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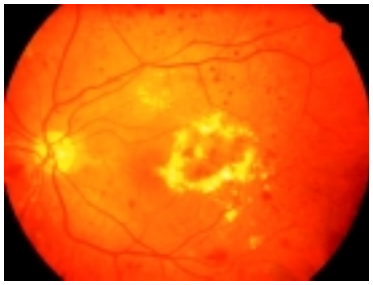

PHILIPPINE JOURNAL OF
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GUEST EDITORIAL

# The significance of evidence-based ophthalmology in clinical practice: why bother?

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PRACTICING eye care and thinking about evidence is a paradigm shift.

We were taught traditionally that A causes B and that C is the treatment for E. No questions were asked—there was no uncertainty. It was probably different in the days when José Rizal studied ophthalmology because then they knew so much less and minds had to be kept open to force progress. Since then, much has been discovered and certainty has become the preferred approach—it's simpler to be sure about things but, in the end, less interesting. With an evidence-based approach, every "certainty" is questioned, every assertion challenged. And because of this, medicine is becoming interesting again. We move from learning facts by rote to understanding uncertainty and being able to estimate its dimensions.

Relative risks or odds ratios with confidence limits estimate the extent to which the risk or probability of an outcome might be modified by an intervention or exposure. This is a more sophisticated approach to the simple dichotomous concept, perhaps inevitably preferred by surgeons, that a treatment will work or not as the case may be. Naturally, surgeons prefer a high benefit to risk ratio; a high probability of a positive outcome to justify submitting the patient to the knife. Physicians are more used to relatively small risk modifications in their interventions and perhaps this is why evidence-based medicine is so called and that evidence-based surgery is a less widespread phenomenon.

Ophthalmologists are fortunate to practice both medicine and surgery in "general practice," though many of us are becoming superspecialized to the extent that some of us are now only performing one operation.

Cataract surgery dominates our practice and we are fortunate to have such an excellent intervention where the benefits are large and the risks are small. We still need to quantify those risks and evidence to inform patients about the likelihood of an adverse outcome. These risks—especially rare but serious adverse events—cannot be well quantified from randomized, controlled trials and better data are provided from large and representative outcome studies (sometimes termed phase 4 "open-label" studies).

Changes in practice are generally justified by the provision of good evidence that the new treatment is better. This has not always been the case in eye care. Phacoemulsification was implemented across the world without a single RCT justifying the change in practice. The desire to be modern and the perhaps obvious advantage of a small incision not needing sutures were sufficient to justify the change. But what about the cost?

Ultimately, a trial was carried out in the UK and the cost issue in particular was addressed.[1] In the context of publicly funded practice in the affluent

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western world, cost benefit could be demonstrated on the basis of a reduced requirement for outpatient follow-up. But what about poorer countries where the cost of "disposable" consumables might be a problem? This has been addressed by a series of excellent trials from Pune, India comparing traditional extracapsular surgery (ECCE) to small-incision sutureless cataract surgery (SISCS) and SISCS to Phaco. SISCS is as cheap as ECCE and has outcomes nearly as excellent as those of phaco.[2, 3, 4]

Surgical trials can be problematic when skills must be acquired in a new technique before optimum outcomes can be achieved—the learning curve. Sometimes it might be difficult for the same surgeon to be equally skilled in both techniques. In the Moorfields trial, the trialists admitted to having to relearn their ECCE skills in order to take part in the study.

An alternative trial design is to randomize participants to surgery performed by experts in the specific technique under comparisons so that the learning curve is avoided and optimum surgical skill is employed in all arms of comparison.[5] ECCE in skilled hands probably achieves equally excellent outcomes but requires refinement in section design and suturing technique. In fact, there are numerous variables at play in determining the excellence of outcome, and these are not just about surgical technique. There are many questions about calculating intraocular-lens power and selecting the most suitable lens material and shape and the way the lens is introduced into the eye.

Abandoning the ECCE technique has meant that certain skills, such as suturing a corneal or limbal wound, have been lost to the trainee. It is hard to measure the impact of such a development, but it is clearly not desirable when the ability—necessary to manage the closure of corneal perforations and to convert when small incision surgery has failed—is lost.

The assumption that phaco was a doubtless benefit is even less clear when we realize that our younger surgeons have become dependent on high technology and expensive consumables. We should realize that equal to the challenge we face in finding better treatments for common blinding diseases is that of simply delivering a basic standard of care equitably to those less advantaged in the world where, of course, there is the greatest need. I believe this is a much greater challenge than pushing forward the frontiers of technology—minimal gains for greater cost in richer countries when major gains for much less cost can be made in poorer ones.

We need to reflect carefully and employ the highest standards of evidence-based methodology when we make major decisions about changes in our practice. When a new product is being heavily marketed, it becomes even more important that at least some intelligent eye surgeons ask questions about evidence and cost benefit and effectiveness. Otherwise, scarce resources can easily be wasted on the latest modern technology that turns out to provide minimal additional clinical benefit at huge additional cost.

In Britain, the National Institute of Clinical Excellence (NICE) has been established to make evidence-based decisions about providing new treatments in the National Health Service. They have considered the provision of Photodynamic Therapy for the treatment of neovascular age-related macular degeneration.[6] Their review refers to our Cochrane Review, a recently updated version of which appears in this issue. We could not conclude benefit, and in particular, cost benefit could not be demonstrated from the existing evidence. There were doubts about the validity of the subgroup analyses and we concluded that more evidence was needed. A particular concern is the opportunity cost of such new treatment when it has already been demonstrated in the UK that services for the provision of simple low-vision aids and rehabilitation for the visually impaired are unevenly and inequitably distributed across the country.

The Philippine Academy of Ophthalmology is well ahead of the field in considering the importance of evidence in determining practice. Their last meeting was dominated by an EBM theme and numerous trainees are now engaged in the conduct of systematic reviews for the Cochrane Collaboration. It is essential that this culture grows for the scientific and equitable development of eye care and for the prevention of blindness throughout the world.

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COCHRANE REVIEW

# Photodynamic therapy for neovascular age-related macular degeneration

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## ABSTRACT

**Background**

In neovascular age-related macular degeneration (ARMD) 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.

**Objective**

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

**Search strategy**

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which includes the Cochrane Eyes and Vision Group Trials Register) on *The Cochrane Library* (Issue 1, 2005), MEDLINE (1966 to January 2005), EMBASE (1980 to January 2005). We used the Science Citation Index to search for reports that cited relevant studies. We contacted experts in the field and searched the reference lists of relevant studies.

**Selection criteria**

We included randomized trials of PDT in people with choroidal neovascularization due to ARMD.

**Data collection and analysis**

Two authors independently extracted the data. Relative risks were combined using a fixed-effect model after testing for heterogeneity.

**Main results**

Two published trials were identified that randomized 948 participants to verteporfin therapy compared to 5% dextrose in water. Both trials were performed by the same investigators using largely the same clinical centers and funded by manufacturers of verteporfin. Outcome data were available at 12 and 24 months after the first treatment. Participants received on average five treatments over two years. The relative risk of losing three or more lines of visual acuity at 24 months comparing the intervention with the control

***Keywords:*** *Photodynamic therapy, Neovascularization, Age-related macular degeneration*

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group was 0.77 (95% confidence interval 0.69 to 0.87). The relative risk of losing six or more lines of visual acuity at 24 months comparing the intervention with the control group was 0.62 (95% confidence interval 0.50 to 0.76). The results at 12 months were similar to those at 24 months. The most serious adverse outcome, acute (within 7 days of treatment) severe visual acuity decrease, occurs in about one in 50 patients.

**Reviewers' conclusions**

Photodynamic therapy in people with choroidal neovascularization due to ARMD is probably effective in preventing visual loss though there is doubt about the size of the effect. Outcomes and potential adverse effects of this treatment should be monitored closely. 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.

## BACKGROUND

Age-related macular degeneration (ARMD) 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 ARMD. 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 ARMD.

There are 2 main types of ARMD. In geographic atrophy (dry) ARMD, the retinal pigment epithelium is lost completely in localized areas. In neovascular (wet) ARMD, subretinal 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 hemorrhage that leads to larger scars or macular edema and significant loss of vision. This review was concerned with treatment for neovascular age-related macular degeneration.

Subretinal 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 2 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.

Trials have shown that early laser photocoagulation of classic extrafoveal membranes (those not directly underneath the fovea at the center of the macula) could delay the loss of vision in a small number of patients.[1] However, most patients present with subfoveal membranes, and while 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 (PDT), 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. This light is strong enough to activate the chemicals, causing them to emit free radicals that destroy the blood vessels, but is not strong enough to cause damage to the overlying retina.

## OBJECTIVE

The aim of this review was to examine the effects of photodynamic therapy in the treatment of neovascular ARMD.

## CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

**Types of studies**

We included randomized controlled trials.

**Types of participants**

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

**Types of interventions**

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

**Types of outcome measures**

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.

The secondary outcomes for this review were:

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

## SEARCH STRATEGY

**Electronic searches**

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Group Trials Register) on *The Cochrane Library*, Medline, and EMBASE.

We used the following strategy to search CENTRAL Issue 1, 2005:

#1 MACULAR DEGENERATION
#2 RETINAL DEGENERATION
#3 NEOVASCULARIZATION PATHOLOGIC
#4 (macula* or retina* or choroid*)
#5 (degenerat* or neovascular*)
#6 (#4 and #5)
#7 maculopath*
#8 (#1 or #2 or #3 or #6 or #7)
#9 PHOTOCHEMOTHERAPY
#10 PHOTOSENSITIZING AGENTS
#11(photosensit* or photodynamic* or pdt or verteporfin or visudyne)
#12 (#9 or #10 or #11)
#13 (#8 and #12)

We used the following strategy combined with the Cochrane highly sensitive search strategy[2] to search MEDLINE on SilverPlatter to January 2005.

#1 explode "Macular-Degeneration"/all SUBHEADINGS in MIME,MJME
#2 explode "Retinal-Degeneration" / all SUBHEADINGS in MIME,MJME
#3 explode "Choroidal-Neovascularization" / all SUBHEADINGS in MIME,MJME
#4 ( ((macul* or retina* or choroid*)near (degener* or neovasc*)) in TI )or( ((macul* or retina* or choroid*)near (degener* or neovasc*)) in AB )
#5 maculopath* in TI
#6 maculopath* in AB
#7 #1 or #2 or #3 or #4 or #5 or #6
#8 explode "Photochemotherapy-" / all SUBHEADINGS in MIME,MJME
#9 explode "Photosensitizing-Agents" / all SUBHEADINGS in MIME,MJME
#10 ( ((photosensiti* near agent*)or porphyrin* or benzoporphyrin*) in AB )or( ((photosensiti* near agent*)or porphyrin* or benzoporphyrin*) in NM ) or ( ((photosensiti* near agent*)or porphyrin* or benzoporphyrin*) in TI )
#11 ( (photodynamic* or PDT) in AB ) or ( (photodynamic* or PDT) in TI )
#12 ( (verteporfin or visudyne) in AB )or ( (verteporfin or visudyne) in TI )
#13 #8 or #9 or #10 or #11 or #12
#14 #7 and #13

We used the following strategy to search EMBASE on Ovid to January 2005.

1. exp Retina Macula Age Related Degeneration/
2. exp Retina Degeneration/
3. exp "Neovascularization (Pathology)"/
4. exp Subretinal Neovascularization/
5. ((macul$ or retina$ or choroid$) adj5 (degener$ or neovasc$)).ab,ti.
6. maculopath$.ab,ti.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp Photodynamic Therapy/
9. exp Photosensitizing Agent/
10. (photodynamic$ or PDT).ab,ti.
11. (photosensit$ adj3 agent$).ab,ti.
12. (verteporfin or visudyne).ab,tn,ti.
13. 8 or 9 or 10 or 11 or 12
14. 7 and 13

To identify randomized controlled trials, we combined this search with the following strategy:

#1 Randomized Controlled Trial/
#2 exp Randomization/
#3 Double Blind Procedure/
#4 Single Blind Procedure/
#5 random$.ab,ti.
#6 #1 or #2 or #3 or #4 or #5
#7 (animal or animal experiment).sh.
#8 human.sh.
#9 #7 and #8
#10 #7 not #9
#11 #6 not #10
#12 Clinical Trial/
#13 (clin$ adj3 trial$).ab,ti.
#14 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).ab,ti.
#15 exp PLACEBO/
#16 placebo$.ab,ti.
#17 random$.ab,ti.
#18 experimental design/
#19 Crossover Procedure/
#20 exp Control Group/
#21 exp LATIN SQUARE DESIGN/
#22 #12 or #13 or #14 or #15 or #16 or #17 or #18 or#19 or #20 or #21
#23 #22 not #10
#24 #23 not #11
#25 exp Comparative Study/
#26 exp Evaluation/
#27 exp Prospective Study/
#28 (control$ or prospectiv$ or volunteer$).ab,ti.
#29 #25 or #26 or #27 or #28
#30 #29 not #10
#31 #30 not (#11 or #23)
#32 #11 or #24 or #31

**Manual searches**

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.

## METHODS OF THE REVIEW

**Selection of trials**

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.

**Assessment of methodological quality**

Two authors independently assessed study quality according to methods set out in Section 6 of the *Cochrane Handbook for Systematic Reviews of Interventions*.[3] 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.

**Data collection**

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 4.2 (The Cochrane Collaboration, Oxford, United Kingdom) and we checked any inconsistencies between the two against the study report.

**Data synthesis**

Our original data analysis plan was to summarize data from studies collecting similar outcome measures with similar follow-up times using the Peto method, after testing for heterogeneity between trial results using a standard chi square test. The main outcome analyzed, loss of three or more lines of visual acuity at 12 and 24 months follow up, occurred relatively frequently in the trial cohort. The odds ratio, therefore, does not approximate the relative risk. We present relative risks in this review. We planned to conduct sensitivity analyses to determine the effect of excluding studies given a grade of C (inadequate) on any parameter of quality but to date this has not been necessary.

## DESCRIPTION OF STUDIES

**Finding the trials**

The original electronic searches identified 76 reports. We found one randomized controlled trial (TAP 1999).[4] Since the searches were updated in February 2001, May 2002, and January 2003, one further study has been identified and included in the review (VIP 2001) (Table 1).[5]

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,[6] central-visual-field function,[7] and subretinal neovascular morphology.[8] In addition we found one systematic review,[9] a metaanalysis of safety results in

Table 1. **Characteristics of included studies.**

| Study | Methods | Participants | Interventions | Outcomes | Notes | Allocation concealment |
|---|---|---|---|---|---|---|
| TAP 1999[a] | Randomized controlled trial: 1 eye per patient was randomized in a 2:1 (treatment:control) ratio. | 609 people with subfoveal CNV lesions caused by ARMD with evidence of classic CNV and best corrected acuity of approximately 20/40 to 20/200. | Photodynamic therapy following verteporfin injection versus photodynamic therapy following intravenous 5% dextrose. | Visual acuity at 12 and 24 months. | | A |
| VIP 2001[b] | Randomized controlled trial: 1 eye per patient was enrolled. Randomization in sealed envelopes stratified by clinical center. | 339 people with subfoveal CNV caused by ARMD. | Photodynamic therapy following verteporfin injection versus photodynamic therapy following intravenous 5% dextrose. | Visual acuity at 12 and 24 months; Secondary outcomes include contrast sensitivity and changes in angiographic outcomes. | Randomized 2:1 to verteporfin treatment. | A |

[a]Published and unpublished data
[b]Published data only
ARMD – age-related macular degeneration
CNV – choroidal neovascularization

TAP and VIP[10] and a cost-utility analysis.[11] A report on severe visual-acuity decrease in TAP and VIP[12] was also considered relevant. An outcome study reporting visual function and related quality of life was found.[13] A number of papers from the TAP and VIP studies were found including guidelines for evaluation of fluorescein angiographic findings and treatment,[14] determinants of outcome according to lesion size, visual acuity and lesion composition,[15] baseline lesion composition's impact on vision outcome,[16] and natural history of minimally classic lesions.[17]

We found no reports from ongoing trials (Table 2) but one traditional review of PDT[18] mentions trials on other agents, such as etiopurpurin (Purlytin) and motexafin lutetium (Optrin) undergoing phase III and phase II trials respectively.

**Summary of the characteristics of included studies**

Table 1 shows the summary and details of the included studies.

TAP 1999 was a multicenter study that investigated 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 neovascularization (CNV) caused by ARMD. The majority of participants were white (98%) with a mean age of 75 years. TAP 1999 was originally devised as 2 concurrent trials in order to comply with regulatory agency requirements. The study protocols were identical. Ten of the clinical centers were assigned to study A and 12 to study B. As the results of the trials were similar and the investigators analyzed and presented the data as one trial we have also assessed them 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, most 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/cm2 at an intensity of 600 mW/cm2 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 3 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 5 treatments were necessary to stabilize the situation.[19, 20] 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 control 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,

Table 2. **Characteristics of ongoing studies.**

| Study | Trial name or title | Participants | Interventions | Outcomes | Completion date | Contact information |
|---|---|---|---|---|---|---|
| ADD-V[a] | Addition of an anti-inflammatory called Voltaren Ophthalmic® | | | | | |
| Japan[a] | Visudyne for CNV due to ARMD | | | | Results expected at end 2003 | Nic Gwatkin Head of Marketing Novartis Ophthalmics |
| VALIO[a] | Altered light treatment using delayed light after Visudyne in occult ARMD | | | | | Nic Gwatkin Head of Marketing, Novartis Ophthalmics |
| VER[a] | Visudyne in early retreatment phase IIIB clinical trial | People with predominantly classic CNV (321 people at 31 sites enrolled) | Visudyne therapy every 3 months (standard) versus more frequent regimen | | Results expected at end 2003 | Nic Gwatkin Head of Marketing Novartis Ophthalmics |
| VIM[a] | Visudyne in minimally classic study | | Visudyne therapy versus Visudyne therapy with reduced light intensity versus placebo | | | Nic Gwatkin Head of Marketing Novartis Ophthalmics |
| VIO[a] | Visudyne therapy in occult phase III trial | People with occult but no classic CNV due to ARMD | | | | Nic Gwatkin Head of Marketing Novartis Ophthalmics |

[a]Published data only

1.8 and 2.4 treatments were given in the verteporfin and control groups, respectively.

**Methodological quality of included studies**

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 stratified by clinical center. 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 1 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 are of different colors (green versus colorless), the solutions and the intravenous tubing were covered with foil. The fundus appearance did not change during treatment to indicate whether verteporfin or placebo had been infused. There was no other physical evidence of treatment as verteporfin dye is excreted in the feces and does not cause any color change; neither does it alter the color of the skin or urine. It was, therefore, unlikely that participants were aware of their treatment status. In TAP 1999, the study investigators reported 2 cases where the participants who were unmasked and 4 cases where the ophthalmologists who were unmasked 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 2 treatment groups. The analysis was intention-to-treat, and subgroup analyses were planned a priori (Bressler N, personal communication). 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 inputted using the method of last observation carried forward.

