studies from this group."All study participants and outcome assessors, including vision examiners, photographers, ophthalmologists, Photograph Reading Center personnel and clinic monitors, were masked to the treatment assignment." Main report published Archives of Ophthalmology 2005, page 450
Blinding? All outcomes	Yes	"All study participants and outcome assessors, including vision examiners, photographers, ophthalmologists, Photograph reading Center personnel and clinic monitors, were masked to the treatment assignment. The ophthalmologist responsible for applying the laser light was not masked to the fluence rate because the treating ophthalmol-

		ogist was responsible for the light fluence rate being applied to the study participant's retina. Only the study coordinators and any other person who might assist in the setup of verteporfin or placebo solutions were aware of the treatment assignment with respect to verteporfin or placebo; these individuals were trained to make every reasonable attempt to maintain masking of participating patients and all other study personnel. However treatment assignment was unmasked for a total of 3 patients. Investigators were unmasked to the treatment assignment of 2 patients. One patient was identified by the Reading Center as having a predominantly classic lesion at the initial visit; the other was identified by the Reading Center as having a predominantly classic lesion at the 6-week examination. In both cases the treating ophthalmologist believed that verteporfin therapy should not be delayed until the next scheduled visit. A third patient was inadvertently unmasked to the sponsor by the study coordinator at the site were the patient was being treated because the coordinator asked the sponsor what the site should do with the reconstituted vial of verteorfin, thus indirectly and inadvertently revealing the treatment assignment for a particular randomisation number. The success of masking otherwise was not evaluated formally" Main report published Archives of Ophthalmology 2005, page 450
Incomplete outcome data addressed? 12 month follow up	Yes	Follow-up good and equal between groups. 38/40 (95%) of placebo group seen at 12 months compared to 36/38 (95%) of reduced fluence group and 36/39 (92%) of the standard fluence group. Main report published Archives of Ophthalmology 2005, figure 1, page 451
Incomplete outcome data addressed? 24 month follow up	Unclear	Follow-up a little lower in the treatment groups. 37/40 (93%) of placebo group seen at 24 months compared to 34/38 (89%) of reduced fluence group and 32/39 (82%) of the standard fluence group. Main report published Archives of Ophthalmology

		2005, figure 1, page 451
Free of selective reporting?	Unclear	Primary outcome specified but secondary outcomes less clearly specified. Main outcome of interest to this review reported

VIO 2007

Methods	2-year randomized, placebo-controlled, double-masked, multi-centre, Phase III study of the treatment of occult with no classic subfoveal CNV lesions secondary to AMD using Visudyne therapy compared with placebo
Participants	364 people over 50 years with occult but no classic CNV due to AMD enrolled at 43 centres in North America randomised 2:1 active versus placebo treatment. "The VIO study was to confirm the treatment effect shown in patients with occult CNV and evidence of recent disease progression in the VIP AMD study. Most of the patients in VIP AMD study had occult with no classic CNV (258 of 339 patients: 76%). Nevertheless, VIO study included a more restricted patient population who showed a greater treatment benefit in the VIP AMD study."
Interventions	Visudyne administered as a 10 minute intravenous infusion followed 15 minutes after the start of the infusion by light application of 600mW/cm2 for 83 seconds (dose of 50J/cm^2) . Treatments maybe repeated every 3 months in the event of recurrent neovascularisation up to a maximum of 4 treatments in a year. No information is provided in the report about how the double masked placebo intervention was delivered
Outcomes	"Four co-primary analyses of the patients' responder rates were planned: proportion of patients who lose, at Month 12 and at Month 24, fewer than 15 letters (<3 lines) and fewer than 30 letters (<6 lines) of best-corrected visual acuity in the study eye from baseline."
Notes	Trial was sponsored by Novartis Pharma AG and QLT Inc (see http://clinicaltrials.gov/ct2/show/NCT00121407?term=NCT00121407&rank=1)

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	"Patients were randomly assigned to verteporfin or placebo in a 2 : 1 ratio". *Patients and methods page 1854. .*
Allocation concealment?	Unclear	Not reported.
Blinding? All outcomes	Unclear	"All study participants and outcome assessors were masked to the treatment assignment" *Patients and methods page 1854.*

VIO 2007 (*Continued*)

Incomplete outcome data addressed? 12 month follow up	Yes	At 12 months 219/244 (90%) verteporfin and 111/364 (93%) placebo group given visual acuity assessment. *Figure 1, page 1856.* Missing data were imputed using last observation carried forward
Incomplete outcome data addressed? 24 month follow up	Yes	"At month 24, 198/244 patients (81%) in the verteporfin group and 108/120 (90%) patients in the placebo group had a VA assessment (Figure 1)." *Results page 1855* Missing data were imputed using last observation carried forward Increased death rate in intervention arm attributed to chance alone
Free of selective reporting?	Unclear	No prior publication of trial protocol