## RESULTS

The realistic aim of photodynamic therapy is to slow down the progression of ARMD, not to produce normal vision. Outcomes were, therefore, expressed as risks of a

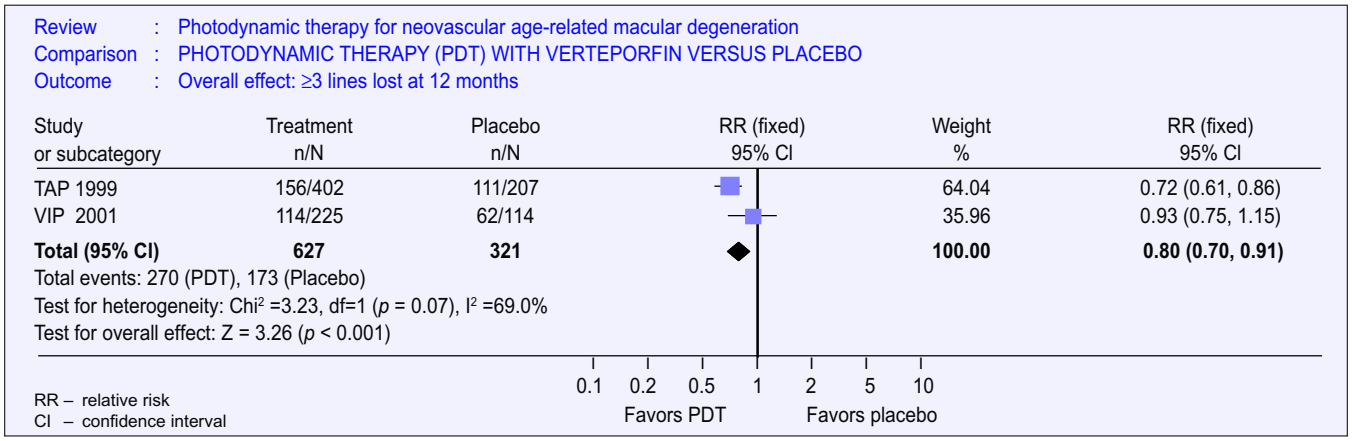


**Figure 1.** Overall effect: loss of 3 or more lines of visual acuity at 12 months.

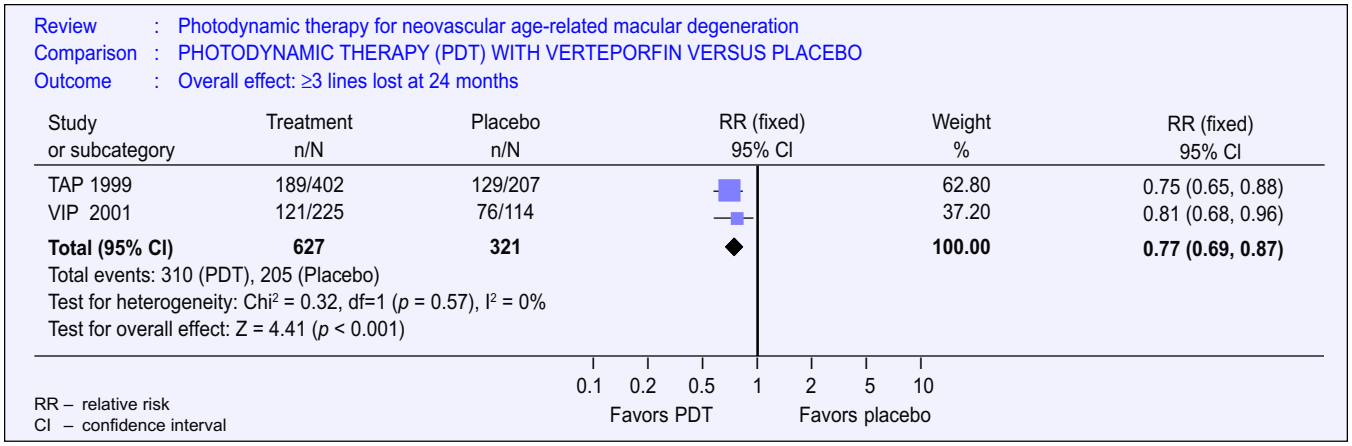


**Figure 2.** Overall effect: loss of 3 or more lines of visual acuity at 24 months.

poor outcome rather than as improvements in vision. All results were based on the comparison of patients randomized to receive verteporfin with those randomized to receive placebo (control).

**Overall analysis**

*Loss of 3 or more lines of visual acuity*

A total of 948 participants from TAP 1999 and VIP 2001 were included in the metaanalysis. At 12 months, the pooled relative risk (RR) of losing 3 or more lines of visual acuity was 0.80 (Figure 1) and the relative risk reduction (RRR) was, therefore, 0.20 (95% CI 0.09 to 0.30). This analysis was done using a fixed-effects model. A random-effects model gave a nonsignificant result, largely because it placed more weight on the VIP study (pooled RR 0.82; 95% CI 0.64 to 1.04).

At 24 months, the pooled RR was 0.77 (Figure 2) and the RRR was, therefore, 0.23 (95% CI 0.13 to 0.31). The random-effects model yielded a similar result.

*Loss of 6 or more lines of visual acuity*

At 12 months, the RR of losing 6 or more lines of visual acuity was 0.62 (Figure 3) (TAP 1999 only, data not reported for VIP 2001). The RRR was, therefore, 0.38 (95% CI 0.13 to 0.56). At 24 months, the pooled RR was 0.62 (Figure 4). The RRR was 0.38 (95% CI 0.24 to 0.50).

*Mean number of lines lost*

In TAP 1999, the mean number of lines of vision lost at 12 months was 2.2 in the intervention group and 3.5 in the control group. The difference was 1.3, with fewer lines lost in the intervention group. The $p$ value for the difference in the mean number of lines lost was reported as $p < 0.001$ (Wilcoxon rank sum test). At 24 months, the mean number of lines of vision lost was 2.7 in the intervention group and 3.9 in the control group, a difference of 1.2 lines ($p < 0.001$). The standard deviations for the mean numbers of lines lost were not reported and, therefore, the confidence intervals could not be calculated.

Data on mean number of lines lost for the whole VIP 2001 study group were not reported.

**Subgroup analyses**

Subgroup data were available only for the outcome "loss of 3 or more lines of visual acuity" in TAP 1999 but for both outcomes (loss of 3 lines and loss of 6 lines) in VIP 2001.

*Evidence of occult choroidal neovascularization*

In TAP 1999, the RR of losing 3 or more lines of visual acuity at 12 months was 0.90 if CNV was present (95% CI 0.73 to 1.11) and 0.34 if occult CNV was absent (95% CI

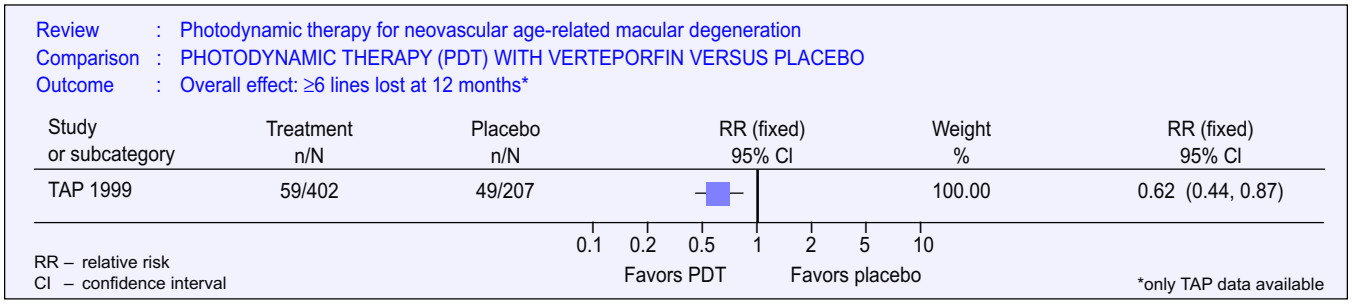


**Figure 3.** Overall effect: loss of 6 or more lines of visual acuity at 12 months.

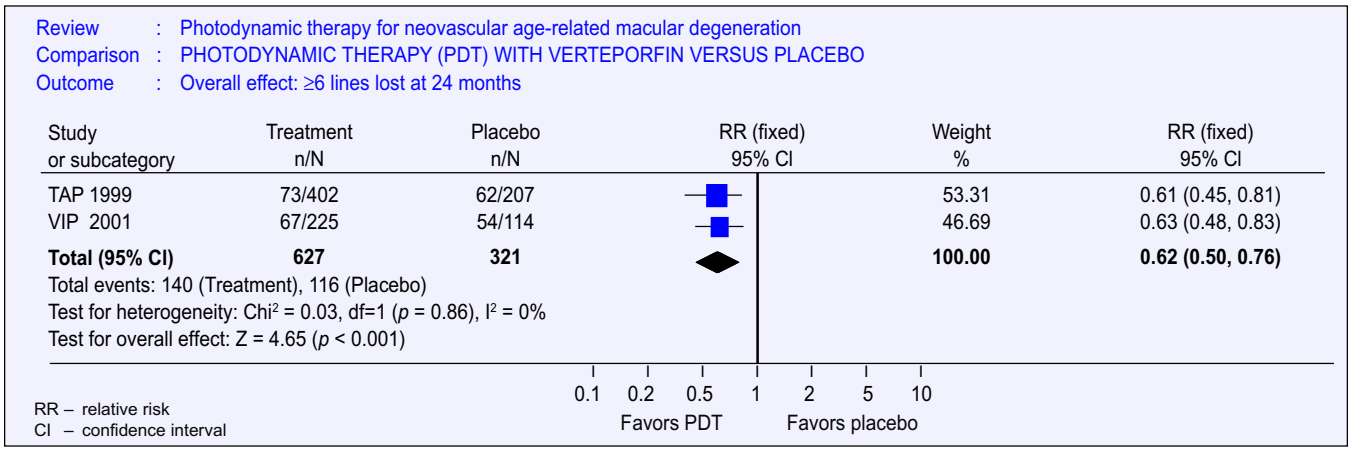


**Figure 4.** Overall effect: loss of 6 or more lines of visual acuity at 24 months.

0.22 to 0.51). At 24 months, the relative risks 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 2 subgroups was significant. Neither the 95% nor the 99% confidence intervals for these 2 subgroups overlap.

*Lesion area composed of classic choroidal neovascularization*

In TAP 1999, the proportion of the lesion composed of classic CNV was estimated as 0%; greater than 0% but less than 50%; greater than 50%. The proportion was unknown in 4 participants (3 in the treatment group and 1 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.

The pooled RR for losing 3 or more lines of visual acuity at 12 months for the group with 0% CNV was 0.84 (95% CI 0.68 to 1.04). Results for 3 or more lines lost at 12 months were not reported for the other two subgroups in the VIP 2001 study. In TAP 1999, the RR for losing 3 or more lines of visual acuity at 12 months in people with more than 0% but less than 50% CNV was 0.99 and 0.54 for greater than 50% CNV (Figure 5).

At 24 months, the pooled RR for losing 3 or more lines of visual acuity were 0.77, 0.93, and 0.60 (95% CI 0.48 to 0.75) respectively (Figure 6).

These results suggested 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 composed of classic CNV. 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 among these 3 subgroups was not statistically significant ($p = 0.066$).

**Number needed to treat**

We calculated the numbers needed to treat (NNTs) to prevent 1 person from losing 3 or more lines and, where possible, 1 person from losing 6 or more lines of vision. These NNTs were derived from the study population, that is, people with subfoveal CNV and a baseline visual acuity of between 20/40 and 20/200 with approximately 5 treatments over 2 years.

The NNT to prevent one person from losing 3 or more lines of vision at 24 months was 7.1 (95% CI 4.8 to 12.5). The NNT to prevent 1 person from losing 6 or more lines of vision at 24 months was 7.1 (95% CI 5.0 to 12.5).

**Other primary outcomes**

*Contrast sensitivity*

This outcome from the TAP trial was reported by Rubin 2002.[6] It was measured in participants at baseline and at three-month 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 categorized in terms of more than 6 or more than 15 letters lost since baseline. A higher proportion of those treated with placebo lost both more than 6 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 in the PDT group compared to placebo (Figure 7). For 15 letters, the RR was 0.58 (Figure 8).

*Central-visual-field function*

This was reported by Schmidt-Erfurth[7] for 46 participants of the TAP trial based in Germany. Participants in this center had various additional investigations, including Scanning Laser Ophthalmoscopic (SLO) perimetry of the

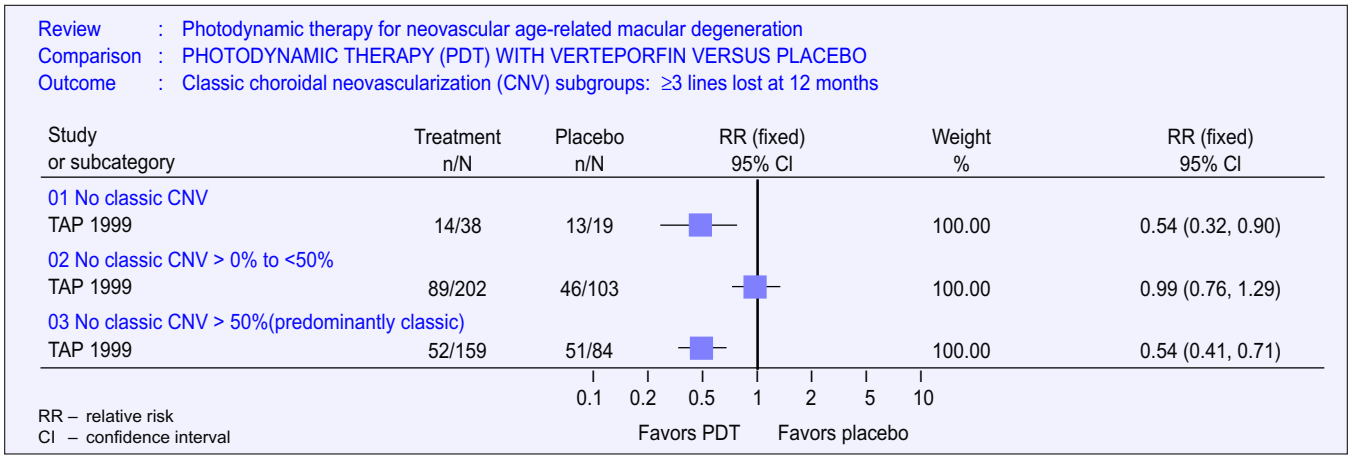


**Figure 5.** Classic CNV subgroups: loss of 3 or more lines of visual acuity at 12 months.

macula to measure the size of the central scotoma in treated and placebo groups. It was given as mean area in mm.[2] The mean area of the absolute scotoma increased in both groups but significantly more in 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 the size of the relative scotoma between groups. These differences were statistically significant at the level of $p < 0.001$ though neither standard errors of these means nor 95% confidence intervals were provided.

**Secondary outcomes**

*Neovascular-membrane morphology*

Schmidt-Erfurth's group also reported on the outcome of Confocal Indocyanine Green (ICG) angiography in the subgroup of the TAP trial participants in Germany.[8] In this case, outcomes for 60 participants were reported. It is not clear why there was a discrepancy between the 60 participants in this analysis and the 46 who underwent measurement of central scotoma as described above. Presumably 14 patients did not have SLO perimetry but did have ICG angiography.

This paper reported 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 was reported as highly significant ($p = 0.008$), but no standard errors or confidence limits were provided apart from graphically represented error bars that were not specified in the legend.

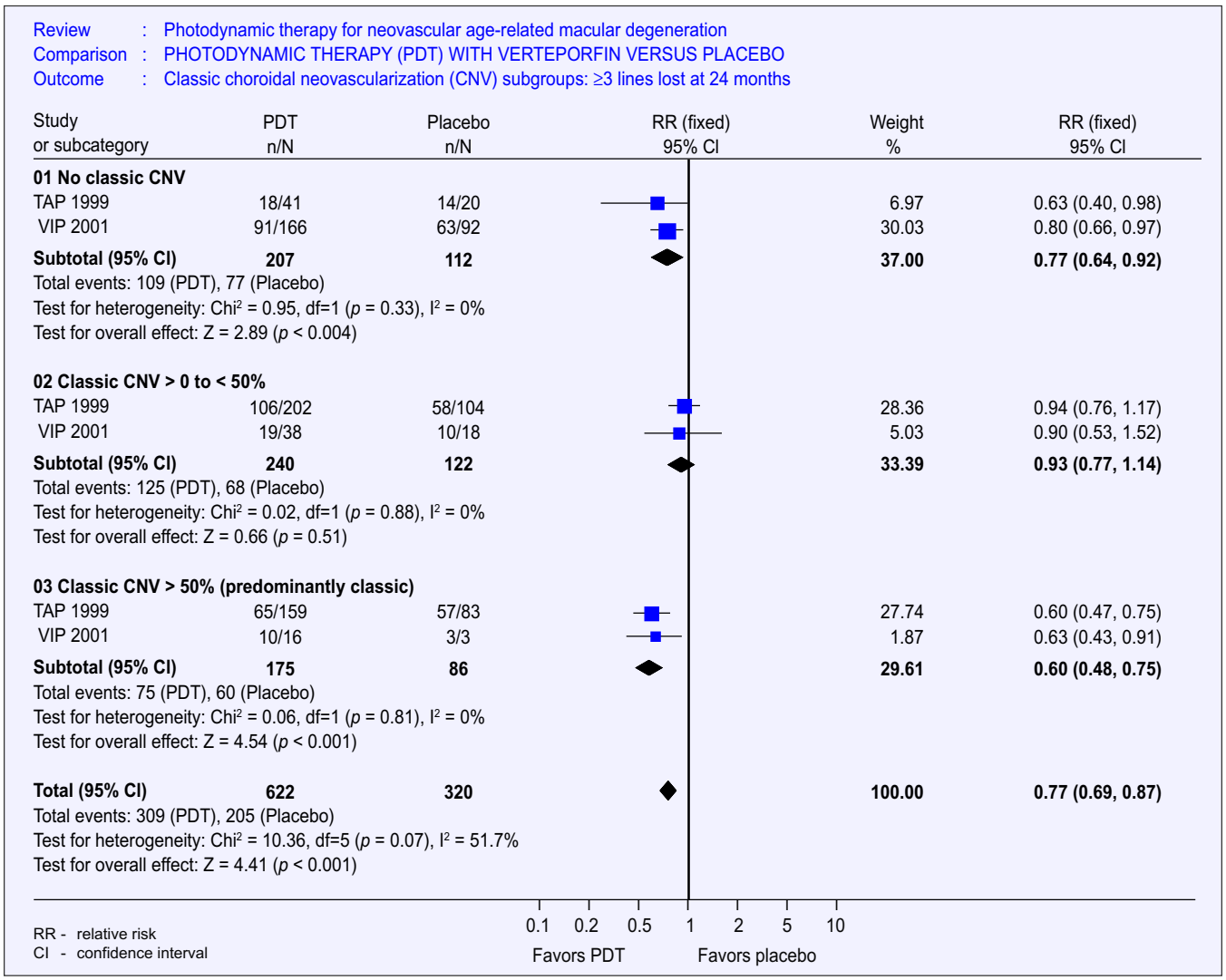


**Figure 6.** Classic CNV subgroups: loss of 3 or more lines of visual acuity at 24 months.

*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*

More information on this has become available for this update. In particular, the risk of severe and profound visual loss has been better estimated. This has been provided by two reports from the TAP[12] and VIP[10] investigators and a large phase 4, open-label study that reported on the outcomes of verteporfin PDT in 4,435 patients called the VAM study.[21]

Arnold 2004[12] focused on the occurrence of acute severe visual-acuity decrease (ASVAD). This was defined as at least a 20-letter loss (equivalent to 4 lines) within 7 days after treatment. Even though this paper reported this outcome from 2 RCTs, they described the study as an observational case series and a fairly detailed account was given of 15 events in 14 eyes. One of these was later judged as unlikely to be due to PDT. All but 2 events occurred shortly after the first treatment and only in the treated arm. Three of these events occurred in the TAP trial and 10 in the VIP. All 13 events occurred within 3 days of treatment. The absolute risk difference for both studies is 0.02 (Figure 9). The number needed to harm (NNH)