VIP 2001

Methods	Randomised controlled trial: one eye per patient was enrolled. Randomisation in sealed envelopes stratified by clinical centre
Participants	339 people with subfoveal CNV caused by AMD.
Interventions	Photodynamic therapy following verteporfin injection versus photodynamic therapy following intravenous 5% dextrose
Outcomes	Visual acuity at 12 and 24 months. Secondary outcomes include contrast sensitivity and changes in angiographic outcomes
Notes	Randomised 2:1 to verteporfin treatment.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	"Random assignments were prepared by Statprobe (Ann Arbor, MI). Statprobe also prepared sealed envelopes with random assignments and distributed them to the clinical centers. Patients were randomized in a ratio of 2:1 to verteporfin treatment or placebo (to gather more safety data on patients receiving verteporfin), with only one eye of a patient to be randomized. For cases in which an enrolling ophthalmol-

		ogist believed that both eyes of a patient were eligible, the patient and ophthalmologist chose which eye would be enrolled in the study. Randomization was stratified by clinical center. Separate groups of color-coded envelopes were used to distinguish patients participating in the VIP Trial with pathologic myopia from those with AMD. A study coordinator was instructed to open the sealed envelope only after a patient was judged to meet all of the eligibility criteria and only after the enrolling ophthalmologist and the patient agreed to the patient's participation in the trial. Treatment was to begin the same day that the treatment assignment was revealed by opening the envelope." VIP report number 1, page 843
Allocation concealment?	Yes	See above
Blinding? All outcomes	Yes	"Masking was carried out in a manner identical to procedures followed in the TAP Investigation.7 All patients were to remain masked until all of them had completed the month 24 examination and the data collection and entry was completed." VIP report number 1, page 843 referring to TAP report number 1 (see risk of bias table for TAP study)
Incomplete outcome data addressed? 12 month follow up	Yes	Follow-up good and similar between treatment groups. 210/225 (93%) in verteporfin group and 104/114 (91%) seen in placebo group at 12 months. VIP report number 2, figure 1, page 548
Incomplete outcome data addressed? 24 month follow up	Yes	Follow-up good and similar between treatment groups. 193/225 (86%) in verteporfin group and 99/114 (87%) seen in placebo group at 24 months. VIP report number 2, figure 1, page 548
Free of selective reporting?	Yes	Usual vision and clinical outcomes reported and report suggests these were decided a priori

AMD: age-related macular degeneration
CNV: choroidal neovascularisation

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

Study	Reason for exclusion
ADD-V	No detailed publication ever found but was a study looking at the effect of combining photodynamic therapy with an anti-inflammatory agent so falls outside the remit of this review
Japan 2003	Non-randomised open label case series
Schmidt-Erfurth 1999	Non-randomised open-label phase I and II trial

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

VER 2004

Methods	Prospective randomised controlled trial randomised 1:1 to standard or more frequent photodynamic therapy treatments
Participants	People with predominantly classic choroidal neovascularisation. 323 people at 31 sites enrolled
Interventions	Visudyne therapy every 3 months (standard) versus more frequent regiment every 1.5 months
Outcomes	Mean visual acuity decrease, proportion of participants losing 15 letters or more from baseline
Notes	Methods reported as ARVO abstract in 2001 and twelve month outcomes reported again as an ARVO abstract in 2004. In 2005, an abstract published by the macula disease society published the 24 month outcomes. The 12 month results were also published in German in 2004 in the Spektrum der Augenheilkunde and we are currently seeking a copy for translation

DATA AND ANALYSES

Comparison 1. PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Loss of 3 or more lines (15 or more letters) visual acuity at 12 months	4	1386	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.69, 0.93]
2 Loss of 3 or more lines (15 or more letters) visual acuity at 24 months	4	1381	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.73, 0.88]
3 Loss of 6 or more lines (30 or more letters) visual acuity at 12 months	4	1305	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.56, 0.88]
4 Loss of 6 or more lines (30 or more letters) visual acuity at 24 months	4	1381	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.53, 0.83]
5 Loss of 6 or more letters of contrast sensitivity at 24 months	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Loss of 15 or more letters of contrast sensivitiy at 24 mths	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Gain of 3 or more lines (15 or more letters) of visual acuity at 12 months	3	941	Risk Ratio (M-H, Random, 95% CI)	2.19 [0.99, 4.83]
8 Gain of 3 or more lines (15 or more letters) of visual acuity at 24 months	3	941	Risk Ratio (M-H, Random, 95% CI)	2.55 [1.31, 4.99]
9 Subgroup analysis: lesion area composed of classic CNV. Loss of 3 or more lines at 12 months	4	1267	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.68, 0.87]
9.1 No classic CNV	3	645	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.67, 0.96]
9.2 Classic CNV > 0% to < 50%	2	379	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.70, 1.14]
9.3 Classic CNV > 50% (predominantly classic)	1	243	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.41, 0.71]
10 Subgroup analysis: lesion area composed of classic CNV. Loss of 3 or more lines at 24 months	4	1375	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.73, 0.89]
10.1 No classic CNV	3	683	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.72, 0.95]
10.2 Classic CNV > 0 to < 50%	3	431	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.77, 1.10]
10.3 Classic CNV > 50% (predominantly classic)	2	261	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.48, 0.75]
11 Adverse effects: acute severe visual acuity decrease	3	1075	Risk Ratio (M-H, Fixed, 95% CI)	3.75 [0.87, 16.12]

12 Adverse effects: visual disturbance	3	1075	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [1.21, 2.01]
13 Adverse effects: injection site	3	1075	Odds Ratio (M-H, Fixed, 95% CI)	2.09 [1.29, 3.39]
14 Adverse effects: infusion-related back pain	4	1439	Risk Ratio (M-H, Fixed, 95% CI)	9.93 [2.82, 35.02]
15 Adverse effects: allergic reactions	2	948	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.34, 2.56]
16 Adverse effects: photosensitivity reactions	2	948	Odds Ratio (M-H, Fixed, 95% CI)	5.37 [1.01, 28.60]
17 Subgroup analysis: lesion area composed of classic CNV. Loss of 3 or more lines at 12 months	3	662	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.67, 0.97]
17.1 No classic CNV	2	588	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.69, 1.01]
17.2 Classic CNV > 0% to < 50%	1	74	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.31, 1.09]
17.3 Classic CNV > 50% (predominantly classic)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
18 Subgroup analysis: lesion area composed of classic CNV. Loss of 3 or more lines at 24 months	3	766	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.74, 0.97]
18.1 No classic CNV	2	622	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.73, 0.98]
18.2 Classic CNV > 0 to < 50%	2	125	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.63, 1.20]
18.3 Classic CNV > 50% (predominantly classic)	1	19	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.42, 1.19]

Analysis 1.1. Comparison 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO, Outcome 1 Loss of 3 or more lines (15 or more letters) visual acuity at 12 months.

Review: Photodynamic therapy for neovascular age-related macular degeneration

Comparison: 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

Outcome: 1 Loss of 3 or more lines (15 or more letters) visual acuity at 12 months

Study or subgroup	PDT n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
TAP 1999	156/402	111/207		38.9 %	0.72 [0.61, 0.86]
VIM 2005	10/36	18/38		5.4 %	0.59 [0.31, 1.09]
VIP 2001	114/225	62/114		31.4 %	0.93 [0.75, 1.15]
VIO 2007	91/244	54/120		24.3 %	0.83 [0.64, 1.07]
Total (95% CI)	**907**	**479**		**100.0 %**	**0.80 [0.69, 0.93]**

Total events: 371 (PDT), 245 (Placebo)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 4.26$, df = 3 (P = 0.23); $I^2 = 30\%$

Test for overall effect: Z = 2.91 (P = 0.0036)

Analysis 1.2. Comparison 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO, Outcome 2 Loss of 3 or more lines (15 or more letters) visual acuity at 24 months.

Review: Photodynamic therapy for neovascular age-related macular degeneration

Comparison: 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

Outcome: 2 Loss of 3 or more lines (15 or more letters) visual acuity at 24 months

Study or subgroup	PDT n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
TAP 1999	189/402	129/207		43.5 %	0.75 [0.65, 0.88]
VIM 2005	17/32	23/37		5.7 %	0.85 [0.57, 1.29]
VIP 2001	121/225	76/114		30.4 %	0.81 [0.68, 0.96]
VIO 2007	114/244	63/120		20.4 %	0.89 [0.72, 1.11]
Total (95% CI)	**903**	**478**		**100.0 %**	**0.80 [0.73, 0.88]**
Total events: 441 (PDT), 291 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.64$, df = 3 (P = 0.65); $I^2 = 0.0\%$					
Test for overall effect: Z = 4.42 (P < 0.00001)					

Analysis 1.3. Comparison 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO, Outcome 3 Loss of 6 or more lines (30 or more letters) visual acuity at 12 months.

Review: Photodynamic therapy for neovascular age-related macular degeneration

Comparison: 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

Outcome: 3 Loss of 6 or more lines (30 or more letters) visual acuity at 12 months

Study or subgroup	PDT n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
TAP 1999	59/402	49/207		44.8 %	0.62 [0.44, 0.87]
VIM 2005	3/36	6/38		3.0 %	0.53 [0.14, 1.95]
VIP 2001	37/166	30/92		30.9 %	0.68 [0.45, 1.03]
VIO 2007	39/244	20/120		21.3 %	0.96 [0.59, 1.57]
Total (95% CI)	**848**	**457**		**100.0 %**	**0.70 [0.56, 0.88]**

Total events: 138 (PDT), 105 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.25$, df = 3 (P = 0.52); $I^2 = 0.0\%$

Test for overall effect: Z = 3.10 (P = 0.0019)

Analysis 1.4. Comparison 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO, Outcome 4 Loss of 6 or more lines (30 or more letters) visual acuity at 24 months.

Review: Photodynamic therapy for neovascular age-related macular degeneration

Comparison: 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

Outcome: 4 Loss of 6 or more lines (30 or more letters) visual acuity at 24 months

Study or subgroup	Treatment n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
TAP 1999	73/402	62/207		34.5 %	0.61 [0.45, 0.81]
VIM 2005	4/32	13/37		4.7 %	0.36 [0.13, 0.98]
VIP 2001	67/225	54/114		36.6 %	0.63 [0.48, 0.83]
VIO 2007	55/244	30/120		24.2 %	0.90 [0.61, 1.33]
Total (95% CI)	**903**	**478**		**100.0 %**	**0.66 [0.53, 0.83]**

Total events: 199 (Treatment), 159 (Placebo)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 4.35$, df = 3 (P = 0.23); $I^2 = 31\%$

Test for overall effect: Z = 3.59 (P = 0.00033)

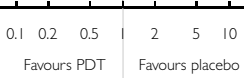
Analysis 1.5. Comparison 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO, Outcome 5 Loss of 6 or more letters of contrast sensitivity at 24 months.

Review: Photodynamic therapy for neovascular age-related macular degeneration

Comparison: 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

Outcome: 5 Loss of 6 or more letters of contrast sensitivity at 24 months

Study or subgroup	PDT n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
TAP 1999	86/402	94/207		0.47 [0.37, 0.60]
VIP 2001	32/161	31/90		0.58 [0.38, 0.88]



Analysis 1.6. Comparison 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO, Outcome 6 Loss of 15 or more letters of contrast sensivitiy at 24 mths.