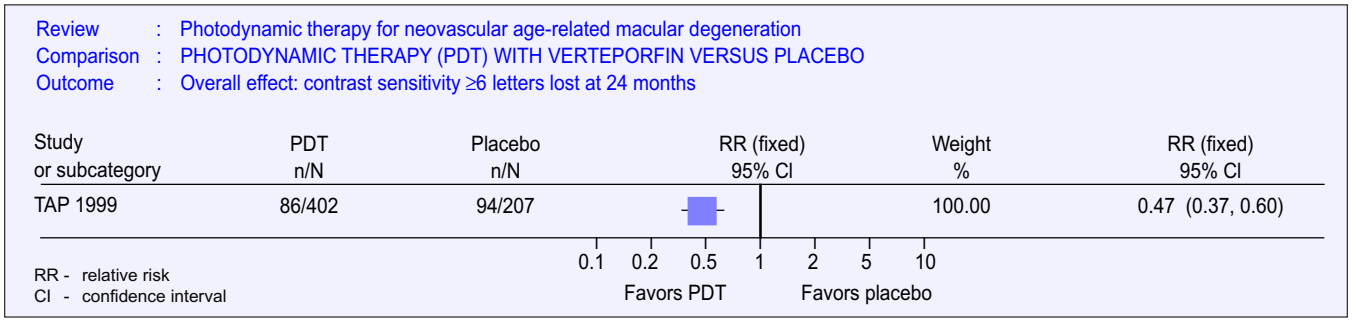


**Figure 7.** Contrast sensitivity: loss of 6 letters at 24 months.

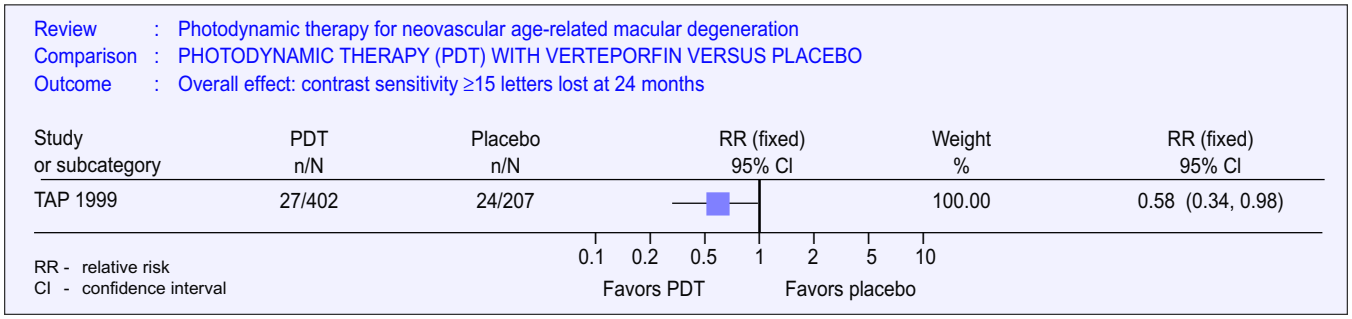


**Figure 8.** Contrast sensitivity: loss of 15 letters at 24 months.

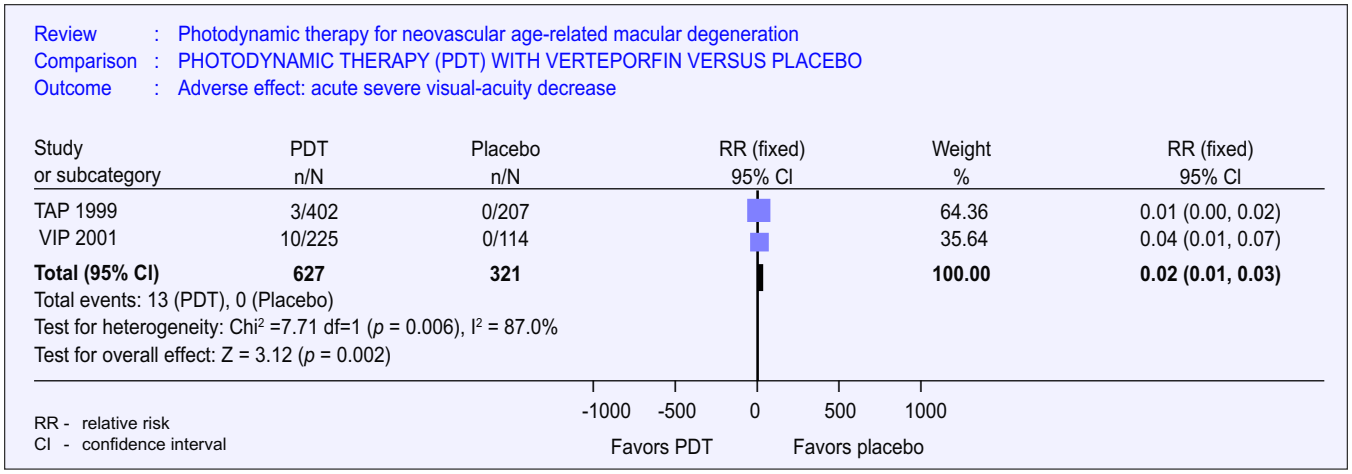


**Figure 9.** Adverse effect: acute severe visual-acuity decrease.

is estimated at 50 (range 30 to 100). That is, 1 eye will experience ASVAD in 50 treatments.

Azab 2004[10] provided these data in the context of all other adverse events reported for the 2 trials. This report was described as a metaanalysis although data were only combined for the 2 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.

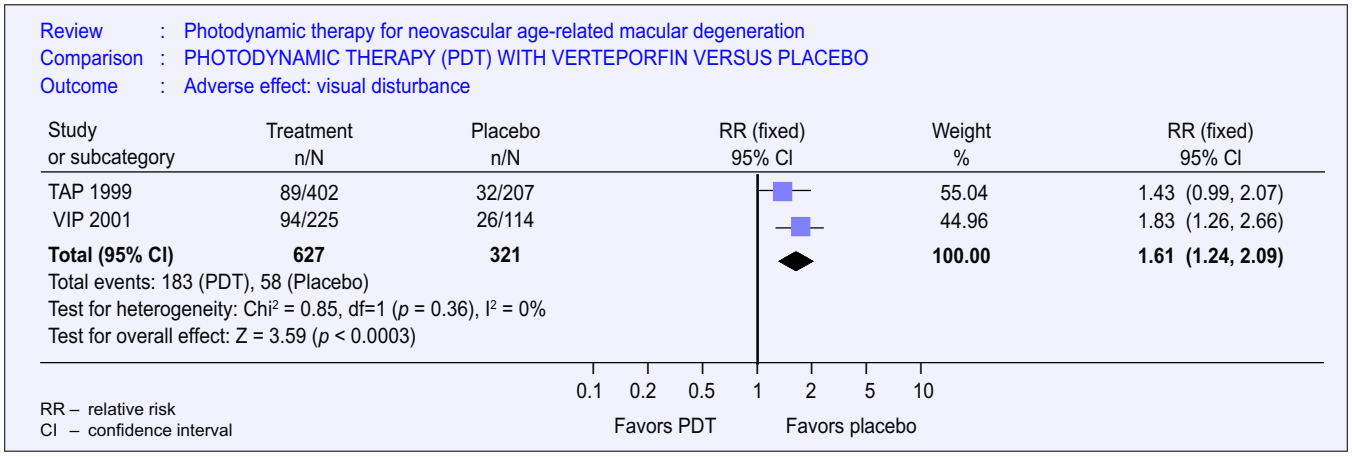


**Figure 10.** Adverse effect: visual disturbance.

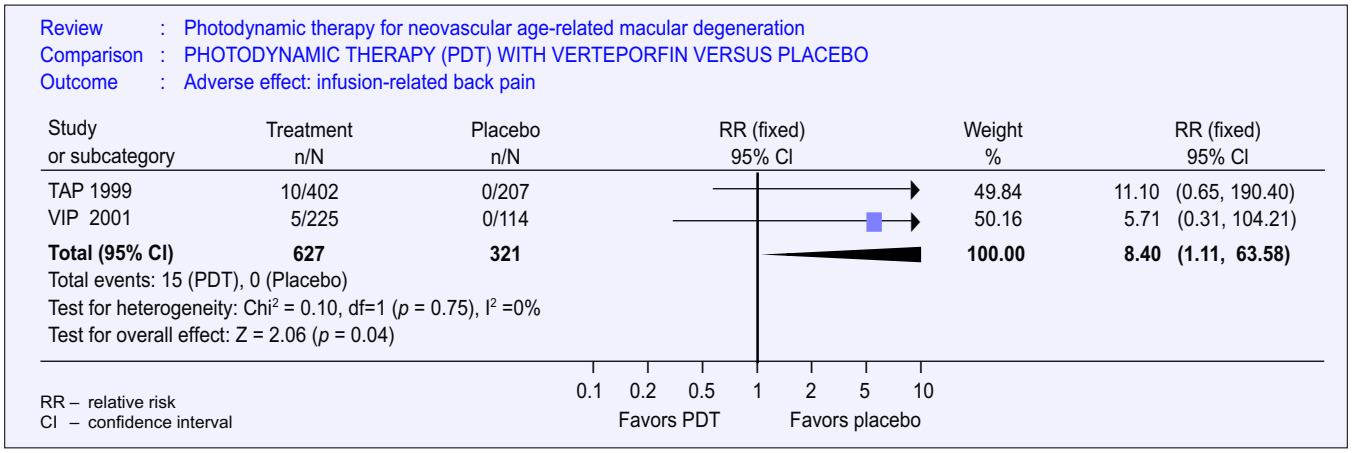


**Figure 11.** Adverse effect: infusion-related back pain.

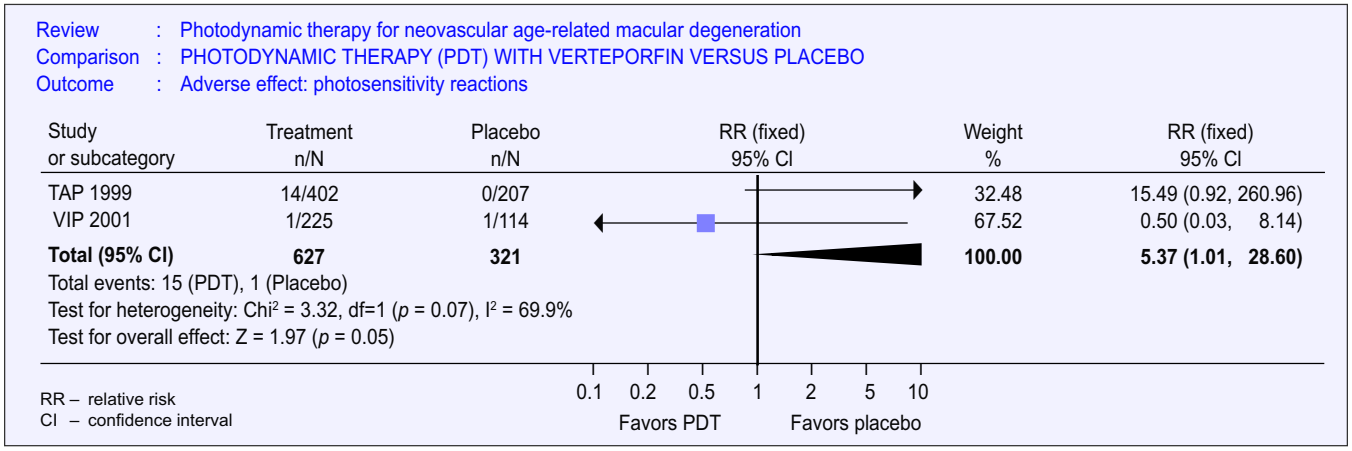


**Figure 12.** Adverse effect: photosensitivity reactions.

The VAM study[21] reported the outcomes from a larger number of patients recruited from 222 centers in North America (10 times the number in TAP) between September 1999 and June 2000 when verteporfin became commercially available. Maximum follow-up was 9 months. About half the study population had 6 months follow-up. This study provided further information on the risk of adverse events outside an RCT setting, but as this is an open-label study with no comparator group, relative risks or risk differences (and hence NNH) cannot be calculated. However, it was assumed that, as in TAP and VIP, no events would have occurred in an untreated arm, hence the risk became the same as the risk difference. Of the 4,435 enrolled, 115 (2.6%) reported abnormal or decreased vision, of whom 25 experienced ASVAD (0.6%) (NNH at 166). ASVAD was thought to be caused by bleeding under the retina after PDT. One series from Wilmer[22] reported this outcome in 52 patients; unfortunately, the denominator (the overall number of persons and eyes receiving PDT) was not given. Vision loss can be profound in this group, and the data from TAP and VIP suggested it may be more likely to occur in people with better initial visual acuity.

Visual disturbance (reports of "abnormal vision," "decreased vision," and visual-field defect) occurred in 1 in every 4 people who took part in the TAP 1999 and VIP 2001 studies. This is perhaps unsurprising as participants had neovascular ARMD. However, people treated with verteporfin were more likely to report visual disturbance (pooled relative risk 1.61) (Figure 10). 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 (Figure 11) and 2.4% had photo-sensitivity reactions (Figure 12). Problems with the injection site occurred in 13.1% of people treated with verteporfin compared with 5.6% people in the control group (Figure 13). Few allergic reactions were seen and these were equally likely in the treatment and control groups (Figure 14).

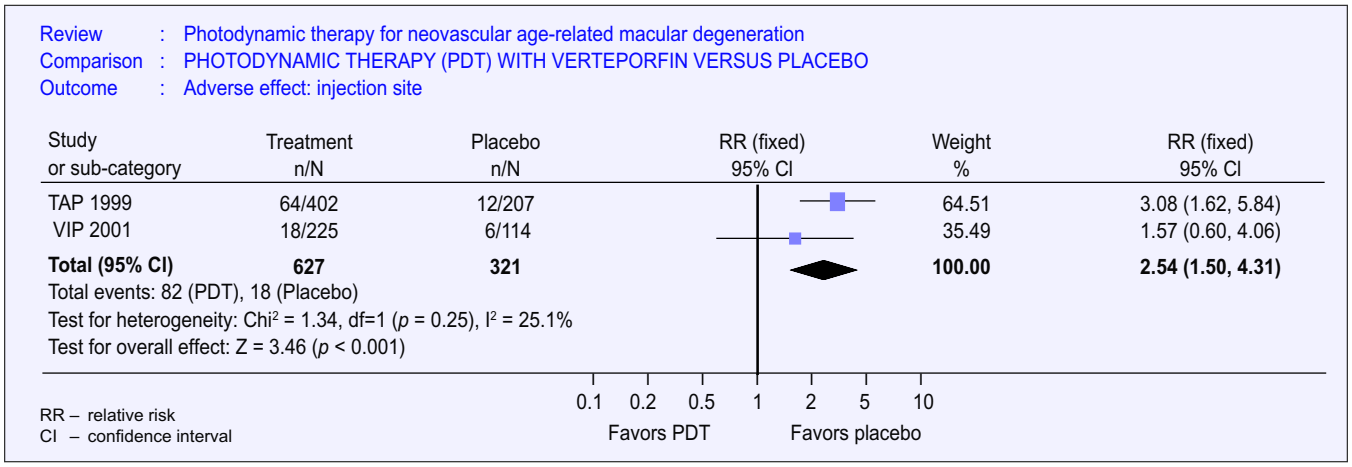


**Figure 13.** Adverse effect: injection site.

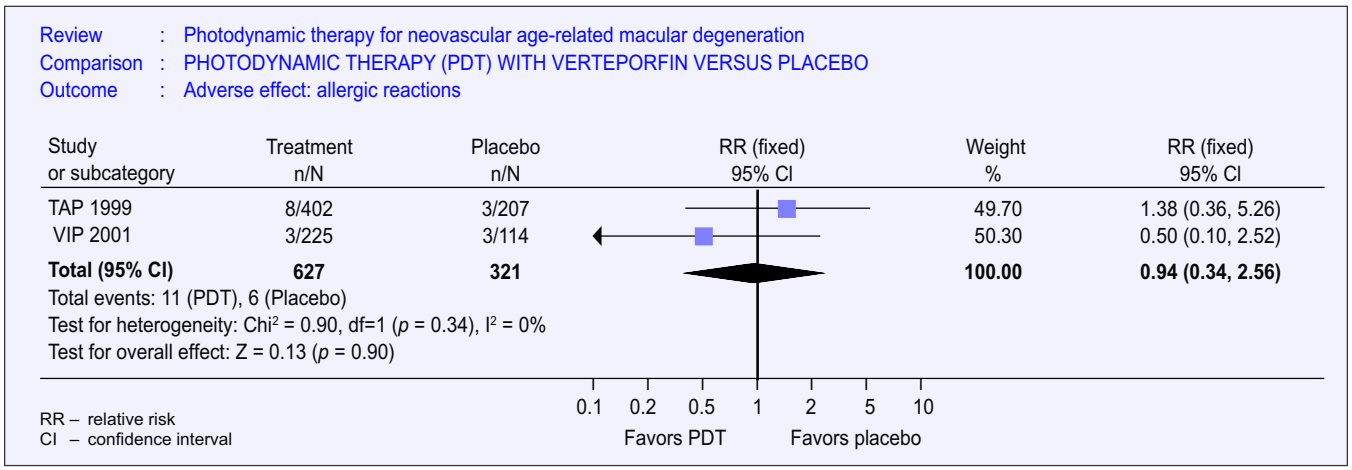


**Figure 14.** Adverse effect: allergic reactions.

*Economic outcomes*

No economic analyses have been reported from either TAP or VIP.

## DISCUSSION

The absence to date of any effective treatment for neovascular ARMD (except for a few patients in whom laser photocoagulation works) means that there will be intense interest in PDT for the many millions of sufferers of the disease worldwide. Unfortunately, PDT, like photocoagu-lation, 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 in 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 them, the publicity surrounding the launch of verteporfin (Visudyne) would have raised false hopes. However, this review indicates that for people with active neovascular disease, PDT 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 2 years. An open-label extension of the TAP 1999 study indicated that vision outcomes remained relatively stable for 24 to 48 months.[23] There have been no further reports of longer outcomes.

Another important issue is how many presenting patients will benefit from PDT. 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 clearly suggests that purely classic neovascular membranes do well. Subgroup analysis of the TAP 1999 study suggested that PDT is not 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 was 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 neovascularization and demonstrated treatment benefit at 12 and 24 months. 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 cast serious doubt on the validity of the subgroup analyses.[9]

Subsequent reports of "exploratory" analyses (presumably not specified a priori) have been published from the TAP trials (Bressler 2002[16]) and from the TAP and VIP trials (Blinder 2003[15]), which found that 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 2004[17]) examined the natural history of minimally classic lesions that had poorer outcomes in the TAP trial treated group. Of the 207 randomized 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 predominantly classic so that the 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.

We are not told in the available reports the extent to which clinicians and the Photograph Reading Center personnel were able to agree on the subgroup classification of classic or occult lesions. It was likely that there was much variation in opinion on this. The necessary skill to report on fluorescein angiograms and recognize 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 images slightly laterally displaced from one another, providing a nonsimultaneous 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.[14] 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[24] for the same angiographic criteria as for TAP and VIP. Agreement was not quite as good for both intra- and interobserver as for the reporting center 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 centers that had treatable lesions. The verbal estimate from one trialist was approximately 25% and from another expert between 5% and 7%. This is crucial in estimating the impact of this new treatment on health-care budgets.

ARMD is a bilateral disease, although 1 eye is usually affected before the other. With a lesion present in 1 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 1 eye to watch for the onset of symptoms in the second eye and to seek treatment as soon as they notice the symptoms 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 that 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 that 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 would 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 1 year.[13] 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 with the control group. However, this was not reflected in the visual-acuity outcomes. Infusion-related back pain occurred in 2.4%, substantially lower than in some other studies. For example, in a series of 250 people treated with verteporfin, 9.6% experienced verteporfin-associated pain, mostly back pain.[25] It is now clear that acute severe visual-acuity decrease is a relatively small but serious risk of poor outcome of treatment. This review estimates this risk to be approximately 1 in 50 patients.

The trials included in this review appear to have been performed to high standards and were closely supervised by the United States Food and Drug Administration. Both trials were sponsored by the manufacturers of the drug (CIBA Vision and Novartis Ophthalmics) and declared potential conflicts of interest existed for a number of the trialists who held 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 had access to the main protocol or to the revisions, a CIBA representative had 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.

New reviews have not drawn any conflicting conclusions or 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 United Kingdom (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 2 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)[11] examined cost utility for PDT for predominantly classic neovascular ARMD using data from the TAP trial in 2 cost-utility models for 2 case scenarios. They concluded that, as the only available treatment for some forms of neovascular ARMD, 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 regarding one of the conclusions of the trialists' post hoc analyses—that those with poorer presenting vision fare better in terms of number 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.

## REVIEWERS' CONCLUSIONS

**Implications on practice**

This review provides evidence that PDT in patients with classic and occult CNV due to ARMD is probably effective in preventing visual loss though the size of the effect remains in doubt. On the basis of existing evidence, 7 people need to be treated with an average of 5 treatments over 2 years to prevent 1 person from losing 3 or more lines of visual acuity. One in every 50 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.

Two trials were included in this review. Both trials were performed by the same investigators using largely the same clinical centers 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.

There are major implications for health services, both in terms of potential expenditure and organization, if PDT is 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.

**Implications on 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 ARMD, 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.

Descriptive epidemiology on the population at risk and the numbers likely to benefit from these kinds of interventions remain 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 ARMD 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 are required.

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**Contribution of the reviewers**

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

JE and 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.

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ORIGINAL ARTICLE

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# Diabetic-retinopathy progression following phacoemulsification

## A metaanalysis

### ABSTRACT

**Purpose**

To determine the effect of phacoemulsification on the progression of diabetic retinopathy.

**Methods**

We conducted an electronic search of the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Group Trials Register) on *The Cochrane Library* (Issue 1, 2005), MEDLINE, and the reference lists of identified trials evaluating the effects of phacoemulsification on the progression of diabetic retinopathy. There were no language or date restrictions in the electronic search. Two reviewers independently assessed the articles for inclusion. Odds ratio at 95% confidence interval was determined using Review Manager 4.2.2 (The Cochrane Collaboration, Oxford, United Kingdom).

**Results**

No randomized controlled trials were found. Five nonrandomized, prospective, case-controlled trials involving a total of 804 eyes were included in this review. All 5 trials studied the effects of phacoemulsification on the progression of diabetic retinopathy using the fellow nonoperated eye as control. Pooled analysis showed weak evidence to support the progression of diabetic retinopathy (RR=1.36: 95%; CI 0.95-1.96) in eyes that underwent phacoemulsification compared with eyes that did not.

**Conclusion**

The available literature consists mainly of retrospective case reviews and case-controlled trials that are difficult to compare and analyze due to variations in the definition of progression and retinopathy assessment and surgical technique. However, the 5 studies reviewed show that uncomplicated phacoemulsification had minimal or no effect on the progression of diabetic retinopathy. Further randomized, controlled trials are needed to confirm this finding.

***Keywords:*** *Metaanalysis, diabetic retinopathy, cataract extraction, phacoemulsification*

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THE GLOBAL prevalence of diabetes is increasing rapidly, estimated at 110 million in 1994 and projected to reach 221 million by 2010.[1] The risk of developing a visually significant cataract is significantly increased in diabetic patients, in whom surgical management is disproportionately more problematic compared with nondiabetic patients.[2] Both the postoperative progression of diabetic retinopathy and macular edema are considered common causes of poor visual acuity in diabetic patients after uncomplicated cataract surgery,[3, 4] and whether these represent the natural course of the disease or are direct effects of the surgery is still uncertain.

Cataract surgery in diabetic patients has been marked with a high incidence of intraoperative and postoperative complications, which have been implicated in postoperative progression of diabetic retinopathy.[5] Studies point to retinopathy severity and macular edema as the principal determinants of postoperative visual acuity, and link improved visual outcomes to the shift from conservative management to earlier surgical intervention.[6]

The degree of diabetic retinopathy has been correlated with visual outcome in a metaanalysis of extracapsular cataract extractions (ECCE) that analyzed proportions of eyes achieving 20/40 or better central acuity.[7] Earlier cataract extraction in diabetic patients has been proposed to improve visualization and monitoring of the fundus, which would allow prompt treatment and increase long-term visual outcome.[8] Postoperative progression has also been related to the presence and stage of retinopathy at baseline. However, the postulated risk factors have not been consistent; the presence of background retinopathy has been implicated in some reports and active proliferative retinopathy in others. A more favorable visual outcome has been observed with preoperative treatment of retinopathy when indicated and the use of newer, small-incision cataract-surgery techniques such as phacoemulsification.

An evidence-based approach to the practice of medicine is becoming more important in the face of increasing pressure on health-care professionals to deliver quality and cost-effective care. The decision to surgically remove cataracts in patients with diabetic retinopathy to improve visualization of the fundus and allow monitoring and treatment must outweigh the risk of possible progression of the retinopathy. The conflicting conclusions in studies investigating the progression of diabetic retinopathy after phacoemulsification prompt a systematic review of the best available evidence on the effect of phacoemulsification on the postoperative progression of diabetic retinopathy.

This review was done to determine the effect of phacoemulsification on the progression of diabetic retinopathy.

## METHODOLOGY

### Criteria for inclusion of studies in this review

*Types of studies.* This review intended to include randomized controlled trials. However, none was found, and the results of 5 prospective, case-controlled trials comparing the progression of diabetic retinopathy after phacoemulsification versus no surgery were included.

*Types of participants.* Study participants were patients diagnosed clinically with diabetes mellitus who have undergone phacoemulsification in 1 eye and no surgery in the fellow eye.

*Types of interventions.* Unilateral phacoemulsification and implantation of an intraocular lens compared with no surgery in the fellow eye among diabetic patients.

*Types of outcome measures.* The primary outcome measure was the occurrence or progression of any type of diabetic retinopathy for at least 6 months following phacoemulsification.

### Search strategy for identification of studies

Two independent searches of PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Group trials register) on *The Cochrane Library* (Issue 1, 2005) were conducted to identify all published articles on the progression of diabetic retinopathy following phacoemulsification. Clinical queries focusing on phacoemulsification, cataract surgery, and diabetic retinopathy were used to provide a broad search of all available clinical trials. There were no date or language restrictions in the electronic searches. Manual searches of the reference lists of included studies, other reviews, and book chapters on surgery for cataracts and diabetic retinopathy to find additional trials were conducted. Trial investigators and experts in the field were contacted to identify additional published and unpublished studies. Manual searches of journals or conference proceedings were not done.

### Methods of the review

*Selection of trials.* Two reviewers independently assessed the titles and abstracts resulting from the electronic searches. Full copies of potentially relevant reports were obtained. No studies fulfilled the criteria for randomized, controlled trials. We then proceeded to look for other types of studies pertinent to our search queries.

*Assessment of methodological quality.* Assessment of methodological quality was based on the methods in section 6 of the *Cochrane Reviewers' Handbook*. Four parameters were considered:

1. Allocation concealment and method of allocation to treatment
2. Masking of providers and recipients of care
3. Masking of outcome assessment
4. Completeness of follow-up.

Each parameter was graded as follows: A = adequate, B = unclear, or C = inadequate.

*Data extraction and synthesis.* Data from studies were summarized collecting similar outcomes and using similar follow-up times after testing for heterogeneity between trial results using a standard chi-square test. For dichotomous data, results were expressed as odds-ratio estimates (95% confidence interval). For continuous data, the mean and standard deviations were obtained. Standard errors were converted to standard deviations and summarized as weighted mean differences (95% confidence intervals).

**Description of studies**

The electronic searches identified 49 reports of studies on progression of diabetic retinopathy after cataract surgery. There were no randomized controlled clinical trials assessing the progression of diabetic retinopathy after phacoemulsification. Five nonrandomized, prospective, case-controlled studies of similar study design were identified as follows:

- Krepler K, Biowski R, Schrey S, Jandrasits K, Wedrich A. Cataract surgery in patients with diabetic retinopathy: visual outcome, progression of diabetic retinopathy, and incidence of diabetic macular oedema. *Graefes Arch Clin Exp Ophthalmol* 2002; 240: 735-738.
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- Kato S, Fukada Y, Hori S, et al. Influence of phacoemulsification and intraocular lens implantation on the course of diabetic retinopathy. *J Cataract Refract Surg* 1999; 25: 788-793.
- Wagner T, Knaflic D, Rauber M, Mester U. Influence of cataract surgery on the diabetic eye: a prospective study. *Ger J Ophthalmol* 1996; 5: 79–83.

**Methodological quality**

No assessment of quality was undertaken for the 5 prospective nonrandomized, case-controlled studies because they were different in study design from the criteria set in the *Cochrane Reviewers' Handbook*. All 5 studies investigated the effect of the progression of diabetic retinopathy among patients undergoing monocular phacoemulsification using the fellow eye as control. The subjects were followed up for at least 6 months after the surgery. The characteristics of the 5 studies are summarized in Table 1.

## RESULTS

The data of the 5 case-controlled studies were pooled and analyzed based on a fixed-effect model as shown in the Forest plot (Figure 1). Analysis was based on a total sample size of 804 eyes with the weight of each study on the overall effect as follows: Wagner et al. 55.51%, Kato et al. 21.28%, Flesner et al. 3.29%, Krepler et al. 7.07%, and Squirrell et al. 12.84%. Tests for heterogeneity (chi-quare)

Table 1. **Description of nonrandomized, prospective studies.**

| Study | Population | Intervention | Comparison | Outcome Measure | Method |
|---|---|---|---|---|---|
| Krepler, et al. | 42 diabetic patients for unilateral cataract surgery | Phacoemulsification and in-the-bag implantation of an intraocular lens (IOL) | Unoperated fellow eye | Progression of diabetic retinopathy (EDTRS classification) | Prospective, case control |
| Squirrell, et al. | 50 diabetic patients for unilateral cataract surgery | Phacoemulsification and in-the-bag implantation of an intraocular lens (IOL) | Unoperated fellow eye | Progression of diabetic retinopathy (EDTRS classification) | Prospective, case control |
| Flesner, et al. | 39 diabetic patients for unilateral cataract surgery | Phacoemulsification and in-the-bag implantation of an intraocular lens (IOL) | Unoperated fellow eye | Progression of diabetic retinopathy (EURODIAB IDDM complications study grading system) | Prospective, case control |
| Kato, et al. | 66 diabetic patients for unilateral cataract surgery | Phacoemulsification and in-the-bag implantation of an intraocular lens (IOL) | Unoperated fellow eye | Progression of diabetic retinopathy (Fukuda Classification) | Prospective, case control |
| Wagner, et al. | 205 diabetic patients for unilateral cataract surgery | Phacoemulsification and in-the-bag implantation of an intraocular lens (IOL) | Unoperated fellow eye | Progression of diabetic retinopathy (EDTRS classification) | Prospective, case control |

showed homogenous results. The overall event rate showed that 81 of the 363 eyes that underwent phacoemulsification and 63 of the 363 control eyes had progression of diabetic retinopathy. The relative risk-point estimate was 1.36, which was not statistically significant (95% confidence interval, 0.95–1.96).

## DISCUSSION

There is a large body of literature on the progression of diabetic retinopathy after phacoemulsification, but it consists mainly of retrospective studies, cohort studies, or case series. This review found no randomized, controlled trials on the subject. Five nonrandomized, prospective, case-controlled studies of similar study design were found dealing with the topic. The results of the 5 studies show that uncomplicated phacoemulsification and in-the-bag placement of an intraocular lens (IOL) did not result in increased progression and is, therefore, not contraindicated in patients with diabetic retinopathy. The observed progression after the surgical invasion is postulated to be a part of the natural course of the disease and not a result of the surgery. In all studies, improvement in visual acuity and the ability to better visualize the fundus to monitor and treat the retinopathy outweighed the risks of the surgical procedure and the possibility of later progression.

There is growing evidence to support a more interventional approach to the management of cataract in patients with diabetes mellitus. This refinement in the approach to the timing of cataract surgery in diabetic patients seems to be the most important development in this field. However, it must be emphasized that the studies cited in this review are subject to methodological variation. The definition of retinopathy and determining its severity may vary due to inherent difficulties in grading retinopathy in eyes with cataract. The surgical techniques employed may vary among centers, likewise the indications for laser therapy. Grading the progression of retinopathy and follow-up monitoring can be different among the studies. Thus, the need is apparent for a well-designed, randomized, controlled clinical trial that will assess the progression of diabetic retinopathy after phacoemulsification.

### Implications on practice

There are no randomized controlled trials to strongly support conclusions regarding the progression of diabetic retinopathy after phacoemulsification. The available studies reviewed have methodological flaws inherent in a nonrandomized or uncontrolled study design. Nonetheless, it seems that modern, uncomplicated, small-incision cataract surgery has minimal influence on the progression of diabetic retinopathy. Meticulous follow-ups are still needed for early detection and treatment of the retinopathy should it progress as a natural course of the disease in order to preserve the visual improvement gained from the cataract surgery.

### Implications on research

Prospective randomized controlled trials should be conducted in eyes with nonproliferative and proliferative diabetic retinopathy undergoing unilateral phacoemulsification to determine the risk factors for progression of the retinopathy. A well-designed study with adequate sample size, blinded outcome assessment, and long-term follow-up will surely provide statistically significant results to show whether phacoemulsification and any attendant complications are risk factors for progression of diabetic retinopathy.

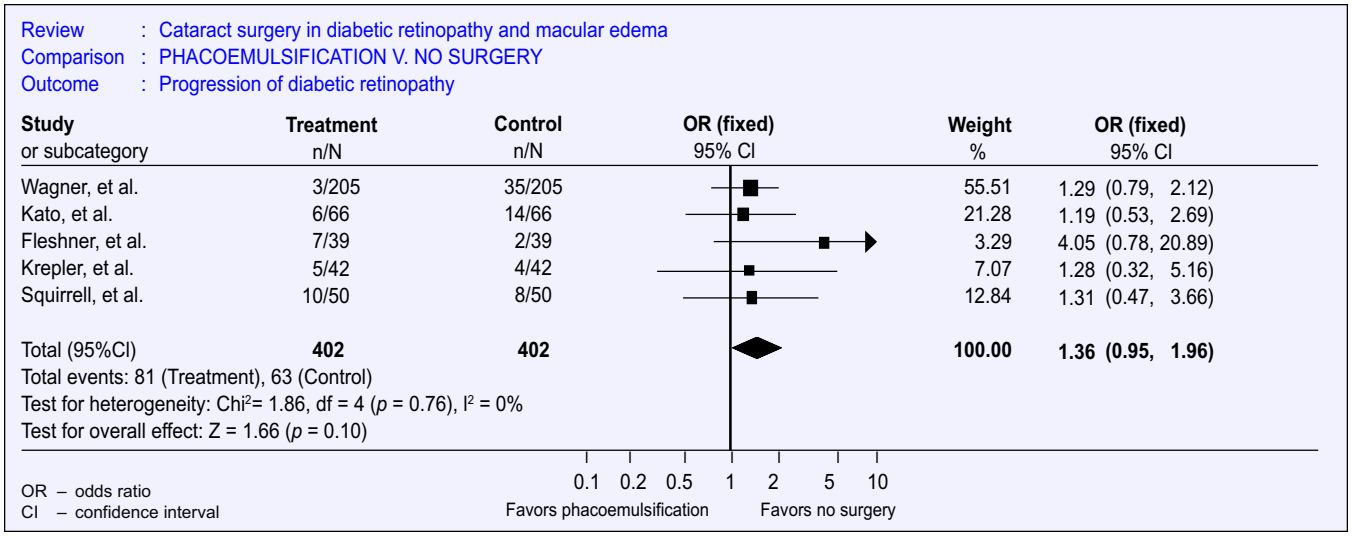


**Figure 1**. Phacoemulsification v. no surgery in the progression of diabetic retinopathy.

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REVIEW

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# Intravenous methylprednisolone versus oral prednisone for initial attacks of optic neuritis

## A review of evidence

### ABSTRACT

**Objective**

To review current available evidence that addresses the question regarding the efficacy of intravenous methylprednisolone and oral-prednisone treatment regimens in improving vision among optic-neuritis patients.

**Methods**

A literature search for randomized controlled trials on the treatment of optic neuritis in adults using steroids was conducted. A total of 23 studies were identified in the search. Of these, the Optic Neuritis Treatment Trial (ONTT) was identified as the largest multicenter, randomized controlled trial that evaluated the effect of steroids in the treatment of optic neuritis in adults. The initial article regarding the results of this landmark study published in 1992 and follow-up reports focusing on the five-year and ten-year visual outcomes published in 1997 and 2004 were appraised for this review.

**Results**

Treatment with high dose intravenous methylprednisolone followed by oral prednisone produced short-term accelerated visual recovery but provided no long-term benefit to vision. Most patients retained good to excellent vision following an attack of optic neuritis regardless of treatment received. A significantly increased risk of recurrence of optic neuritis in either eye (19%) was noted in the oral-prednisone treatment group. There were no significant differences among the treatment groups in the risk of development of clinically definite multiple sclerosis.

**Conclusion**

Intravenous methylprednisolone followed by oral prednisone may be considered as treatment for patients with acute optic neuritis in whom there is a need to speed up recovery of vision. Considering that the use of oral prednisone alone was associated with an increased risk of recurrence of optic neuritis in either eye, no treatment is an option.

***Keywords:*** *Methylprednisolone, Prednisone, Optic neuritis, Multiple sclerosis*

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OPTIC neuritis, an inflammatory disorder of the optic nerve, has been cited as the most common optic neuropathy in adults, particularly individuals below 46 years of age.[1] The common presentation of acute optic neuritis is that of an isolated clinical event manifesting with periocular pain, abnormal decrease in visual function, a relative afferent pupillary defect and abnormal electrophysiologic optic-nerve findings. Fundus findings range from a normal appearance of the optic nerve to optic-nerve-head edema (papillitis). Using magnetic resonance imaging, changes in the form of white matter abnormalities similar to those in multiple sclerosis are seen in 50 to 70% of patients with monosynaptic optic neuritis.[1]

Steroids have long been used in the treatment of optic neuritis. Their effectiveness has been assessed utilizing clinical outcomes, particularly their effect on improving the visual function of patients. However, due to the high cost of intravenous methylprednisolone in the Philippines, local ophthalmologists often use oral-steroid preparations instead. It is the objective of this paper to review current available evidence that addresses the efficacy of intravenous methylprednisolone compared with oral steroids in improving vision among patients with optic neuritis.

## SEARCH METHOD

An electronic literature search covering the years from 1980 to 2005 was performed using Medline (PubMed). The key words utilized were "optic neuritis," "steroids," and "vision." The search was further limited to randomized controlled trials, metaanalysis, or reviews published in the English language. Free-text and MeSH search methods were employed to maximize the number of hits. Table 1 presents the search process performed.

Titles and abstracts identified from items 5, 7, 8, and 9 in Table 1 were reviewed for appropriateness in answering the clinical question. Twenty-three citations listed among the randomized controlled trials were considered appropriate to answer the clinical question. Most of these were reports concerning the results of the Optic Neuritis Treatment Trial (ONTT), a multicenter, randomized controlled trial sponsored by the National Eye Institute of the United States National Institutes of Health. [2-11, 13-16]

Only 1 metaanalysis and 5 reviews from the search qualified. Of these, only 2 were retrieved for further evaluation.[1, 12] It is noteworthy that the metaanalysis and reviews made primary reference to the ONTT.

The first major article on the results of this landmark study published in 1992[11] and the follow-up reports on the five-year and ten-year visual outcomes published in 1997 and 2004 were reviewed and appraised for purposes of answering the clinical question.[2, 15] Additional information regarding specific aspects of the trial was likewise referred to when necessary.[3-10, 13-14, 16]

## CITATION

Beck RW, Cleary PA, Anderson MM, et al. A randomized controlled trial of corticosteroids in the treatment of acute optic neuritis. *N Engl J Med* 1992; 326: 581-588.

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**Study characteristics of the Optic Neuritis Treatment Trial**

The study involved 457 patients who met the following inclusion criteria: between 18 and 46 years old, history consistent with acute unilateral optic neuritis, visual symptoms lasting 8 days or less, evidence of a relative pupillary defect and associated with visual-field defect. Patients with history of previous optic neuritis or ophthalmoscopic signs of optic atrophy and clinical evidence of systemic diseases other than multiple sclerosis causing the optic neuritis were excluded from the study. Eligible patients were randomly assigned to one of three groups: intravenous methylprednisolone (IVMP) (n=151), oral prednisone (n=156), or placebo (n=150). The IVMP group received 250 mg of methylprednisolone intravenously every 6 hours for 3 days. This was followed by oral prednisone at a dose of 1 mg per kilogram of body weight per day for 11 days. The oral-prednisone group received prednisone at a dose of 1 mg per kilogram of body weight per day for 14 days and the placebo group received oral placebo on the same schedule as the oral prednisone group. Patients in both oral groups received

Table 1. **Search process employed.**

| Search Word/s | No. of Citations |
|---|---|
| 1. Optic neuritis MeSH | 3,632 |
| 2. Steroids MeSH | 489,308 |
| 3. Optic neuritis MeSH and steroids MeSH | 316 |
| 4. Randomized controlled trials MeSH | 36,736 |
| 5. (Optic neuritis MeSH and steroids MeSH) and randomized controlled trials MeSH | 15 |
| 6. (Optic neuritis MeSH and steroids MeSH) and metaanalysis MeSH | 0 |
| 7. (Optic neuritis MeSH and steroids MeSH) and reviews | 28 |
| 8. Optic neuritis (limit: randomized controlled trials) | 59 |
| 9. Optic neuritis (limit: metaanalysis) | 3 |

their treatment as a single morning dose. The dose was subsequently reduced to 20 mg on day 15 and 10 mg on days 16 and 18 for both prednisone treatment arms.[11]

The primary outcome measures were visual fields and contrast sensitivity. Visual acuity and color vision were secondary measures. Subjects were also monitored for occurrence of new attacks in either eye and the development of multiple sclerosis.