Review: Photodynamic therapy for neovascular age-related macular degeneration

Comparison: 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

Outcome: 6 Loss of 15 or more letters of contrast sensivitiy at 24 mths

Study or subgroup	PDT n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
TAP 1999	27/402	24/207		0.58 [0.34, 0.98]

Analysis 1.7. Comparison 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO, Outcome 7 Gain of 3 or more lines (15 or more letters) of visual acuity at 12 months.

Review: Photodynamic therapy for neovascular age-related macular degeneration

Comparison: 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

Outcome: 7 Gain of 3 or more lines (15 or more letters) of visual acuity at 12 months

Study or subgroup	PDT n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
TAP 1999	24/402	5/207		69.8 %	2.47 [0.96, 6.38]
VIP 2001	5/166	2/92		23.9 %	1.39 [0.27, 7.00]
VIM 2005	1/36	0/38		6.3 %	3.16 [0.13, 75.20]
Total (95% CI)	**604**	**337**		**100.0 %**	**2.19 [0.99, 4.83]**

Total events: 30 (PDT), 7 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.42$, df = 2 (P = 0.81); $I^2 = 0.0\%$

Test for overall effect: Z = 1.93 (P = 0.053)

Test for subgroup differences: Not applicable

Analysis 1.8. Comparison 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO, Outcome 8 Gain of 3 or more lines (15 or more letters) of visual acuity at 24 months.

Review: Photodynamic therapy for neovascular age-related macular degeneration

Comparison: 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

Outcome: 8 Gain of 3 or more lines (15 or more letters) of visual acuity at 24 months

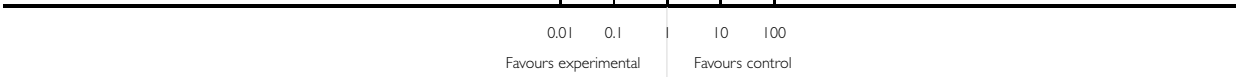
Study or subgroup	PDT n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
TAP 1999	36/402	8/207		80.3 %	2.32 [1.10, 4.89]
VIP 2001	8/166	1/92		10.5 %	4.43 [0.56, 34.90]
VIM 2005	3/36	1/38		9.1 %	3.17 [0.35, 29.06]
Total (95% CI)	**604**	**337**		**100.0 %**	**2.55 [1.31, 4.99]**

Total events: 47 (PDT), 10 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.38$, df = 2 (P = 0.83); $I^2 = 0.0\%$

Test for overall effect: Z = 2.74 (P = 0.0061)

Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO, Outcome 9 Subgroup analysis: lesion area composed of classic CNV. Loss of 3 or more lines at 12 months.

Review: Photodynamic therapy for neovascular age-related macular degeneration

Comparison: 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

Outcome: 9 Subgroup analysis: lesion area composed of classic CNV. Loss of 3 or more lines at 12 months

Study or subgroup	PDT n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 No classic CNV					
TAP 1999	14/38	13/19		6.0 %	0.54 [0.32, 0.90]
VIO 2007	66/219	45/111		20.7 %	0.74 [0.55, 1.01]
VIP 2001	85/166	51/92		22.8 %	0.92 [0.73, 1.17]
Subtotal (95% CI)	**423**	**222**		**49.6 %**	**0.80 [0.67, 0.96]**
Total events: 165 (PDT), 109 (Placebo)					
Heterogeneity: Chi^2 = 3.91, df = 2 (P = 0.14); I^2 =49%					
Test for overall effect: Z = 2.46 (P = 0.014)					
2 Classic CNV > 0% to < 50%					
TAP 1999	89/202	46/103		21.2 %	0.99 [0.76, 1.29]
VIM 2005	10/36	18/38		6.1 %	0.59 [0.31, 1.09]
Subtotal (95% CI)	**238**	**141**		**27.2 %**	**0.90 [0.70, 1.14]**
Total events: 99 (PDT), 64 (Placebo)					
Heterogeneity: Chi^2 = 2.27, df = 1 (P = 0.13); I^2 =56%					
Test for overall effect: Z = 0.87 (P = 0.38)					
3 Classic CNV > 50% (predominantly classic)					
TAP 1999	52/159	51/84		23.2 %	0.54 [0.41, 0.71]
Subtotal (95% CI)	**159**	**84**		**23.2 %**	**0.54 [0.41, 0.71]**
Total events: 52 (PDT), 51 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.31 (P = 0.000017)					
Total (95% CI)	**820**	**447**		**100.0 %**	**0.77 [0.68, 0.87]**
Total events: 316 (PDT), 224 (Placebo)					
Heterogeneity: Chi^2 = 14.45, df = 5 (P = 0.01); I^2 =65%					
Test for overall effect: Z = 4.10 (P = 0.000041)					

Analysis 1.10. Comparison 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO, Outcome 10 Subgroup analysis: lesion area composed of classic CNV. Loss of 3 or more lines at 24 months.