## DISCUSSION

### Validity criteria

The Optic Neuritis Treatment Trial was first appraised for validity in addressing the following issues:

*Selection bias.* Patients were randomly assigned in equal numbers to the 3 treatment groups. Allocation concealment was attained by using permuted blocks with a separate sequence for each clinical center. Adverse effects and associated events were recorded at each visit.[11]

In all 3 groups, patients were predominantly female Caucasians. Age distribution was also similar for all groups with a median of 32 years. Median weight did not differ significantly among the 3 treatment groups. Clinical characteristics described included duration of visual symptoms, presence of ocular pain, and optic-disk swelling. Baseline measurements of visual function (contrast sensitivity, visual-field deviation, visual acuity, and color vision) of patients did not differ significantly among the 3 groups. The number of patients diagnosed with multiple sclerosis was, however, lower for the IVMP group (3 patients) compared with the oral-prednisone and placebo groups (7 patients each). In terms of patient characteristics, the 3 groups did not differ significantly.[8]

*Performance bias.* Both subjects and outcome assessors were blinded as to the treatment received in the oral-intervention arms of the study. The IVMP arm was not blinded since the subjects assigned to this group required hospitalization and were, therefore, aware of the treatment they were receiving. While it would have been ideal to have a direct comparison between IVMP and IV placebo, administration of placebo via the IV route was not possible for ethical reasons. Nevertheless, efforts were also made to mask the outcome assessors in the evaluation of the IVMP group.[11] Thus, every effort was taken to ensure that performance bias was kept to a minimum.

*Exclusion bias.* The authors of the study were able to account for all patients for the duration of the study. Mention was made of exclusion of 2 patients after randomization because of misdiagnosis, but they were included in the data analysis based on their original group assignment. There were 26 dropouts by the end of the six-month period, 8 in the oral prednisone group and 9 each for the placebo and IVMP groups.[11] The dropout rate, however, was below the acceptable limit of 20%.

At the conclusion of the trial in 1992, 410 patients consented to continue follow-up until 1997. Beyond 1997, 387 patients consented to continue follow-up to complete the ten-year period. The five- and ten-year reports published by the Optic Neuritis Study Group were based on results from this cohort of patients. The ten-year report on visual recovery stated that of the 387 patients who gave their consent, examination was completed for 319 patients (82%). The status of the 135 original ONTT patients who did not complete the ten-year examination was, however, accounted for. Comparison of the characteristics of the 319 patients who completed the examination with the 135

Table 2. **Validity criteria.**

| Criteria | Answer |
|---|---|
| 1. Were patients randomized? | Yes |
| 2. Was randomization concealed (blinded ormasked)? | Yes |
| 3. Were the patients analyzed in groups to which they were randomized? | Yes |
| 4. Were patients in the treatment and control groups similar with respect to known prognostic factors? | Yes |
| 5. Were patients unaware of group allocation? | No. Blinding of patients was not possible with the IVMP group |
| 6. Were clinicians unaware of group allocation? | Yes |
| 7. Were outcome assessors unaware of group allocation? | Yes<br>Yes |
| 8. Was follow-up complete? | Yes |

Table 3. **Relative risk of normal-function recovery at 6 months.**

| **Placebo v. intravenous methylprednisolone** | | | | |
|---|---|---|---|---|
| **Outcome** | **Patients with Unrecovered Visual Function (%)** | | **Relative Risk (Unadjusted)** | **95% Confidence Interval** |
| | **Placebo** | **IVMP** | | |
| Contrast sensitivity | 45.3 | 37.7 | 0.83 | 0.60 – 1.16 |
| Visual field | 25.3 | 19.9 | 0.78 | 0.47 – 1.32 |
| Visual acuity | 41.3 | 39.1 | 0.95 | 0.68 – 1.33 |
| Color vision | 43.3 | 33.1 | 0.76 | 0.53 – 1.09 |
| **Placebo v. oral prednisone** | | | | |
| **Outcome** | **Patients with Unrecovered Visual Function (%)** | | **Relative Risk (Unadjusted)** | **95% Confidence Interval** |
| | **Placebo** | **Oral Prednisone** | | |
| Contrast sensitivity | 45.3 | 44.2 | 0.98 | 0.71 – 1.33 |
| Visual field | 25.3 | 25.6 | 1.00 | 0.63 – 1.63 |
| Visual acuity | 41.3 | 45.5 | 1.10 | 0.80 – 1.51 |
| Color vision | 43.3 | 43.6 | 1.00 | 0.73 – 1.38 |

patients who did not showed that they were similar with respect to age, sex distribution, proportion with abnormal baseline brain magnetic-resonance-imaging results, and proportion of patients with multiple sclerosis at baseline. Patients not completing the examination were, however, more likely to be African–Americans and, on average, had slightly worse acuity in the affected eye at baseline.[2] Since all patients were accounted for by the investigators, exclusion bias was, therefore, kept to a minimum.

Table 2 presents a summary of the answers to the various validity criteria set for treatment trials. Despite incomplete masking, it is safe to conclude that the study was valid.

**Results of the study**

In the data analyses, each steroid group was compared with placebo, but no direct comparison between the 2 steroid regimens was made.

*Visual function.* The relative risk for nonrecovery of visual function for the different outcomes is presented in Table 3. A relative risk (RR) less than 1.0 would be indicative of benefit from the intervention (steroid) while a relative risk greater than 1.0 would imply harm. Stratified results (based on visual function at the time of study entry) can be obtained from the original article.

The visual outcomes in the IVMP group seemingly showed better chances of recovery (point estimates) compared with those in the placebo group. The oral-prednisone group showed no benefit or reduction in risk in all outcome measures, except in contrast sensitivity, compared with the placebo group. These trends were, however, satistically insignificant based on the confidence intervals. In a separate report that evaluated correlation between several parameters and factors predictive of visual recovery, student t-test and least squares regression demonstrated that baseline visual acuity was a statistically significant predictor of the six-month visual acuity (Table 4). However, most patients with severe initial visual loss eventually had good recovery of vision, implying that the significance was more statistical than clinical.[7]

Patients who consented to participate beyond the original study duration were examined in the fifth and tenth year posttreatment.[2, 15] Visual-function tests in the fifth year were normal or slightly abnormal in the affected and fellow eyes of most patients. Contrast sensitivity was frequently abnormal compared with the other visual-function parameters in affected eyes. There was minimal change in vision from the sixth-month to the fifth-year exam.[6, 7, 9] There was no significant difference in visual function after 5 years among the 3 treatment groups.

Most patients retained good to excellent vision in the tenth year, with normal or slightly abnormal visual-function-test results. There was no significant difference in visual function among the 3 treatment groups.

Table 4. **Correlation of factors predictive of visual outcome at 6 months.**

| Parameter | Regression Coefficient* | Student t Test | *p* |
|---|---|---|---|
| Treatment | | | |
| *Intravenous* | –0.04 | –0.44 | 0.66 |
| *Oral prednisone* | 0.07 | 0.92 | 0.36 |
| Age | 0.01 | 2.26 | 0.02 |
| Baseline Visual Acuity | 0.32 | 7.04 | <0.001 |

*Coefficient of multiple determination $R^2 = 0.11$

Table 5. **Relative risk for recurrence of optic neuritis within 6 months.**

| **Placebo v. Intravenous Methylprednisolone** | | | | |
|---|---|---|---|---|
| **Eye** | **Patients with Recurrence (%)** | | **Relative Risk** | **95% Confidence Interval** |
| | **Placebo** | **IVMP** | | |
| Either eye | 15 | 13 | 0.81 | 0.45 – 1.47 |
| Affected eye | 10 | 9 | 0.86 | 0.42 – 1.76 |
| Contralateral eye | 7 | 5 | 0.65 | 0.23 – 1.81 |
| **Placebo v. Oral Prednisone** | | | | |
| **Eye** | **Patients with Recurrence (%)** | | **Relative Risk** | **95% Confidence Interval** |
| | **Placebo** | **Oral Prednisone** | | |
| Either eye | 15 | 27 | 1.79 | 1.08 – 2.95 |
| Affected eye | 10 | 15 | 1.40 | 0.74 – 2.65 |
| Contralateral eye | 7 | 16 | 2.50 | 1.15 – 5.46 |

Table 6. **Comparison of rates to development of multiple sclerosis in the ONTT within the 6 to 24 months follow-up period.**

| Compared groups | Relative Risk* | 95 % Confidence Interval |
|---|---|---|
| IVMP v. placebo | 0.70 | 0.37 – 1.31 |
| Oral prednisone v. placebo | 1.20 | 0.71 – 2.02 |
| IVMP v. oral prednisone | 0.58 | 0.32 – 1.06 |

* Based on unadjusted results

*Recurrence of optic neuritis.* The ONTT results showed that while the risk of recurrence for the affected eye did not differ significantly between the placebo and oral-prednisone groups, it was significantly increased for the contralateral eye. Comparing the risk of recurrence in either eye also showed a significantly higher risk for the oral-prednisone group (Table 5). Comparisons between the placebo and IVMP groups revealed insignificant differences in risk of recurrence for either the affected or contralateral eye as supported by the confidence intervals.

The five-year results reported the cumulative probability of having a new episode of optic neuritis during the 5 years of follow-up at 19% for the affected eye, 17% for the fellow eye, and 30% for either eye. In consonance with

Table 7. **Development of multiple sclerosis in the first two years of follow-up (adjusted results).**

| Outcome | IVMP v. Placebo | | Oral Prednisone v. Placebo | | IVMP v. Oral Prednisone | |
|---|---|---|---|---|---|---|
| | Rate Ratio (95% CI) | *p* | Rate Ratio (95% CI) | *p* | Rate Ratio (95% CI) | *p* |
| Definite MS | 0.34 (0.16-0.74) | 0.006 | 0.90 (0.48 – 1.71) | 0.75 | 0.38 (0.17 – 0.83) | 0.015 |
| Probable or definite MS | 0.40 (0.22-0.72) | 0.002 | 0.90 (0.54 – 1.49) | 0.67 | 0.45 (0.25 – 0.80) | 0.007 |

CI – confidence interval
IVMP – intravenous methylprednisolone
MS – multiple sclerosis

Table 8. **Summary of outcomes of the ONTT.**

| Outcome | Comparative Risk | |
|---|---|---|
| | IVMP v. Placebo | Oral Prednisone v. Placebo |
| Nonrecovery of normal vision (based on visual-acuity-test results) | ↓ 5%[a] | ↑ 10%[a] |
| Recurrence of optic neuritis in either eye | ↓ 19%[a] | ↑ 19%[b] |
| Development of multiple sclerosis | ↓ 30%[a] | ↑ 20%[a] |

↓ indicates a decrease in relative risk of steroid group compared to placebo
↑ indicates increase in relative risk of steroid group compared to placebo
a – not statistically significant
b – statistically significant

the data reported from the two-year follow-up period, the probability of a new attack in either eye in the oral-prednisone group was almost twofold (41%) that in either the placebo or intravenous group (25%). In addition, 14% of the patients in the oral-prednisone group had more than one episode in either eye compared with 7% in both the placebo and IVMP groups.[15]

Among the patients who completed the ten-year follow-up examination, 35% had a documented recurrence of optic neuritis in the affected eye (at study entry), at least 1 attack of optic neuritis in the fellow eye, or both after entry into the ONTT. The proportion of patients with a recurrence in either eye was significantly higher in the oral-prednisone group (44%) than in the IVMP (29%, $p = 0.03$) or placebo group (31%, $p = 0.07$).[2]

*Development of multiple sclerosis.* Within the 6 to 24 months follow-up period, multiple sclerosis developed in 20% (28 patients) in the placebo group, 14% (20 patients) in the intravenous group, and 24% (35 patients) in the oral-prednisone group.[11] While these results showed that administration of intravenous methylprednisolone tended to have some beneficial effect in preventing the development of multiple sclerosis and oral-prednisone intake showed some tendency to harm, they were not significant as evidenced by the confidence intervals (Table 6).

A separate report that focused on the development of multiple sclerosis within the first 2 years among patients enrolled in the ONTT, compared the IVMP and oral-prednisone groups with placebo and with each other (Table 7). The adjusted results favored the IVMP group, which showed a reduced rate of development of multiple sclerosis.[8]

The latest report noted that the overall risk of developing clinically definite multiple sclerosis was 38% (95% CI 33% – 43%) over 10 years and 40% (95% CI 35% – 45%) over 12 years from the initial attack of optic neuritis. The ten-year risk was, however, similar in the 3 original ONTT treatment groups.[3]

Table 8 summarizes the results of the study. Except for the results comparing the percentage of patients who developed new episodes of optic neuritis between the oral prednisone and placebo groups, the rest of the results were insignificant. It should be noted, however, that the probability of nonrecovery of vision, having a new episode of optic neuritis, or development of multiple sclerosis was lower in the IVMP group than in the oral-prednisone group.

*Side effects.* Reported side effects were generally mild. Serious side effects were reported in only 2 patients, both in the IVMP group. One patient had an acute transient depression that required treatment and another had acute pancreatitis. Both cases resolved without sequelae. Minor side effects were more common in the 2 steroid groups than in the placebo group. These included sleep disturbance, mild mood change, stomach upset, and facial flashing. The mean percentage of weight gain was also higher in the steroid groups than in the placebo group ($p < 0.001$).[11]

## STUDY AUTHORS' CONCLUSIONS

In most patients with optic neuritis, recovery of vision is rapid—within 2 to 3 weeks after the onset of symptoms even without treatment. The only factor of value in predicting the visual outcome is the initial severity of vision loss. However, even when initial loss is severe, recovery of vision is still good in most patients. In the ONTT, treatment with high-dose intravenous methylprednisolone followed by oral prednisone accelerated recovery of vision but provided no long-term benefit to vision. Most patients retained good to excellent vision 5 to 10 years following

an attack of optic neuritis regardless of the type of treatment they received.[2, 11, 15]

The probability of a new attack of optic neuritis in either eye was higher in the oral-prednisone group than in the other 2 groups. The probability of recurrence in either eye was greater among patients in whom clinically definite multiple sclerosis was diagnosed by the fifth and tenth year of follow-up.[2, 11, 15]

Treatment with high-dose intravenous methylprednisolone followed by oral prednisone produced a short-term reduction in the rate of development of clinically definite multiple sclerosis, but there were no significant differences among treatment groups in either the risk of development of clinically definite multiple sclerosis or in the degree of neurologic disability among patients who developed clinically definite multiple sclerosis 5 or 10 years following the initial attack of optic neuritis. [2, 11, 15]

Intravenous methylprednisolone was generally well tolerated. Only 2 patients reported serious side effects, both cases of which resolved without sequelae.[11]

## REVIEWER'S CONCLUSIONS

Intravenous methylprednisolone should be considered for use in patients with acute optic neuritis if there is a need to speed up recovery of vision. Since long-term visual outcomes were comparable in the 3 treatment groups, and the oral-prednisone regimen, in doses given in this trial, was found to be associated with an increased risk of recurrence of optic neuritis in either eye, no treatment is an option for patients with an initial attack of optic neuritis.

Baseline MRI studies should ideally be done for patients suspected of having optic neuritis in order to assess their odds of developing clinically significant multiple sclerosis.

The clinical applicability of study results should be considered from the point of view of patient characteristics, values, and preferences. The cost of a three-day course of IVMP should be considered in treating any patient with optic neuritis in the local setting. Studies utilizing oral prednisone at doses other than that used in the ONTT study may be explored as alternative treatment. In recent years, results of a trial comparing the administration of interferon with IVMP have been published. These should also be reviewed.


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PERSPECTIVE

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# Evidence-based medicine: What it is, what it is not

SCENARIO 1. As a conscientious ophthalmologist you desire to be up-to-date on the current accepted clinical practice. You read several journals, but you are not sure which to adopt and which to reject. You attend conferences and seminars, but you are not sure that the "experts" are providing you unbiased justification for their recommendations.

Scenario 2. Representatives of pharmaceutical companies visit you and provide you with reprints in support of their product. How much value should you give to the information they provide?

Scenario 3. A patient whom you have been treating for some time visits you and asks about a new treatment that he picked up from the Internet. You admit that you are not aware of the treatment but promised to look it up. How will you find the answer?

The answers to your dilemma in the above or similar scenarios may very well be found in the use of the principles of evidence-based medicine (EBM). What follows is an abstract of the Introduction to Sackett's book.[1] EBM is the integration of the best research evidence with clinical expertise and patient values.

The first part of EBM involves finding the best research evidence. This has been made difficult because of:

- the daily need for valid information about diagnosis, prognosis, therapy, and prevention (up to 5 times for inpatient[2] and twice for every 3 outpatient[3]);
- the inadequacy of traditional sources of information because they are out-of-date (textbook[4]), frequently wrong (experts[5]), ineffective (didactic continuing education[6]), or too voluminous (journals[7]);
- the disparity between our diagnostic skills and clinical judgment, which increases with experience, and our up-to-date knowledge[8] and clinical performance,[9] which decline;
- our inability to set aside more than half an hour per week for general reading and study,[10] or more than a few seconds per patient for assimilating this evidence.[11]

Five developments have made these seeming insurmountable problems amenable to full-time clinicians:

- the development of strategies for efficiently tracking down and appraising evidence (for its validity and relevance);[1]
- the creation of systematic reviews and concise summaries on the effect of health care;[12]

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• the creation of evidence-based journals of secondary publication;

• the creation of information systems and bringing the information to clinicians in seconds; [10] and

• the identification and application of effective strategies for life-long learning and for improving our clinical performance.[13]

The practice of EBM is composed of 5 steps:

Step 1. Convert the need for information into an answerable question.

Step 2. Track down the best evidence to answer the question.

Step 3. Critically appraise the evidence for its validity, impact, and applicability.

Step 4. Integrate the critically appraised evidence with clinical expertise and the patient's values and circumstances.

Step 5. Evaluate the effectiveness and efficiency in executing steps 1-4 and seek ways to further improve the process.

(The reader is referred to the book or other references for details in undertaking the above steps.)

What are the limitations of EBM?

1. There is no indication that evidence-based medicine improves outcomes of patient care. Randomized clinical trials are difficult to conduct in certain instances due to problems of sample size, blinding, contamination, long-term follow-up, and ethical considerations.

2. The difficulty of looking for the best available evidence from the scientific literature, which is not coherently and consistently catalogued.

3. The difficulty of applying the best available evidence to the care of a particular patient.

4. The limitations and barriers to the practice of quality medicine.

5. The need for developing the skills in critical appraisal.

6. The limited time of busy clinicians to apply and master EBM.

EBM provides the clinician with an opportunity for adding the best clinical evidence to the usual clinical paradigm of understanding the pathophysiology of the disease, common sense, experience, and expert opinion. EBM does not provide the answer, only the evidence that the clinician integrates with his expertise and the patient's circumstances.

The practice of EBM, particularly for the beginner, is difficult and time-consuming. The application of the best available evidence in clinical practice appears logical but there is no evidence that it is cost-effective. On the other hand, the clinician will be on the defensive for not using the best available evidence in case of litigation.

The following articles will provide you with a glimpse of what EBM can and cannot do.


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CRITICALLY APPRAISED TOPIC

# Laser *in situ* keratomileusis (LASIK) for high myopia

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EXCIMER laser vision correction in the form of LASIK and PRK/LASEK has been proved to be highly effective and safe in the treatment of low to moderate myopia (less than –6 diopters [D]) and astigmatism. It is the most common refractive-surgery procedure done worldwide. However, the outcome of laser vision correction among those with high myopia (greater than –6D) may not be the same as in those with low to moderate myopia.

## CLINICAL SCENARIO

A 26-year-old, female, myopic patient unhappy with spectacle correction and contact lenses heard about LASIK and sought opinion regarding the probability of her achieving 20/20 vision. Her last refraction was –7.00 sphere –1.00 cylinder x 100 in the right eye (OD) and –9.00 sphere –0.50 cylinder x 90 in the left eye (OS). Best-corrected visual acuity (BCVA) was 20/20 OD and 20/20 OS. Her refraction has been stable for 5 years.

## CLINICAL QUESTION

The patient has high myopia and is concerned about her chances of seeing 20/20 after undergoing laser vision correction. Among patients with high myopia, how effective is LASIK in achieving 20/20 vision?

## SEARCH METHOD

An electronic literature search was performed using MEDLINE (PubMed). The following search terms were used: "Myopia," "LASIK," "laser in situ keratomileusis," "technology assessment." The search was further limited to the English language and human studies published from 1968 to April 2005. The search yielded 5 articles but only one was relevant to the clinical question.

## CITATION

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## STUDY CHARACTERISTICS

The article is a systematic review on the safety and efficacy of LASIK for myopia. The authors performed an electronic search using Medline and Cochrane. The literatures were limited to the English language and to peer reviewed journals published from 1968 to May 2001. Search term used was LASIK or Laser *in situ* keratomileusis. The search yielded 729 articles; 160 were chosen for evaluation and 47 were finally included in the review. The articles were submitted to a panel of methodologists for review and were classified as follows:

- Level 1 (RCT): 7 articles
- Level 2 (Cohort and Case Control): 10 articles
- Level 3 (Case Series): 30 articles

## DISCUSSION

**Validity criteria**

The article was valid based on the 4 validity criteria for systematic reviews (Table 1).

A focused clinical question is essential in a systematic review, and should apply across a range of patients where an intervention will have similar impact. The focused question also serves as the inclusion criteria to avoid bias in the selection of studies. It also limits the scope of the search and helps readers decide if they share the same interest as the authors.[1] As stated in the article, the focus of the authors' assessment was to address the following questions: What is the efficacy (predictability, stability) of LASIK for myopia and astigmatism? What are the complications of LASIK?

The clinical question is sensible because it fulfills the components of a good clinical question, namely: population (patients with myopia and astigmatism), intervention (LASIK), outcome (efficacy and complications).

The search included all published articles in the peer-reviewed literature but was limited to those in the English language. Although some relevant studies could have been missed, it is unlikely that major studies were not included since these studies are usually published in English language publications.

All the selected studies were reviewed and assessed by a Panel of Methodologists and each paper was rated. Level I rating was assigned to properly conducted, well-designed randomized clinical trials; Level II to well-designed cohort and case-control studies; and Level III to case series. In this systematic review, only 7 papers merited a rating of Level I.

Table 1. **Validity criteria.**

| Criteria | Answer |
|---|---|
| 1. Did the review explicitly address a sensible clinical question? | Yes |
| 2. Was the search for relevant studies detailed and exhaustive? | Yes |
| 3. Were the primary studies of high methodologic quality? | Yes |
| 4. Were assessments of studies reproducible? | Yes |

**Results**

The systematic review was done for the purpose of an ophthalmic technology assessment of LASIK for myopia and astigmatism. As such, it covered the entire range from low to moderate to high myopia. Table 2 is a summary of results from different studies relevant to the clinical question and included in the systematic review.

The studies by Hersh and Steinert were randomized controlled trials with at least 6 months of follow-up comparing LASIK with PRK in the treatment of moderate to high myopia and astigmatism. Visual acuity of 20/20 was achieved after LASIK in 26% and 36% of eyes, respectively. The studies by Casebe and Perez-Santonja, both level II studies, did not provide any data on the percentage of patients who achieved 20/20 vision. The case series by McDonald has the most number of patients with 20/20 post LASIK vision; however, the range of myopia was from –1 to –11 diopters. The articles by Kawesch and Reviglio concentrated on very high myopia, which are beyond the range of the myopia described in the case scenario.

Table 2. **Visual acuity after LASIK for moderate to high myopia.**

| Study | Number of Eyes | Level of Evidence | Range of Preop Myopia (D[1]) | Mean Preop Refraction (D[1]) | Postop UCVA[2] ≥ 20/20 (%of eyes) | Postop UCVA[2] ≥ 20/40 (% of eyes) |
|---|---|---|---|---|---|---|
| Hersh, et al. 1998 | 115 | I | –6 to –15 | –9.3 | 26.2 | 55.7 |
| Steinert, et al. 1998 | 76 | I | –9 to –12 | –9.2 | 36.0 | 85.0 |
| Casebe, et al. 1997 | 911 | II | –7 to –10 | NR | NR | 68.0 |
| Perez-Santonja, et al. 1995 | 143 | II | –8 to –20 | –13.2 | NR | 46.4 |
| McDonald, et al. 1999 | 347 | III | –1 to –11 | NR | 57.0 | 95.0 |
| Kawesch, et al. 1998 | 290 | III | –9 to –22 | NR | NR | 85.1 |
| Reviglio, et al. 1999 | 126 | III | –10 to –25 | –12.7 | 9.8 | 78.4 |

[1]Diopter
[2]Uncorrected visual acuity

**Applicability**

All these studies involved the use of LASIK for the correction of moderate to high myopia with UCVA as 1 of the outcome measures. However, only the studies by Hersh and Steinert are applicable to the clinical scenario because the range of myopia in their studies is similar to the case. Other outcome measures considered were postoperative refraction within $\pm$0.50 D and $\pm$1.0 D, loss of $\geq$2 lines of best-corrected visual acuity, and frequency of operative (button holes, flap striae, etc.) and postoperative (diffuse lamellar keratitis, infections, dry eye, glare and haloes, reduced contrast sensitivity, etc.) complications. When evaluating the safety and efficacy of refractive-surgery results, it is important to consider not only visual acuity, but also other relevant clinical outcomes like quality of vision and patient satisfaction.

Refractive surgery, specifically laser vision correction, is a rapidly evolving field and is intimately related to the development of new technology. Although the basic principles of LASIK have remained essentially the same since it was first introduced by Pallikaris in 1990,[2, 3] many new developments have occurred since then. Excimer laser machines have evolved from broad-beam lasers to high-frequency, small-diameter, flying-spot lasers with active eye trackers. Better understanding of corneal biomechanics and high-order optical aberrations led to the development of new nomograms and wavefront-guided customized LASIK. Microkeratomes have become safer with smoother stromal beds and more consistent flap thickness. It is, therefore, essential that any published results of studies on LASIK should be interpreted in the light of the existing technology when the study was done. Results may no longer be applicable to a particular case if the technology and techniques used were not similar.

## STUDY AUTHORS' CONCLUSIONS

For low to moderate myopia, results from studies in the literature have shown that LASIK is effective and predictable in terms of obtaining very good to excellent uncorrected visual acuity and that it is safe in terms of minimal loss of visual acuity. For moderate to high myopia (>6.0 D), the results are more variable, given the wide range of preoperative myopia. The results are similar for treated eyes with mild to moderate degrees of astigmatism (<2.0 D). Serious adverse complications leading to significant permanent visual loss such as infections and corneal ectasia probably occur rarely in LASIK procedures; however, side effects such as dry eyes, night-time starbursts, and reduced contrast sensitivity occur relatively frequently. There were insufficient data in prospective, comparative trials to describe the relative advantages and disadvantages of different lasers or nomograms.

## REVIEWERS' CONCLUSIONS

The appraised article on the safety and efficacy of LASIK for myopia and astigmatism is a valid systematic review. The results of the different studies included in the review are applicable only to the period and setting when the studies were performed. Constant updates should be made to reevaluate the procedure. Uniform methodology guidelines must be agreed upon and followed when these studies are done to allow for metaanalysis. Clinically relevant outcome measures like quality of vision and patient satisfaction must be emphasized.

## RESOLUTION OF THE CLINICAL SCENARIO

The refraction of the patient in the scenario falls within the range of the cited studies for high myopia. She can be advised that the probability of her achieving 20/20 visual acuity after LASIK is 26% to 36%, assuming that the same excimer laser machine, microkeratome, operative technique, surgeon's expertise, and postoperative medications will be used as those mentioned in the cited studies.


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CRITICALLY APPRAISED TOPIC

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# Globe-sparing interventions in the management of intraocular retinoblastoma

RETINOBLASTOMA is the most common malignant intraocular tumor in children; it is also one of the most highly curable pediatric solid tumors if detected early. The conventional treatment of retinoblastoma is primary enucleation. Recent research reported a trend toward decreasing frequency of enucleation in the management of retinoblastoma.[1] The trend toward globe-sparing interventions has been largely attributed to earlier diagnosis and recent success with conservative globe-sparing treatment options. Currently, globe-sparing interventions include first-line chemotherapy or chemoreduction, subconjunctival chemotherapy, systemic chemotherapy for metastasis, transpupillary thermotherapy (TTT), chemothermotherapy (CTT), laser photocoagulation, cryotherapy, brachytherapy, and external beam radiotherapy (EBRT). Expanded clinical options currently available have markedly decreased the overall enucleation rate for retinoblastoma.[2]

## CLINICAL SCENARIO

A 10-month old boy is brought to an ophthalmologist because of cat's eye reflex in the left eye. The patient had undergone enucleation of his right eye for glaucomatous stage retinoblastoma 6 months earlier. Examination revealed the presence of a solitary retinal mass of about 12 mm in diameter, located nasal to the disc. There was no evidence of vitreous seeding.

Realizing that this was the only eye of the patient, the ophthalmologist wants to do everything humanly possible to preserve it. He has heard about chemothermotherapy (CTT) but is not sure if this was the best alternative he can offer.

## CLINICAL QUESTION

Among patients with retinoblastoma, is chemoreduction combined with adjuvant treatment effective in preserving the globe and vision?

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***Keywords:*** *Retinoblastoma, Globe, Intraocular tumor, Chemotherapy, Enucleation*

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## SEARCH METHOD

An electronic search of the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Group Trials Register) on *The Cochrane Library* (Issue 1 2005) and MEDLINE on PubMed was performed. The literature search was limited to the English language with no date restrictions. The search terms used were retinoblastoma and chemothermotherapy, thermochemotherapy, or chemoreduction. The search yielded 70 articles, 22 were chosen for evaluation and 8 were included in the review. Two reviewers independently assessed the articles for inclusion.

**Selection criteria**

This review was designed to include clinical trials in which treatment of retinoblastoma with chemoreduction combined with adjuvant therapy was compared with another treatment or no treatment.

## CITATIONS


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8. Shields CL, Shields JA, Needle M, et al. Combined


Table 1. **Study characteristics.**

| Study | Patients | Intervention | Outcome | Method | Ocular preservation |
|---|---|---|---|---|---|
| Schiavetti, et al. *J Pediatr Hematol Oncol* 2005 | 58 eyes, 46 patients | Chemoreduction (carboplatin/ etoposide)[+] Adjuvant treatment (laser or cryo) | Tumor response rate | Prospective, nonrandomized clinical trial | 67% |
| Shields, et al. *Am J Ophthalmol* 2004 | 457 tumors (193 eyes, 125 patients) | Chemoreduction (vincristine, etoposide, carboplatin) [±] Adjuvant treatment (cryo, thermo, or both) | Tumor recurrence | Prospective, single-center, interventional case series | 98% (22%[++]) |
| Schueler, et al. *Br J Ophthalmol* 2003 | 55 tumors (26 patients with bilateral RB) | Chemothermotherapy (CTT) | Tumor recurrence | Prospective, nonrandomized clinical trial | 96% (38%[++]) |
| Lumbroso, et al. *Ophthalmology* 2002 | 103 tumors (65 eyes, 51 children) | Chemothermotherapy (CTT) | Local tumor control | Noncomparative, interventional case series | 92% |
| Shields, et al. *Am J Ophthalmol* 2002 | 364 tumors (158 eyes, 103 patients) | Chemoreduction plus focal treatment (cryo, thermo, plaque) | Need for EBR or enucleation | Interventional case series | 61% |
| Shields, et al. *Arch Ophthalmol* 2002 | 30 patients with unilateral RB | Chemoreduction plus focal treatment (cryo, thermo, plaque) | Need for EBR or enucleation | Prospective, nonrandomized single-center clinical trial | 71% (33%[+]) |
| Wilson, et al. *Ophthalmology* 2001 | 36 eyes | Chemotherapy (carboplatin & vincristine) (focal treatment given only when disease progressed) | Disease progression, delay of EBR, ocular survival | Noncomparative, prospective case series | 19.50% |
| Shields, et al. *Ophthalmology* 1997 | 130 tumors (52 eyes, 32 patients) | Chemoreduction (vincristine, etoposide, carboplatin) + Adjuvant treatment (cryo, laser, thermo, CTT, plaque, EBR) | Tumor control | Prospective, nonrandomized clinical trial | 58% |

[+] Reese–Ellsworth V
[++] Tumor-recurrence rate

cryo – cryotherapy
thermo – thermotherapy

EBR – external beam radiotherapy
RB – retinoblastoma

chemoreduction and adjuvant treatment for intraocular retinoblastoma. *Ophthalmology* 1997; 104: 2101-2111.

## DISCUSSION

**Data collection and analysis**

No randomized controlled clinical trials were found. The available literature consists mostly of prospective nonrandomized clinical trials and interventional case series (Level 4 evidence). The reviewers extracted data and assessed trial quality of the included studies. Due to the variability in treatment methods and main outcome measures, no statistical summary measure was calculated.

**Main results**

Eight trials were included in this review (Table 1). The highest rate of globe preservation (98%) was shown in a study of 193 eyes in 125 children (457 tumors) treated with chemotherapy plus adjuvant therapy, consisting of either cryotherapy or transpupillary thermotherapy or both. In this study, the rate of recurrence leading to subsequent enucleation or external beam radiation rose with greater tumor thickness and when the tumors were at the macula. Two other trials on chemothermotherapy (CTT), which consisted of intravenous (IV) administration of carboplatin followed shortly by transpupillary thermotherapy (TTT), yielded globe-salvage rates of 92% to 96%. This intervention was particularly effective in small to medium tumors (up to 12 mm). Globe-preservation rates were much lower (58% - 67%) when chemoreduction was combined with other modes of adjuvant or focal treatments (cryotherapy, laser therapy, plaque radiotherapy). Chemotherapy alone posted the lowest globe-preservation rate of 19.5%. In most trials, globe-preservation rates were much lower for tumors classified as Reese–Ellsworth (RE) V. Two trials studied the factors that led to treatment with enucleation or external beam radiation. Results were not consistent.

Table 2. **Reese–Ellsworth (RE) classification for conservative treatment of retinoblastoma.***

| Group | Likelihood of Globe Salvage | Features |
|---|---|---|
| I | Very favorable | • Solitary tumor, less than 4 disc diameters, at or behind equator<br>• Multiple tumors, none over 4 disc diameters, all at or behind equator |
| II | Favorable | • Solitary tumor, 4 to10 disc diameters, at or behind equator<br>• Multiple tumors, 4 to 10 disc diameters, behind equator |
| III | Doubtful | • Any lesion anterior to equator<br>• Solitary tumors larger than 10 disc diameters behind equator |
| IV | Unfavorable | • Multiple tumors, some larger than 10 disc diameters<br>• Any lesion extending anteriorly to ora serrata |
| V | Very unfavorable | • Massive tumors involving more than half of retina<br>• Vitreous seeding |

*Refers to chances of salvaging the affected eye and not systemic prognosis.

## STUDY AUTHORS' CONCLUSIONS

Classifications of retinoblastoma based on disease severity have been developed to aid in the prediction of globe salvage. The Reese–Ellsworth classification, which correlates the likelihood of globe salvage with tumor extent, is widely used in most research studies (Table 2).

The available treatment methods for retinoblastoma for globe salvage in the management of retinoblastoma include intravenous chemoreduction, thermotherapy, cryotherapy, laser photocoagulation, plaque radiotherapy, external beam radiotherapy, and systemic chemotherapy for metastatic disease.[3]

Chemoreduction with or without adjunctive focal measures and thermotherapy alone have been the most promising of the globe-sparing modalities described.

**Chemoreduction**

Chemoreduction is a method of reducing tumor volume by means of chemotherapeutic agents. This allows the use of adjunctive therapeutic measures that are more focused and less damaging, increasing the likelihood of globe salvage. The chemotherapeutic agents employed are varied and depend on the preference of the pediatric oncologist, but consist mainly of a combination of the following agents: carboplatin, etoposide, and vincristine. The chemotherapy regimen is generally given in 6 cycles for adequate tumor reduction. Adjunctive focal therapy if given is delivered at cycle 2 after achieving adequate tumor reduction. Chemoreduction allows for a reduction in tumor size that permits focal treatments to be applied to a smaller area, preserving more vision and delaying or possibly avoiding enucleation.[4]

*Schiavetti, et al.* J Pediatr Hematol Oncol *2005*

Although all groups of patients with intraocular retinoblastoma responded to carboplatin/etoposide chemotherapy associated with focal therapy, all the cases in RE group V relapsed. This approach is questionable in RE group V, where delaying aggressive treatment in a very young child may be justified.

*Shields, et al.* Am J Ophthalmol *2004*

Chemoreduction alone or combined with cryotherapy or thermotherapy is effective for treatment of retinoblastoma, but tumor recurrence rate is highest when

the tumor is thicker (risk ratio of 1.13 per 1 mm increase) or located in the macula (risk ratio 3.58).

*Shields, et al.* Am J Ophthalmol *2002*

Chemoreduction offers satisfactory retinoblastoma control for RE groups I-IV, with treatment failure necessitating additional external beam radiotherapy in only 10% of eyes and enucleation in 15% of eyes at five-year follow-up. RE group V requires external beam radiotherapy in 47% and enucleation in 53% at 5 years.

*Shields, et al.* Arch Ophthalmol *2002*

Chemoreduction is an option for selected eyes with unilateral retinoblastoma. Those with advanced RE group V retinoblastoma showed poorest results, while those with less advanced groups I through IV disease showed best results, maintaining the globe in 71% of eyes, occasionally with satisfactory functional visual acuity.

*Wilson, et al.* Ophthalmology *2001*

Multiagent chemotherapy alone does not ensure a cure for multifocal intraocular retinoblastoma. Supplemental focal therapy is needed to control disease progression.

*Shields, et al.* Ophthalmology *1997*

Chemoreduction and adjuvant treatment of intraocular retinoblastoma with seeding provide good retinal tumor control, even in eyes with advanced disease. Chemoreduction alone generally is not adequate to achieve complete tumor seed control. Cautious follow-up of affected patients is recommended because the risk for recurrent vitreous and subretinal seeds is substantial and proper treatment is critical for salvaging the eye.

*Thermochemotherapy*

Thermotherapy is a focal or adjunctive treatment modality that applies focused heat to tissue at subphotocoagulation levels to induce tumor necrosis in the treatment of intraocular masses. A transpupillary diode-laser system is used to selectively increase temperature in the tumor. The goal is to attain a focal temperature rise of 42° to 60° Celsius, which is below the coagulative threshold sparing the surrounding retinal tissues.[5] The thermal action has been found to have a synergistic effect by increasing the cytotoxic effects of platinum analogues in the treatment of retinoblastoma.[6] The combination of heat and chemotherapy is called chemothermotherapy (CTT).

*Schueler, et al.* Br J Ophthalmol *2003*

Chemothermotherapy using an indirect laser ophthalmoscope with a spot size of about 400 µm was efficient for retinoblastoma with a tumor height less than 4 mm. In larger tumors, the recurrence rate was unacceptably high (risk ratio 1.36). Fish flesh regression after TCT correlates with a higher rate of local tumor recurrence (risk ratio 4.88). Treatment-related complications occurred in less than 9% of the treated eyes.