Review: Photodynamic therapy for neovascular age-related macular degeneration

Comparison: 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

Outcome: 10 Subgroup analysis: lesion area composed of classic CNV. Loss of 3 or more lines at 24 months

Study or subgroup	PDT n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 No classic CNV					
TAP 1999	18/41	14/20		5.0 %	0.63 [0.40, 0.98]
VIO 2007	114/244	63/120		22.4 %	0.89 [0.72, 1.11]
VIP 2001	91/166	63/92		21.5 %	0.80 [0.66, 0.97]
Subtotal (95% CI)	**451**	**232**		**49.0 %**	**0.82 [0.72, 0.95]**
Total events: 223 (PDT), 140 (Placebo)					
Heterogeneity: Chi^2 = 1.98, df = 2 (P = 0.37); I^2 =0.0%					
Test for overall effect: Z = 2.72 (P = 0.0064)					
2 Classic CNV > 0 to < 50%					
TAP 1999	106/202	58/104		20.3 %	0.94 [0.76, 1.17]
VIM 2005	17/32	23/37		5.7 %	0.85 [0.57, 1.29]
VIP 2001	19/38	10/18		3.6 %	0.90 [0.53, 1.52]
Subtotal (95% CI)	**272**	**159**		**29.6 %**	**0.92 [0.77, 1.10]**
Total events: 142 (PDT), 91 (Placebo)					
Heterogeneity: Chi^2 = 0.17, df = 2 (P = 0.92); I^2 =0.0%					
Test for overall effect: Z = 0.92 (P = 0.36)					
3 Classic CNV > 50% (predominantly classic)					
TAP 1999	65/159	57/83		19.9 %	0.60 [0.47, 0.75]
VIP 2001	10/16	3/3		1.5 %	0.71 [0.42, 1.19]
Subtotal (95% CI)	**175**	**86**		**21.4 %**	**0.60 [0.48, 0.75]**
Total events: 75 (PDT), 60 (Placebo)					
Heterogeneity: Chi^2 = 0.36, df = 1 (P = 0.55); I^2 =0.0%					
Test for overall effect: Z = 4.46 (P < 0.00001)					
Total (95% CI)	**898**	**477**		**100.0 %**	**0.80 [0.73, 0.89]**
Total events: 440 (PDT), 291 (Placebo)					
Heterogeneity: Chi^2 = 10.76, df = 7 (P = 0.15); I^2 =35%					
Test for overall effect: Z = 4.32 (P = 0.000015)					

Analysis 1.11. Comparison 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO, Outcome 11 Adverse effects: acute severe visual acuity decrease.

Review: Photodynamic therapy for neovascular age-related macular degeneration

Comparison: 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

Outcome: 11 Adverse effects: acute severe visual acuity decrease

Study or subgroup	PDT n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
VIM 2005	1/87	1/40		50.9 %	0.46 [0.03, 7.17]
TAP 1999	3/402	0/207		24.5 %	3.61 [0.19, 69.61]
VIP 2001	10/225	0/114		24.6 %	10.69 [0.63, 180.74]
Total (95% CI)	**714**	**361**		**100.0 %**	**3.75 [0.87, 16.12]**

Total events: 14 (PDT), 1 (Placebo)

Heterogeneity: Chi^2 = 2.77, df = 2 (P = 0.25); I^2 =28%

Test for overall effect: Z = 1.78 (P = 0.076)

Analysis 1.12. Comparison 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO, Outcome 12 Adverse effects: visual disturbance.

Review: Photodynamic therapy for neovascular age-related macular degeneration

Comparison: 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

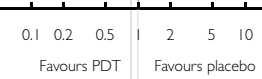
Outcome: 12 Adverse effects: visual disturbance

Study or subgroup	PDT n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
TAP 1999	89/402	32/207		51.4 %	1.43 [0.99, 2.07]
VIP 2001	94/225	26/114		42.0 %	1.83 [1.26, 2.66]
VIM 2005	7/87	4/40		6.7 %	0.80 [0.25, 2.59]
Total (95% CI)	**714**	**361**		**100.0 %**	**1.56 [1.21, 2.01]**

Total events: 190 (PDT), 62 (Placebo)

Heterogeneity: Chi^2 = 2.16, df = 2 (P = 0.34); I^2 =7%

Test for overall effect: Z = 3.42 (P = 0.00062)



Analysis 1.13. Comparison 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO, Outcome 13 Adverse effects: injection site.

Review: Photodynamic therapy for neovascular age-related macular degeneration

Comparison: 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

Outcome: 13 Adverse effects: injection site

Study or subgroup	PDT n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
TAP 1999	64/402	12/207		51.4 %	3.08 [1.62, 5.84]
VIP 2001	18/225	6/114		28.2 %	1.57 [0.60, 4.06]
VIM 2005	3/87	4/40		20.4 %	0.32 [0.07, 1.51]
Total (95% CI)	**714**	**361**		**100.0 %**	**2.09 [1.29, 3.39]**

Total events: 85 (PDT), 22 (Placebo)

Heterogeneity: Chi^2 = 7.38, df = 2 (P = 0.03); I^2 =73%

Test for overall effect: Z = 2.98 (P = 0.0029)

Analysis 1.14. Comparison 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO, Outcome 14 Adverse effects: infusion-related back pain.

Review: Photodynamic therapy for neovascular age-related macular degeneration

Comparison: 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

Outcome: 14 Adverse effects: infusion-related back pain

Study or subgroup	PDT n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
TAP 1999	10/402	0/207		19.6 %	10.84 [0.64, 184.05]
VIP 2001	5/225	0/114		19.7 %	5.60 [0.31, 100.35]
VIM 2005	9/87	1/40		40.8 %	4.14 [0.54, 31.56]
VIO 2007	25/244	0/120		19.9 %	25.19 [1.55, 410.23]
Total (95% CI)	**958**	**481**		**100.0 %**	**9.93 [2.82, 35.02]**

Total events: 49 (PDT), 1 (Placebo)

Heterogeneity: Chi^2 = 1.30, df = 3 (P = 0.73); I^2 =0.0%

Test for overall effect: Z = 3.57 (P = 0.00036)

Analysis 1.15. Comparison 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO, Outcome 15 Adverse effects: allergic reactions.

Review: Photodynamic therapy for neovascular age-related macular degeneration

Comparison: 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

Outcome: 15 Adverse effects: allergic reactions

Study or subgroup	PDT n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
TAP 1999	8/402	3/207		49.7 %	1.38 [0.36, 5.26]
VIP 2001	3/225	3/114		50.3 %	0.50 [0.10, 2.52]
Total (95% CI)	**627**	**321**		**100.0 %**	**0.94 [0.34, 2.56]**

Total events: 11 (PDT), 6 (Placebo)

Heterogeneity: Chi^2 = 0.90, df = 1 (P = 0.34); I^2 =0.0%

Test for overall effect: Z = 0.13 (P = 0.90)

Analysis 1.16. Comparison 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO, Outcome 16 Adverse effects: photosensitivity reactions.

Review: Photodynamic therapy for neovascular age-related macular degeneration

Comparison: 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

Outcome: 16 Adverse effects: photosensitivity reactions

Study or subgroup	PDT n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
TAP 1999	14/402	0/207		32.5 %	15.49 [0.92, 260.96]
VIP 2001	1/225	1/114		67.5 %	0.50 [0.03, 8.14]
Total (95% CI)	**627**	**321**		**100.0 %**	**5.37 [1.01, 28.60]**

Total events: 15 (PDT), 1 (Placebo)

Heterogeneity: Chi^2 = 3.32, df = 1 (P = 0.07); I^2 =70%

Test for overall effect: Z = 1.97 (P = 0.049)

Analysis 1.17. Comparison 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO, Outcome 17 Subgroup analysis: lesion area composed of classic CNV. Loss of 3 or more lines at 12 months.

Review: Photodynamic therapy for neovascular age-related macular degeneration

Comparison: 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

Outcome: 17 Subgroup analysis: lesion area composed of classic CNV. Loss of 3 or more lines at 12 months

Study or subgroup	PDT n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 No classic CNV					
VIO 2007	66/219	45/111		41.8 %	0.74 [0.55, 1.01]
VIP 2001	85/166	51/92		45.9 %	0.92 [0.73, 1.17]
Subtotal (95% CI)	**385**	**203**		**87.7 %**	**0.84 [0.69, 1.01]**
Total events: 151 (PDT), 96 (Placebo)					
Heterogeneity: Chi^2 = 1.26, df = 1 (P = 0.26); I^2 =21%					
Test for overall effect: Z = 1.85 (P = 0.065)					
2 Classic CNV > 0% to < 50%					
VIM 2005	10/36	18/38		12.3 %	0.59 [0.31, 1.09]
Subtotal (95% CI)	**36**	**38**		**12.3 %**	**0.59 [0.31, 1.09]**
Total events: 10 (PDT), 18 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.68 (P = 0.094)					
3 Classic CNV > 50% (predominantly classic)					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (PDT), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**421**	**241**		**100.0 %**	**0.81 [0.67, 0.97]**
Total events: 161 (PDT), 114 (Placebo)					
Heterogeneity: Chi^2 = 2.55, df = 2 (P = 0.28); I^2 =22%					
Test for overall effect: Z = 2.33 (P = 0.020)					

Analysis 1.18. Comparison 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO, Outcome 18 Subgroup analysis: lesion area composed of classic CNV. Loss of 3 or more lines at 24 months.

Review: Photodynamic therapy for neovascular age-related macular degeneration

Comparison: 1 PHOTODYNAMIC THERAPY WITH VERTEPORFIN VERSUS PLACEBO

Outcome: 18 Subgroup analysis: lesion area composed of classic CNV. Loss of 3 or more lines at 24 months

Study or subgroup	PDT n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 No classic CNV					
VIO 2007	114/244	63/120		41.0 %	0.89 [0.72, 1.11]
VIP 2001	91/166	63/92		39.3 %	0.80 [0.66, 0.97]
Subtotal (95% CI)	**410**	**212**		**80.3 %**	**0.85 [0.73, 0.98]**
Total events: 205 (PDT), 126 (Placebo)					
Heterogeneity: Chi^2 = 0.52, df = 1 (P = 0.47); I^2 =0.0%					
Test for overall effect: Z = 2.23 (P = 0.026)					
2 Classic CNV > 0 to < 50%					
VIM 2005	17/32	23/37		10.4 %	0.85 [0.57, 1.29]
VIP 2001	19/38	10/18		6.6 %	0.90 [0.53, 1.52]
Subtotal (95% CI)	**70**	**55**		**16.9 %**	**0.87 [0.63, 1.20]**
Total events: 36 (PDT), 33 (Placebo)					
Heterogeneity: Chi^2 = 0.02, df = 1 (P = 0.88); I^2 =0.0%					
Test for overall effect: Z = 0.83 (P = 0.41)					
3 Classic CNV > 50% (predominantly classic)					
VIP 2001	10/16	3/3		2.7 %	0.71 [0.42, 1.19]
Subtotal (95% CI)	**16**	**3**		**2.7 %**	**0.71 [0.42, 1.19]**
Total events: 10 (PDT), 3 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.30 (P = 0.19)					
Total (95% CI)	**496**	**270**		**100.0 %**	**0.85 [0.74, 0.97]**
Total events: 251 (PDT), 162 (Placebo)					
Heterogeneity: Chi^2 = 1.03, df = 4 (P = 0.90); I^2 =0.0%					
Test for overall effect: Z = 2.49 (P = 0.013)					