*Lumbroso, et al.* Ophthalmology *2002*

Chemothermotherapy is an effective technique to treat small- to medium-sized retinoblastomas in children, avoiding external beam irradiation.

## REVIEWERS' CONCLUSIONS

The evidence as to the effectiveness of chemoreduction combined with adjuvant or focal therapy comes mainly from nonrandomized, interventional case series (Level 4 evidence). There is evidence that chemothermotherapy provides the best chance for ocular (globe) preservation. Chemoreduction combined with other forms of adjuvant or focal therapy showed poorer outcomes compared with CTT, but is still better than chemotherapy alone. There is no evidence that chemoreduction with adjuvant therapy leads to preservation of vision. If at all possible, further large well-conducted randomized controlled trials, with longer follow-up, are advisable.

## RESOLUTION OF THE CLINICAL SCENARIO

For intraocular tumors ≤10 mm, with no evidence of vitreous and/or retinal seeding (RE I-IV), chemothermotherapy offers the best chance for globe preservation (Grade C recommendation).


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CRITICALLY APPRAISED TOPIC

# Timolol versus latanoprost for primary open-angle glaucoma

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## CLINICAL SCENARIO

A 46-year-old male consulted for refraction. Best-corrected visual acuity was 20/20 for both eyes (OU), Jaeger 1 for near. Slit-lamp examination was normal. Intraocular pressure (IOP) was 25 mm Hg OU. Gonioscopy revealed iridocorneal angles that were open up to the ciliary body band OU. Funduscopy revealed clear media with no exudates or hemorrhages in the retina. Cup–disc ratio was 0.7 vertically and 0.6 horizontally with notching of the inferotemporal neuroretinal rim OU. Automated visual-field examination showed superior arcuate scotomas OU with no threat to fixation. The working diagnosis upon consultation was primary open-angle glaucoma. After all treatment options had been explained to the patient, a trial of medical therapy was chosen. Given the severity of the glaucoma, a target IOP range was initially set at 15 to 17 mm Hg. Nonselective beta-adrenergic blockers and prostaglandin analogues are two classes of medications that will most probably lower the IOP to the desired levels.

## CLINICAL QUESTION

Among patients undergoing initial medical therapy for primary open-angle glaucoma, would latanoprost be more effective in lowering the IOP compared with timolol?

## SEARCH METHOD

An electronic literature search was performed using Medline (PubMed). The key words used were "latanoprost" and "timolol." The search was further limited to randomized clinical trials or metaanalysis published in the English language. Table 1 shows the search process performed.

The search was narrowed down to 5 articles. Abstracts of the articles were reviewed. One article employed ocular hypertensive subjects while another compared brimonidine and timolol. These studies were, therefore, excluded. Among all the metaanalyses obtained from the search, Zhang et al.'s had the most number of subjects and outcome measures. It was for this reason that the article was chosen for appraisal in resolving the clinical scenario.

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***Keywords:*** *Glaucoma, Intraocular pressure, Latanoprost, Timolol*

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## CITATION

Zhang W, A Li Wan Po, Dua H, Azuara-Blanco A. Metaanalysis of RCTs comparing latanoprost with timolol in the treatment of patients with open-angle glaucoma or ocular hypertension. *Br J Ophthalmol* 2001; 858: 983-990.

**Study characteristics**

Randomized controlled trials (RCTs) of latanoprost versus timolol were retrieved systematically in the following databases: (1) Medline, Embase, and Scientific Citation Index; (2) reference lists of original reports and review articles, retrieved through the electronic searches; (3) manufacturers' databases including Pfizer ophthalmology database and Merck glaucoma database. The computerized searches covered the period 1966 to May 2005.

Eleven randomized controlled trials were included in the metaanalysis. These trials were performed in various countries including the United States, Canada, Japan, the Philippines, United Kingdom, and other European nations. Latanoprost 0.005 % or 0.006% eye drops were directly compared with timolol 0.5% eye drops in all of the studies. A total of 1,256 patients were included in the analysis.

The primary outcome measure considered was percentage reduction in IOP. Other outcome measures included iris pigmentation, hyperemia, and systemic adverse reactions. Trials with subjects who had open-angle glaucoma (including primary and secondary open-angle glaucoma) or ocular hypertension were included.

## DISCUSSION

The reviewers in this study addressed a sensible clinical question: To compare the IOP lowering effects of latanoprost versus timolol in primary open-angle glaucoma. As previously mentioned, the method for literature search was explicit and thorough. However, there was no attempt to look for unpublished reports.

The review adhered to strict guidelines in accepting and rejecting trials for the metaanalysis. Two independent investigators performed data extraction. Any disagreement was resolved by discussion. The quality of the articles was assessed based on randomization, masking, and withdrawal as proposed by Jadad.[1] Prior to combining the results of the different trials, test for heterogeneity was performed using Q statistic. In addition, sensitivity analyses were done to assess the effect of the quality of the randomized controlled trials in terms of study design and withdrawal rate.

Table 2 summarizes the answers for the different criteria in assessing the validity of a metaanalysis.

Metaanalysis of the trials revealed that latanoprost causes an additional 5% decrease in IOP (95% CI 3% to 7%) or an average 1.6 mm Hg ($p < 0.001$) compared with timolol.

Other outcomes analyzed were local and systemic side effects, specifically changes in heart rate and blood pressure. Subjects under latanoprost therapy experienced more hyperemia and iris pigmentation than those given timolol. The risk for hyperemia was twice that of timolol (RR = 2.20, 95% CI 1.33 to 3.65). The number needed to harm was computed at 21 relative to timolol. Therefore, treating 21 patients with latanoprost will, on the average, lead to 1 more patient developing hyperemia. Moreover, 4.39% of the patients treated with latanoprost developed iris pigmentation. In contrast, none of the patients treated with timolol experienced this effect. Timolol caused bradycardia in 4 of 236 patients after 3 or 6 months of treatment. These cases returned to baseline level after the paients were switched to latanoprost.

## STUDY AUTHORS' CONCLUSION

The metaanalysis suggests that latanoprost is more effective than timolol in lowering IOP. However, it can cause iris pigmentation in certain groups of patients. While current evidence suggests that this pigmentation is benign, careful lifetime follow-up of patients is still justified.

## REVIEWERS' CONCLUSION

Compared with timolol, latanoprost achieves a greater amount of IOP reduction with less effect on heart rate in

Table 1. **Search process employed.**

| Search Words | No. of Citations |
|---|---|
| 1. Latanoprost | 735 |
| 2. Timolol | 3,248 |
| 3. Latanoprost AND timolol | 220 |
| 4. Latanoprost AND timolol<br>Field: all fields, Limit: randomized, controlled trial | 93 |
| 5. Latanoprost AND timolol AND primary open-angle glaucoma<br>Field: all fields, Limit: metaanalysis | 6 |
| 6. Latanoprost AND timolol AND primary open-angle glaucoma<br>Field: all fields, Limit: English, metaanalysis | 5 |

Table 2. **Validity criteria.**

| Criteria | Answer |
|---|---|
| 1. Did the review explicitly address a sensible clinical question? | Yes |
| 2. Were the methods for searching the literature explicit and reasonably thorough? | Yes |
| 3. Were the criteria used to select the studies for inclusion appropriate? | Yes |
| 4. Was the validity of the included studies assessed? Were the assessments of the studies reproducible? | Yes |
| 6. Was it appropriate to combine the results (for metaanalysis)? | Yes |

patients with primary open-angle glaucoma. In cases where higher levels IOP reduction are required or in patients with bradycardia or heart block, latanoprost would be a better first-line drug than timolol.

A higher incidence of conjunctival hyperemia and increased iris pigmentation is observed with latanoprost than with timolol. However, these minor ocular side effects have been deemed innocuous, and the increased iris pigmentation is not an issue among Asians due to their inherently dark irides.

Although IOP reduction is a proven method of controlling glaucoma progression, future investigations should include preservation of visual field, optic nerve, and retinal-nerve-fiber layer as primary outcome measures. These outcome measures are more clinically significant and definitive than IOP reduction alone. Additional studies are still needed to compare various glaucoma medications with regard to compliance, cost-effectiveness, and their effect on the patient's quality of life.

## RESOLUTION OF THE CLINICAL SCENARIO

For the patient, medical therapy with latanoprost should be considered as initial treatment. Visual prognosis for both eyes is good with the potential for adequate IOP control using a single agent. Cost-wise, the use of timolol may be advantageous. But in the long term, latanoprost would prove to offer more advantages with higher IOP lowering effect, better dosing regimen, and absence of cardiopulmonary side effects.

**Reference**

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CRITICALLY APPRAISED TOPIC

# Evidence on the prevention of postoperative endophthalmitis

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## CLINICAL SCENARIO

An 82-year-old female with no apparent ocular problems, except for a brunescent cataract, underwent phacoemulsification with intraocular-lens (IOL) implantation. Postoperative medication consisted solely of antibiotic-steroid eyedrops. One day after uneventful surgery, the patient developed severe pain, poor vision, and redness in the operated eye. Visual acuity was counting fingers at 1 meter. The eye had ciliary injection, grade 4 flare and cells, a small hypopyon, fibrin extending from the corneal wound, and a mildly edematous cornea. Intraocular pressure (IOP) was 24 mm Hg. Exudates behind the IOL were noted, but visualization was poor. Anterior-chamber and vitreous taps revealed gram-positive cocci. Could the ophthalmologist have prevented this complication?

## CLINICAL QUESTION

Among patients undergoing cataract extraction, what is the most effective regimen that can reduce the risk of endophthalmitis?

## SEARCH METHOD

A Medline search was performed using the keywords "endophthalmitis," "cataract," and "prevention." The search was limited to randomized controlled trials (RCT). No studies were found that compared endophthalmitis rates using different perioperative prophylactic measures. Most studies reported used substitute outcome measures such as periocular bacterial load, intraocular penetration of antibiotics, and anterior-chamber contamination. After reviewing the abstracts, only one RCT was considered relevant to the clinical question.

## CITATION

Soto AM, Mendivil MP. The effect of topical povidone–iodine, intraocular vancomycin, or both on aqueous humor cultures at the time of cataract surgery. *Ophthalmol* 2001; 131: 293-300.

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***Keywords:*** *Cataract, Endophthalmitis, Phacoemulsification, Vancomycin, Povidone–iodine*

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**Study characteristics**

*Patients/Population*

- patients older than 40 years with cataracts (n = 400, age range: 44 to 93)

*Interventions*

- vancomycin (20 µg/ml) in irrigating fluid
- topical 5% povidone–iodine preoperatively

*Comparison*

- Group 1: povidone–iodine and vancomycin
- Group 2: topical placebo and vancomycin
- Group 3: povidone–iodine alone
- Group 4: topical placebo
- 100 patients per group

*Outcome Measure*

- Frequency of positive cultures from anterior-chamber aspirates after phacoemulsification

*Methodology*

Randomized controlled trial

## DISCUSSION

**Validity criteria**

This study was a randomized, double-masked clinical trial involving adult patients with senile cataract. Excluded were patients with black cataracts, uncontrolled glaucoma, ocular or systemic inflammation or infection, history of adverse reactions to vancomycin, antibiotic treatment 10 days before surgery, and previous ocular surgery. All patients underwent a complete ophthalmologic examination and periocular-skin preparation technique, and received the same preoperative medication. The same surgeon performed phacoemulsification with IOL implantation in the capsular bag in all the cases. There were no complications during surgery or after 2 months of follow-up.

This study fulfilled the validity criteria as summarized in Table 1.

**Results**

The proportion of culture-positive anterior-chamber aspirates was significantly lower in the groups that received vancomycin ($p = 0.032$) (Table 2). The groups treated with topical povidone-iodine preoperatively showed a smaller proportion of positive cultures compared with the groups without povidone-iodine. The difference, however, was not statistically significant ($p = 0.59$). Even with significantly higher rates of culture positivity in the placebo group, postoperative endophthalmitis did not develop in any eye during the two-month follow-up period.

The relative risk of bacterial contamination of the anterior chamber after uncomplicated phacoemulsification was 15% with povidone–iodine plus vancomycin, 38% with vancomycin alone, and 85% with povidone–iodine alone (Table 3). To prevent 1 adverse event, i.e., anterior-chamber contamination, 9 patients would have to be treated with povidone–iodine plus vancomycin, 13 with vancomycin, and 50 with povidone-iodine.

## STUDY AUTHORS' CONCLUSION

Vancomycin in the irrigating fluid reduces the rate of positive intraocular cultures after phacoemulsification. "Two hours of contact between the antibiotic solution and bacteria produced results that reached statistical significance ($p = 0.032$)."

## REVIEWERS' CONCLUSION

The results of this study suggest that vancomycin in the infusion fluid during phacoemulsification may reduce anterior-chamber contamination. There is a trend towards

Table 1. **Validity criteria.**

| Criteria | Answer |
|---|---|
| 1. Were patients randomized? | Yes |
| 2. Was randomization concealed (blinded or masked)? | Yes |
| 3. Were patients analyzed in the groups to which they were randomized? | Yes |
| 4. Were patients in the treatment and control groups similar with respect to known prognostic factors? | Yes |
| 5. Were patients unaware of group allocation? | Yes |
| 6. Were clinicians unaware of group allocation? | Yes |
| 7. Were outcome assessors unaware of group allocation? | Yes |
| 8. Was follow-up complete? | Yes |

Table 2. **Culture-positive anterior-chamber (AC) aspirates per group.**

| Group | No. of Culture-Positive (AC) Aspirates |
|---|---|
| 1 (povidone–iodine + vancomycin) | 2 |
| 2 (vancomycin) | 5 |
| 3 (povidone–iodine) | 11 |
| 4 (placebo) | 13 |

Table 3. **Risk of anterior-chamber contamination per group.**

| Group | RR (%) | RRR (%) | ARR (%) | NNT |
|---|---|---|---|---|
| 1 | 15 | 85 | 11 | 9 |
| 2 | 38 | 62 | 8 | 13 |
| 3 | 85 | 15 | 2 | 50 |

RR – Relative risk, RR = y/x, where y= risk with therapy and x = risk without therapy
RRR – Relative risk reduction, RRR = 1- RR
ARR – Absolute risk reduction, ARR = x - y
NNT – Number needed to treat to prevent one adverse event, NNT = 1/ARR

lower culture positivity with the use of preoperative topical povidone-iodine. Results might have reached statistical significance with a larger sample size.

## UPDATES

A related randomized controlled trial,[1] which included a larger sample of 644 eyes in 640 patients, reported similar results. Group 1 (322 eyes) received plain balanced salt solution (BSS) and Group 2 (322 eyes) received vancomycin and gentamycin in BSS. There was a significantly lower rate of culture-positive aqueous aspirates in Group 2 (22 out of 322 or 6.8%) compared to Group 1 (68 out of 322 or 21.1%) ($p < 0.001$). Although two patients in Group 1 developed postoperative endophthalmitis, the number was still not significant ($p = 0.563$, NNT=161.5). The authors concluded that the addition of antibiotics to the irrigating fluid decreased anterior-chamber contamination during phacoemulsification. The United States Centers for Disease Control and Prevention (CDC) has, however, cautioned against the routine use of vancomycin for prophylaxis due to emerging resistance of staphylococcus infections.

In a systematic review of all English-language articles from 1963 to March 2003 cited in PubMed, the pooled estimate of the incidence of acute endophthalmitis from 3,140,650 cataract surgeries was 0.128%.[2] The authors noted a rising trend in endophthalmitis rates from 1992 to 2003, which appeared to coincide with the shift to sutureless, clear-cornea phacoemulsification technique. Moreover, the risk of endophthalmitis seemed to correlate with the type of cataract incision. Table 4 compares the relative risks of endophthalmitis by incision type.

A variety of prophylactic regimens have been proposed to reduce the risk of postoperative endophthalmitis. In a systematic review, Cuilla et al. concluded that only preoperative povidone–iodine was moderately important to clinical outcome (B or intermediate clinical recommendation); all other prophylactic measures, including preoperative topical antibiotics, postoperative subconjunctival antibiotic injection, and antibiotics in irrigating solutions received a C recommendation (possibly relevant but not definitely related to clinical outcome) due to weak and conflicting evidence.[3]

Table 4. **Relative risks of endophthalmitis by incision type.**

| Incision Type (endophthalmitis rate, %) | RR (95% Confidence Interval) |
|---|---|
| Clear corneal (0.19) v. scleral (0.07) | 2.55 (1.75-3.71) |
| Clear corneal (0.19) v. limbal (0.06) | 3.06 (2.48-3.76) |
| Scleral (0.07) v. limbal (0.06) | 1.20 (0.82-1.75) |

RR – Relative risk

Because postoperative endophthalmitis is an uncommon clinical outcome, research in this area has mostly relied on retrospective case series or surrogate end points such as bacterial load in the conjunctiva or aqueous aspirates. Theoretically, reduction of ocular surface flora should decrease the risk of anterior-chamber contamination and endophthalmitis. However, the relationship between positive cultures from ocular tissues and postoperative intraocular infection remains unclear. To evaluate the efficacy of these prophylactic measures, a randomized controlled trial would require thousands of subjects to achieve sufficient power. Such a study is now underway.

The *Antibiotic Prophylaxis for Cataract Surgery* study by the European Society of Cataract and Refractive Surgeons (ESCRS) will compare the efficacy of levofloxacin, cefuroxime, or both to controls in the prevention of post-cataract surgery endophthalmitis (www.clinicaltrials.gov/ct/gui/show/NCT00136344). A total of 35,000 cataract-surgery patients will be randomized to 4 groups (n=8,750/group): (1) perioperative, topical levofloxacin, (2) intracameral cefuroxime, (3) a combination of the two, and (4) placebo. All patients will receive povidone–iodine preoperative prophylaxis and topical levofloxacin from days 1 to 6 after surgery. Expected date of completion is September 2006.

## RESOLUTION OF THE CLINICAL SCENARIO

Current evidence suggests that vancomycin reduces the risk of anterior-chamber contamination. However, there is no evidence that a positive culture from anterior-chamber aspirates will result in endophthalmitis. The use of vancomycin for prophylaxis is strongly discouraged because of concerns regarding antibiotic resistance. Hence, although this 82-year-old patient could have benefited from intraocular vancomycin, it can not be concluded that such a regimen would have prevented endophthalmitis. Factors such as potential ocular toxicity, cost-benefit ratios, as well as compliance with existing guidelines on the judicious use of antibiotics, should always be borne in mind whenever one contemplates using antimicrobial agents for prophylaxis.


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CRITICALLY APPRAISED TOPIC

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# Surgical interventions for the treatment of primary pterygia

## CLINICAL SCENARIO

A 30-year-old overseas contract worker consulted the outpatient department for a noninflamed, large, slightly vascularized, fleshy mass that encroached on the limbus of the right eye and reached the paracentral area of the cornea. The mass gradually increased in size over the past 3 years, associated with occasional redness that spontaneously resolved without any medication. The vision in the right eye degenerated over the last year. There were no other ocular or systemic signs and symptoms, and no surgery was ever done in that eye. Visual acuity was 20/40 (correctable to 20/20) in the right eye (OD) and 20/20 uncorrected in the left eye (OS). Manifest refraction revealed an against-the-rule astigmatism of –2.0 diopters OD and plano OS. The rest of the ophthalmic examination was normal. His agency instructed him to have the mass removed prior to departure for Dubai in about 4 months. Since the mass was already causing astigmatism and reduced uncorrected visual acuity, surgery was contemplated. The ophthalmologist on duty wants to know whether the traditional bare-sclera technique is still the best method to use in treating this disease and preventing recurrence.

## CLINICAL QUESTION

Pertinent data presented include a noninflamed, fleshy mass that over a period of 3 years gradually crossed the limbal border into the paracentral area of the cornea causing a two-diopter against-the-rule astigmatism. In the absence of any previous eye surgery, this picture is compatible with a primary pterygium.

After identifying the ocular condition in the clinical scenario, a clinical question can now be formulated as follows: Among patients with primary pterygia, how effective is bare-sclera technique compared to adjuvant treatment with mitomycin C (MMC) or conjunctival autografting (CA) in minimizing pterygium recurrence?