ADDITIONAL TABLES

Table 1. Summary of reports of the TAP and VIP trials

Title	Year	Content
TAP 1	1999	12 month outcomes
TAP 2	2001	24 month outcomes
TAP 3	2002	Baseline lesion type subgroup analysis
TAP 4	2002	Contrast sensitivity outcomes
TAP 5	2002	Open label 36 month outcomes
TAP 6	2004	Natural history of minimally classic lesions
TAP 7	2005	48 month open label outcomes
TAP 8	2006	60 month open label outcomes
TAP & VIP 1	2003	Effect of baseline lesion characteristics and vision on outcome
TAP & VIP 2	2003	Fluorescein angiography guidelines for grading lesions and repeatability
TAP & VIP 3	2004	Acute Severe Visual Acuity Decrease
VIP 1	2001	12 month outcomes for neovascular membranes due to pathologic myopia
VIP 2	2001	24 month outcomes occult no classic lesions
VIP 3	2003	24 month outcomes for neovascular membranes due to pathologic myopia
VIP 4	2006	Natural history of large occult lesions

Table 2. Outcome reporting grid

	TAP 1999	VIP 2001	VIM 2005	VIO 2007
3+ lines 12 mths	√	√	√	√
3+ lines 24 mths	√	√	√	√
6+lines 12 mths	√	√(subgroup only)	√	√
6+ lines 24 mths	√	√	√	√

Table 2. Outcome reporting grid (*Continued*)

Final mean VA 12 mths	Mean value reported but no measures of variability	√(subgroup only)	Median value only reported	√
Final mean VA 24 mths	Mean value reported but no measures of variability	√(subgroup only)	Median value only reported	√
Change in VA 12 mths	Mean value reported but no measures of variability	√(subgroup only)	Mean change reported in graph but no measures of variability	√
Change in VA 24 mths	Mean value reported but no measures of variability	√(subgroup only)	Mean change reported in graph but no measures of variability	√
Contrast sensitivity 12 mths	√	Outcome probably measured but not clear if analysed	Not reported; unclear if data collected	Not reported; unclear if data collected
Contrast sensitivity 24 mths	√	√(subgroup only)	Not reported; unclear if data collected	Not reported; unclear if data collected
New vessel growth 12 mths	√		"Angiographic progression to predominantly classic CNV"	Clear that angiographic outcomes analysed but only reported as not significant
New vessel growth 24 mths	√		"Angiographic progression to predominantly classic CNV"	Clear that angiographic outcomes analysed but only reported as not significant
Quality of life	QOL study mentioned in protocol but no data reported		Not reported; unclear if data collected	Not reported; unclear if data collected
Adverse outcomes				
Visual disturbance	√	√	√	Not reported
Vitreous haemorrhage	√	Not reported	Not reported	Not reported
Retinal capillary nonperfusion	√	Not reported	Not reported	Not reported
Injection site adverse event	√	√	√	Not reported

Table 2. Outcome reporting grid (*Continued*)

Infusion-related back pain	√	√	√	√
Allergic reactions	√	√	√	Not reported
Photosensitivity reactions	√	√	√	Not reported
Severe vision decrease within 7 days	√	√	√	Not reported
Deaths	Not reported	Not reported	√	√
Retinal vascular occlusive events	Not reported	Not reported	√	Not reported
Subretinal/intraretinal haemorrhage	Not reported	Not reported	√	Not reported
Discontinuation	Not reported	Not reported	Not reported	√

Table 3. Mean change in visual acuity

Number of letters visual acuity lost	12 months			24 months		
	PDT	Placebo	Difference	PDT	Placebo	Difference
TAP 1999*	11	17.5	6.5	13.4	19.6	6.2
VIP 2001	15.6	20.8	5.2	19	25.5	6.5
VIM 2005**	9	13.5	4.5	16	21	5
VIO 2007***	11.2	13.3	2.1	14.8	17.8	3

*calculated from reported number of lines lost

** median score: reported test of difference between 2 groups: P (12 months) =0.36; p(24 months) = 0.12

*** reported test of difference between 2 groups: P (12 months) =0.26; p(24 months) = 0.14

Table 4. Final visual acuity score

Number of letters visual acuity	12 months			24 months		
	PDT	Placebo	Difference	PDT	Placebo	Difference
TAP 1999	42	35	7	39.4	32.9	6.5
VIP 2001	50	44	6	47	40	7
VIM 2005	49	39	10	41.5	36	-5.5
VIO 2007	45.9	42.4	3.5*	42.3	37.8	4.5**

*P = 0.11 (2 tailed ttest calculated from data reported: PDT group SD=19.8, placebo group SD=18.3).
**P = 0.05. (2 tailed ttest calculated from data reported: PDT group SD=20.8, placebo group SD=18.0).

Table 5. Lesion area composed of classic CNV

Lesion area composed of classic CNV	50% or more "predominantly classic"	Some classic CNV but less than 50%	No classic CNV (occult only)	Unclear
TAP 1999	40%	50%	9%	1%
VIP 2001	6%	17%	68%	10%
VIM 2005	0%	78%	13%	9%
VIO 2007	No data provided however patients enrolled in the trial had to have "occult CNV with evidence of disease progression"			

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Macular Degeneration
#2 MeSH descriptor Retinal Degeneration
#3 MeSH descriptor Retinal Neovascularization
#4 MeSH descriptor Choroidal Neovascularization
#5 ((macul* OR retina* OR choroid*) AND (degener* OR neovasc*))
#6 maculopath*
#7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6)
#8 MeSH descriptor Photochemotherapy
#9 MeSH descriptor Photosensitizing Agents
#10 photodynamic* or PDT or photosensit*
#11 MeSH descriptor Porphyrins
#12 verteporfin* or visudyne*
#13 benzoporphyrin* or porphyrin*
#14 (#8 OR #9 OR #10 OR #11 OR #12 OR #13)
#15 (#7 AND #14)

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 macular degeneration/
14. exp retinal degeneration/
15. exp retinal neovascularization/
16. exp choroidal neovascularization/
17. maculopath$.tw.
18. ((macul$ or retina$ or choroid$) adj3 degener$).tw.
19. ((macul$ or retina$ or choroid$) adj3 neovasc$).tw.
20. or/13-19
21. exp photochemotherapy/
22. exp photosensitizing agents/
23. (photodynamic$ or PDT or photosensit$).tw.
24. exp porphyrins/
25. (verteporfin$ or visudyne$).tw.
26. (benzoporphyrin$ or porphyrin$).tw.
27. or/21-26
28. 20 and 27
29. 12 and 28

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$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp retina macula age related degeneration/
34. exp retina macula degeneration/
35. exp retina degeneration/
36. exp subretinal neovascularization/
37. exp neovascularization pathology/
38. maculopath$.tw.
39. ((macul$ or retina$ or choroid$) adj3 degener$).tw.
40. ((macul$ or retina$ or choroid$) adj3 neovasc$).tw.
41. or/33-40
42. exp photodynamic therapy/
43. exp photosensitizing agent/
44. (photodynamic$ or PDT or photosensit$).tw.
45. exp porphyrin/
46. (verteporfin$ or visudyne$).tw.
47. (benzoporphyrin$ or porphyrin$).tw.
48. or/42-47
49. 41 and 48
50. 32 and 49

Appendix 4. Results of searches for previous versions of this review

The original electronic searches identified 76 reports. We found one randomised controlled trial (TAP 1999). Since the searches were updated in February 2001, May 2002 and January 2003 one further study was identified and included in the review (VIP 2001).
A further search update was conducted in January 2005. A total of 284 new reports were found. No reports of new trials were found though there were a number of new reports from existing trials including new outcomes on contrast sensitivity (Rubin 2002), central visual field function (Schmidt-Erfurth 2004) and subretinal neovascular morphology (Schmidt-Erfurth 2003). In addition we found one systematic review (Meads 2004), a meta-analysis of safety results in TAP and VIP (Azab 2004) and a cost-utility analysis (Hopley 2004). A report on severe visual acuity decrease in TAP and VIP (Arnold 2004) was also considered relevant. An outcome study reporting visual function and related quality of life was found (Armbrecht 2004). A number of papers from the TAP and VIP studies were found including guidelines for evaluation of fluorescein angiographic findings and treatment (Barbazetto 2003), determinants of outcome according to lesion size, visual acuity and lesion composition (Blinder 2003), baseline lesion composition's impact on vision outcome (Bressler 2002) and natural history of minimally classic lesions (Bressler 2004a).
We found one traditional review of PDT (Woodburn 2002) mentions trials on other agents, such as etiopurpurin (Purlytin) and motexafin lutetium (Optrin) undergoing phase III and phase II trials respectively.
The search conducted in March 2007 revealed the findings of one new trial - the verteporfin therapy of subfoveal minimally classic choroidal neovascularisation in age-related macular degeneration trial which was previously in the ongoing studies list (VIM 2005). The search found 446 new references and found reports of some of the other studies in abstract form only. (see details of ongoing studies). The VIM 2005 study appeared relevant and worthy of inclusion.

WHAT'S NEW

Last assessed as up-to-date: 22 April 2009.

Date	Event	Description
12 August 2009	New search has been performed	Issue 4, 2009: Updated searches yielded one new trial.

HISTORY

Review first published: Issue 2, 2000

Date	Event	Description
17 September 2008	Amended	Converted to new review format.
22 May 2007	New citation required and conclusions have changed	Substantive amendment. One new trial (VIM 2005) has been added

CONTRIBUTIONS OF AUTHORS

RW participated in protocol development, study selection and assessment and writing up of the original and update of the review.

JE participated in protocol development, study selection and assessment, data abstraction and entry and writing up of the original and update of the review.

LS participated in protocol development, study selection and assessment, data abstraction and entry and writing up of the original and update of the review.

KH abstracted data and entered data into RevMan for the update of the review and participated in the updating of the review text.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Moorfields Eye Hospital NHS Trust, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have added in a new outcome "gain of 3+ lines of visual acuity".

We have assessed risk of bias using the new Cochrane Collaboration's tool for assessing the risk of bias.

INDEX TERMS

Medical Subject Headings (MeSH)

*Photochemotherapy; Glucose [therapeutic use]; Macular Degeneration [complications; *drug therapy]; Photosensitizing Agents [*therapeutic use]; Porphyrins [*therapeutic use]; Randomized Controlled Trials as Topic; Retinal Neovascularization [*drug therapy]

MeSH check words

Humans