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***Keywords:*** *Pterygium, Mass, Bare-sclera resection, Mitomycin C, Conjunctival autograft*

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## SEARCH METHOD

An electronic literature search was performed using Medline (PubMed). The following key words were used: "pterygium," "bare sclera technique," "mitomycin C," "conjunctival autograft." The search was further limited to randomized, controlled trials (RCTs) or metaanalysis (Table 1).

The abstracts found in search terms 6, 7, and 9 were reviewed for appropriateness to our clinical scenario. Of the 9 randomized controlled trials, those that were appropriate for our clinical scenario had sample sizes of less than 20 for each treatment group. Thus, only the single metaanalysis article (search term number 9) was deemed fit for full appraisal.

## CITATION

Sanchez-Thorin JC, Rocha G, Yelin JB. Metaanalysis on the recurrence rates after bare-sclera resection with and without mitomycin C use and conjunctival autograft placement in surgery for primary pterygium. *Ophthalmology* 1998; 82: 661-665.

Table 1. **Search process employed.**

| Keywords | No. of citations |
|---|---|
| 1. Pterygium | 1,625 |
| 2. Bare-Sclera Technique (Limit: randomized controlled trial) | 13 |
| 3. Mitomycin C (Limit: randomized controlled trial) | 688 |
| 4. Conjunctival autograft (Limit: randomized controlled trial) | 18 |
| 5. Pterygium (Limit: randomized controlled trial) | 55 |
| 6. Bare-sclera technique AND Mitomycin C (Limit: randomized controlled trial) | 8 |
| 7. Bare-sclera technique AND Conjunctival Autograft (Limit: randomized controlled trial) | 1 |
| 8. Pterygium AND bare-sclera technique AND Mitomycin C AND Conjunctival autograft (Limit: randomized controlled trial) | 0 |
| 9. Pterygium (Limit : metaanalysis) | 1 |

Table 2. **Validity criteria.**

| Criteria | Answer |
|---|---|
| 1. Did the review explicitly address a sensible clinical question? | Yes |
| 2. Were the methods for searching the literature explicit and reasonably thorough? | Yes |
| 3. Were the criteria used to select the studies for inclusion appropriate? | Yes |
| 4. Was the validity of the included studies assessed? | Yes |
| 5. Were the assessments of the studies reproducible? | Yes |
| 6. Was it appropriate to combine the results (for metaanalysis)? | Yes |

**Study characteristics**

Published studies between 1966 and 1995 involving a comparison of at least 2 of the following surgical treatments of primary pterygia—bare-sclera resection, bare-sclera resection with intraoperative or postoperative mitomycin C application, and conjunctival autograft placement—were searched through Medline. A hand search of all references in relevant papers was also performed. Only controlled clinical trials that involved a preintervention patient-randomization process were included.

Five studies were included in the analysis. The primary outcome measure was recurrence of the pterygia after primary surgical treatment. All studies had similar definitions of recurrence.

## DISCUSSION

**Validity criteria**

A sensible clinical question was addressed by the reviewers: To determine, through a metaanalysis, the risk for postoperative pterygium recurrence comparing bare-sclera resection alone, bare-sclera resection with intraoperative or postoperative mitomycin C application, and bare-sclera resection with conjunctival autograft placement as treatment for primary pterygia. Table 1 shows that all the validity criteria were fulfilled.

The search method for literature was reasonably thorough. Medline search of studies published between 1966 and 1995 and a hand search of all references in relevant papers were performed. Whenever 2 studies included data from the same group of patients, the one with the larger number of subjects or longer follow-up period was included. The inclusion of all studies using mitomycin C, regardless of how mitomycin C was applied, was appropriate. The exclusion of nonrandomized studies, uncontrolled studies, studies that combined the results of primary and recurrent pterygia, and studies using Beta irradiation therapy was also appropriate.

The quality of each clinical trial was graded according to the method outlined by Detsky et al.[1] Only studies with a score of 0.5 or higher were included.

Two independent examiners collected data from each study and performed study calculations using the Mantel–Haenszel method as outlined by Pagano and Gauvreau.[2] A third masked observer mediated disagreements between the 2 independent observers. The final calculations were agreed upon by the 3 examiners.

Test of homogeneity of the data yielded a chi-square of 1.23 for the bare-sclera technique versus conjunctival autograft and 3.06 for bare sclera with or without mitomycin C. The combined data were analyzed using Mantel–Haenszel method at alpha level of 0.05.

Table 3. **Risk of recurrence among the techniques.**

| Technique | Study | Odds Ratio (95% CI) | Cumulative Odds Ratio (95% CI) |
|---|---|---|---|
| Bare-sclera resection v. Bare-sclera resection with MMC | Singh et al. | 109.33 (12.18 - 980.34) | 25.4 (9.02-66.69) |
| | Frucht-Perry et al. | 25.38 ( 4.68 - 136.40) | |
| | Cano-Parra et al. | 18.45 ( 2.24 - 150.27) | |
| | Chen et al. | 12.50 ( 0.81 - 192.92) | |
| Bare-sclera resection v. conjunctival autograft placement | Lewallen | 3.11 ( 0.17 - 55.21) | 6.1 (1.82-18.75) |
| | Chen et al. | 11.67 ( 2.14 - 64.04) | |

CI - confidence interval
MMC - mitomycin C

**Results**

Cumulative odds ratio showed that bare-sclera technique alone had about 25 times higher risk of recurrence compared with bare sclera plus adjuvant mitomycin C therapy. The 95% cumulative confidence interval of 9.02-66.69 implies that the risk of recurrence is at least 9 times, and at most 66.69 times, higher for the bare-sclera technique alone compared with that of bare sclera with adjuvant mitomycin C therapy (Table 3).

Cumulative odds ratio also showed that bare sclera alone had about 6 times higher risk of recurrence compared with conjunctival autograft placement. The 95% cumulative confidence interval of 1.82–18.75 implies that the risk of recurrence is at least 1.82 times, and at most 18.75 times, higher for the bare-sclera technique alone compared with conjunctival autograft placement.

**Applicability**

The RCTs included in the metaanalysis analyzed the recurrence rates after at least 2 of the 3 surgical treatments for primary pterygia. Even though comorbid factors such as dry eye and environmental/occupational factors such as sun and wind exposure were not mentioned, the study is still deemed applicable to the clinical scenario.

## STUDY AUTHORS' CONCLUSIONS

The authors concluded that the risk of recurrence is at least 9 times higher for the bare-sclera technique alone compared to bare sclera with adjuvant mitomycin C therapy, while it is at least 1.82 times higher for the bare-sclera technique compared to conjunctival autograft placement. However, the authors did not compare the 2 adjuvant measures and could not sufficiently say whether one technique would have a lesser probability of recurrence compared to the other.

## REVIEWERS' CONCLUSION

Whereas metaanalyses are subject to publication bias (where studies with nonfavorable results are no longer published), the paucity of large RCTs that deal with our clinical scenario makes this article the best evidence to date.

It is clear that simple bare-sclera technique without any adjunctive therapy has an unacceptable high risk of recurrence compared with the other 2 treatment modalities mentioned. Results of newer RCTs, when available, can be included in an updated metaanalysis to further strengthen the conclusions. Other techniques such as amnion-graft placement are being studied, and may offer another alternative to bare-sclera technique so that recurrence can be prevented. Improvements in the application of mitomycin C can also be studied in the future.

## RESOLUTION OF THE CLINICAL SCENARIO

Surgical removal remains the best option for a patient who has a pterygium that induces corneal astigmatism and significant visual impairment. The traditional bare-sclera technique has a high risk of recurrence. Either the concurrent use of mitomycin C as an adjunctive therapy or the placement of a conjunctival autograft is, therefore, most appropriate for our patient. Other factors to consider are the slight increase in cost, the longer surgery time, the possible mitomycin C-related complications, the skill of the surgeon in performing either surgery, and his/her experience in postoperative care of such procedures.

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GUIDELINES REVIEW

The Evidence-Based Ophthalmology Group
Philippine Academy of Ophthalmology

*http://www.pao.org.ph/EBO/index.php*

# EBO technical review of the validity of Recommendation #14 of the Clinical Practice Guidelines for the Management of Cataract among Adults

## ABSTRACT

**Purpose**

To assess the current validity of Recommendation #14, which states that both phacoemulsification and extracapsular cataract extraction (ECCE) are acceptable techniques among patients undergoing cataract surgery.

**Methods**

Updating the guideline recommendation was done in two stages: (1) identifying significant new evidence by conducting a systematic review of the literature, and (2) assessing whether the new evidence warrants updating or withdrawal by using the delphi method in soliciting the opinion of experts from the original panel that developed the guidelines. We reran the search for primary studies comparing ECCE to phacoemulsification from January 2001 to May 2005. Trials were identified from the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Group Trials Register) on *The Cochrane Library* and Medline. Based on the results of the identified evidence, Recommendation #14 was classified as *"Retain, append new evidence."* The proposed revision was sent to all members of the original panel for approval.

**Results**

Two new metaanalyses and one prospective randomized controlled trial were identified, retrieved, and appraised. Two trials comparing the costs and benefits of ECCE with those of manual small-incision cataract surgery were included to introduce the latter technique as an additional option in addressing the cataract backlog in the Philippines. Among the 21 members of the original panel that developed the guidelines, 15 (71%) responded. All agreed to retain and update Recommendation #14 by appending new evidence. The remaining six (29%) were not able to submit their responses in time for this update.

**Conclusion**

Recommendation #14 of the Clinical Practice Guidelines for the Management of Cataract among Adults should be retained but relevant new information for clinicians needs to be appended.

**Keywords**: *Guidelines, Cataract, Phacoemulsification, Extracapsular cataract extraction*

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PRACTICE variations and the emerging changes in our health-care system have engendered the need for clinical guidelines in medical practice. In response to these changes, the Philippine Academy of Ophthalmology developed and released its first Evidence-Based Clinical Practice Guidelines for the Management of Cataract in March 2001.[1] In the same year, the guidelines became the first in Asia to be included in the National Guideline Clearinghouse,[2] an on-line database of evidence-based clinical practice guidelines put up by the Agency for Healthcare Research and Quality of the United States Department of Health and Human Services.

It has been 4 years since the cataract guidelines were developed. In a rapidly evolving field like ophthalmology, some of the recommendations formulated then may no longer represent the most appropriate in local clinical practice.

The process of updating the entire set of guidelines can be very costly and time-consuming. Thus, the committee on Evidence Based Ophthalmology plans to approach this task by evaluating the document in sections, prioritizing recommendations that are deemed outdated in reference to changes in the evidence, available resources, and values placed on outcomes.

In recent years, a growing number of local ophthalmologists have shifted from extracapsular cataract extraction to phacoemulsification because of the immediate visual rehabilitation and superior visual outcomes seen in the latter. However, in a country burdened with a huge cataract backlog and limited resources, cost-effective methods of delivering eye care may have to be employed.[3]

It is against this background that the committee gave priority to the review of Recommendation #14, which states that both phacoemulsification and extracapsular cataract extraction (ECCE) are acceptable techniques among patients undergoing cataract surgery.

## OBJECTIVE

To assess the current validity of Recommendation #14, which states that both phacoemulsification and extracapsular cataract extraction (ECCE) are acceptable techniques among patients undergoing cataract surgery.

## METHODOLOGY

Using the conceptual model developed by the US Agency for Healthcare Research and Quality,[4,5] the group evaluated Recommendation #14 to determine whether it should be updated or withdrawn. Accordingly, an update was warranted under any of the following circumstances:

1. New preventive, diagnostic, or treatment interventions may have emerged to complement or supersede other interventions.
2. New evidence may require updating of the estimates of benefits and harm for existing interventions.
3. New evidence may identify as important outcomes that were previously unappreciated or wholly unrecognized.
4. Evidence that current practice is optimal may change.
5. The values that individuals or society place on different outcomes may change over time.
6. The resources available for health care may change significantly.

Updating the guideline recommendation was done in 2 stages: (1) identifying significant new evidence by conducting a systematic review of the literature, and (2) assessing whether the new evidence warrants updating or withdrawal by using the delphi method in soliciting the opinion of experts from the original panel that developed the guidelines.

**Search strategy**

We reran the search for primary studies comparing ECCE to phacoemulsification from January 2001 to May 2005. Trials were identified from the Cochrane Controlled Trials Register–CENTRAL/CCTR (which contains the Cochrane Eyes and Vision Group trials register) on the Cochrane Library and MEDLINE.

The following strategy was used to search CENTRAL Issue 2 2004:

#1 CATARACT-EXTRACTION*1:ME
#2 LENS-IMPLANTATION-INTRAOCULAR*1:ME
#3 #1 or #2
#4 CATARACT near EXTRACT*
#5 ((LENS next OPACIT*) and EXTRACT*)
#6 EXTRACAPSULAR or PHACO or PHAKO
#7 EXTRACAPSULAR or MANUAL-SMALL-INCISION
#8 ((INTRAOCULAR next LENS*) near IMPLANT*)
#9 SUTURELESS near CATARACT
#10 #4 or #5 or #6 or #8 or #9
#11 #3 or #10

The following strategy was used to search MEDLINE to August 2005:

#1 EXPLODE "CATARACT-EXTRACTION"/all subheadings
#2 "LENS-IMPLANTATION,-INTRAOCULAR"/all subheadings
#3 #1 or #2
#4 LENS near OPACIT*
#5 (CATARACT or #4) near EXTRACT*
#6 EXTRA?CAPSULAR or PHA?O or
#7 EXTRA?CAPSULAR or MANUAL- SMALL - INCISION
#8 INTRA?OCULAR next LENS*
#9 #7 near IMPLANT*

#10 SUTURELESS near CATARACT
#11 (#5 or #6 or #9 or #10) in TI,AB
#12 #3 or #11

To identify randomized controlled trials, this search was combined with the following:
#1 "RANDOMIZED-CONTROLLED-TRIAL"/all subheadings
#2 "RANDOMIZATION"/all subheadings
#3 "CONTROLLED-STUDY"/all subheadings
#4 "MULTICENTER-STUDY"/all subheadings
#5 "PHASE-3-CLINICAL-TRIAL"/all subheadings
#6 "PHASE-4-CLINICAL-TRIAL"/all subheadings
#7 "DOUBLE-BLIND-PROCEDURE"/all subheadings
#8 "SINGLE-BLIND-PROCEDURE"/all subheadings
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 RANDOM* or CROSS?OVER* or FACTORIAL* or PLACEBO* or VOLUNTEER* in TI,AB
#11 (SINGL* or DOUBL* or TREBL* or TRIPL*) near (BLIND* or MASK*) in TI,AB
#12 #9 or #10 or #11
#13 HUMAN in DER
#14 #12 and #13
#15 #13 not #14
#16 #11 not #15

**Data Collection and Analysis**

Identified evidence was used to assess the current validity of Recommendation #14. These results were used to classify the recommendation into one of the following categories:

*1. Withdraw.* New evidence called into question 1 or more key therapeutic recommendations, or new evidence suggested the need for new key therapeutic guideline recommendations.

*2. Retain, append new evidence.* Key therapeutic recommendations were still valid, but new evidence supported changes to other recommendations, or supported greater refinement of existing recommendations.

*3. Retain.* The guideline continued to represent good clinical care.

Based on the results of the identified evidence, Recommendation #14 was thus classified as *Retain, append new evidence.* The proposed revision was sent to all members of the original guideline developer group for approval.

## RESULTS

Two new metaanalyses[6, 7] and 1 prospective randomized controlled trial[8] were identified, retrieved, and appraised. Two trials comparing the cost and benefits of ECCE with those of manual small-incision cataract surgery[9, 10] were included to introduce the latter technique as an additional option in addressing the cataract backlog in the Philippines. (See Appendix for details.)

Among the 21 members of the original panel that developed the guidelines, 15 (71%) responded. All 15 agreed to retain and update Recommendation #14 by appending new evidence. However, 3 out of the 15 (20%) did not accept all the proposed changes. One remarked that the outcomes should have been expressed in odds ratio or relative risk for the strength of the recommendation to be better appraised. The other 2 suggested that phacoemulsification be singled out as the preferred procedure. The remaining 6 (29%) of the 21 members of the panel were not able to review and submit their responses in time for this update.

Based on the review, 2 studies[11, 12] previously cited were also excluded from the Summary of Evidence.

## CONCLUSION

Based on these data, Recommendation #14 of the Clinical Practice Guidelines for the Management of Cataract among adults should be retained but relevant new information for clinicians needs to be appended.


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# Appendix

## Clinical Practice Guidelines for the Management of Cataract among Adults

## Updated Recommendation #14

### RECOMMENDATION 14

Among patients undergoing cataract surgery, small-incision surgery (either by phacoemulsification or manual phacofragmentation) and extracapsular cataract extraction (ECCE) are acceptable techniques. *(Grade A Recommendation)*

### SUMMARY OF EVIDENCE

Currently, the two most common cataract-extraction procedures being done in the Philippines are phacoemulsification and extracapsular cataract extraction (ECCE).

ECCE by phacoemulsification uses an ultrasonic device that emulsifies the hard nucleus, enabling the surgeon to remove the lens material by a suction device. This method allows smaller incisions. In ECCE by nuclear expression, the hard nucleus is removed from the capsular bag in one piece, and the residual cortex is removed by irrigation and aspiration. This procedure requires a larger incision and several sutures to close the wound.

A metaanalysis by Powe et al. (1994), which involved 90 studies published between 1979 and 1990, reviewed the effectiveness and risks of modern cataract surgery. The study showed that complications of IOL malposition or dislo-cation and retinal detachment were no different for phacoemulsification vs. ECCE (pooled OR of 1.1; 95% CI: 0.5-2.4 and pooled OR 1.1; 95% CI: 0.4-2.8). However, the proportion of eyes with vitreous loss was lower following phacoemulsification than ECCE (pooled OR 0.14; CI 95% 0.05-0.41).[43]

In terms of intraoperative and perioperative adverse events, numerous studies comparing the aforementioned procedures have been done. A one-year prospective study by Oshika et al. (1992) assessed the time course of change in intraocular inflammation after three cataract surgery procedures. It demonstrated that immediate postoperative inflammation was significantly greater in the larger-incision-surgery groups.[44]

Schein (1994) concluded that phacoemulsification was a better procedure than ECCE in terms of immediate post-operative complications (RR of 0.79 and 0.85, respectively). However, four months after the surgery, the two techniques were comparable in terms of adverse-events rate (RR 1.15).[45]

Another study by Montan et al. (1998) revealed that a higher percent of endophthalmitis occurred in patients who had ECCE (0.27%) compared with those who underwent phacoemulsification (0.20%).[46] However, a systematic review by Taban et al. (2005) indicated an increasing incidence of endophthalmitis associated with the development of sutureless clear corneal incisions over the last decade.[72]

The strongest evidence to date is a metaanalysis by Snellingen et al. published in *The Cochrane Library*, Issue 2, 2004.[73] This review included 6 randomized controlled trials evaluating surgical treatment for 7,828 people with age-related cataract. Phacoemulsification gave a better visual outcome than extracapsular surgery. In addition, the costs per procedure were not markedly different between the two techniques. Extrapolation of these results to other parts of the world where cataract surgery is very different must, however, be made with caution.[73]

Another metaanalysis by Wei Li You (2004) likewise showed results in favor of phacoemulsification in providing excellent and immediate visual rehabilitation. [74]

Phacoemulsification is considered the standard of care for cataract surgery in developed countries.[75, 76] But in developing countries, the cost of equipment, training, consumables, and maintenance should be considered. There is evidence pointing to manual phacofragmenta-tion, also known as manual small-incision cataract surgery (MSICS), as an acceptable and cost-effective procedure in addressing the cataract backlog in developing countries.[75] In the single-masked, randomized controlled trial by Gogate et al., MSICS, done through a scleral tunnel that does not need to be sutured, showed better short-term visual results than standard ECCE, particularly before correction, with fewer complications or adverse outcomes and marginally lower cost.[76]

Nonetheless, more local data are needed to compare the value and applicability of these different techniques in the Philippines where cataract is still the leading cause of blindness. Ultimately, the choice of surgical technique depends on the type of cataract, the surgeon's skills, and available resources.


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