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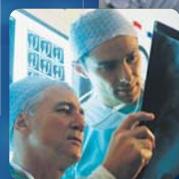
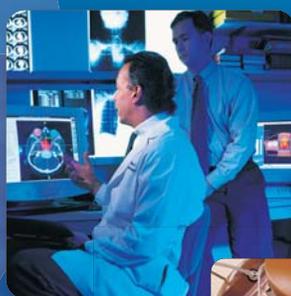


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Management of Neovascular
Age-related Macular Degeneration:
Systematic Drug Class Review and
Economic Evaluation



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Publications can be requested from:

CADTH
600-865 Carling Avenue
Ottawa ON Canada K1S 5S8
Tel. 613-226-2553
Fax. 613-226-5392
E-mail: pubs@cadth.ca

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Canadian Agency for Drugs and Technologies in Health

**Management of Neovascular Age-related Macular
Degeneration: Systematic Drug Class Review
and Economic Evaluation**

Allan Brown BSc MBA MA¹
William Hodge MD PhD FRCSC²
Steve Kymes, PhD MHA³
Alan Cruess MD FRCSC⁴
Gord Blackhouse MBA MSc⁵
Robert Hopkins MA MBA⁵
Lynda McGahan MSc¹
Sanjay Sharma MD MSc (Epid) FRCS MBA⁶
Irene Pan MSc²
Jason Blair MD²
David Vollman MD MBA³
Andra Morrison BSc¹

April 2008

¹ Canadian Agency for Drugs and Technologies in Health, Ottawa ON

² Department of Ophthalmology, University of Ottawa, Ottawa ON

³ Department of Ophthalmology and Visual Sciences, Washington University School of Medicine, St. Louis MO

⁴ Department of Ophthalmology and Visual Sciences, Dalhousie University, Halifax NS

⁵ The Programs for Assessment of Technology in Health (PATH) Research Institute, McMaster University, Hamilton ON

⁶ Department of Ophthalmology and Epidemiology, Queen's University, Kingston ON

Reviewers

These individuals kindly provided comments on this report.

CADTH Peer Review Group Reviewers

Ron Goeree, MA
Director, PATH Research Institute
Associate Professor, McMaster University
Hamilton, ON

Raywat Deonandan, PhD MSc BEd BSc
Epidemiologist, Deonandan Consulting Inc.
Ottawa, ON

External Reviewers

Chris Skedgel, MDE
Research Health Economist
Dalhousie University
Capital Health
Halifax, NS

Peter J. Kertes, MD CM FRCSC
Associate Professor of Ophthalmology
Sunnybrook Health Sciences Centre
The University of Toronto
Toronto, ON

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CADTH takes sole responsibility for the final form and content of this report. The statements and conclusions in this report are those of CADTH and not of its reviewers or Scientific Advisory Panel members.

Authorship

All authors contributed to the response to reviewers’ comments.

Allan Brown, a health economist at CADTH, led the project. He developed the protocol, contributed to designing the literature search and meta-analysis, reviewed abstracts and selected articles for inclusion for the economic, ethical, and psychosocial sections; assessed study quality; extracted and analyzed data, and prepared and revised drafts of the report.

William Hodge is Associate Professor of Ophthalmology at the University of Ottawa Eye Institute. He led the clinical review. He wrote sections of the clinical review and directed the quantitative meta-analysis. He also provided expert content advice on all sections of the report.

Steve Kymes is Assistant Professor in the Department of Ophthalmology at the School of Medicine, Washington University. He had primary responsibility for the economic model and write-up of the associated economic analysis.

Alan Cruess is Professor and Head of the Department of Ophthalmology and Visual Sciences, Dalhousie University. He had primary responsibility for writing the introduction and planning,

implementation, and legal/regulatory issues sections. He also provided expert clinical advice and review for the report.

Gord Blackhouse is a Research Associate at the Programs for Assessment of Technology in Health (PATH) Research Institute, McMaster University. He worked on the economic evaluation, obtained and analyzed economic data, and carried out an in-depth interrogation of the economic model.

Robert Hopkins is a biostatistician at the Programs for Assessment of Technology in Health (PATH) Research Institute, McMaster University. He performed the meta-analysis and wrote sections of the clinical review.

Lynda McGahan is a research officer at CADTH. She reviewed abstracts and selected articles for inclusion in the ethical and psychosocial issues section; abstracted and analyzed data; and prepared and revised the section on ethical and psychosocial issues.

Sanjay Sharma is Founding Director of the Cost-Effective Ocular Health Policy Unit, Associate Professor of Ophthalmology and Epidemiology, and Deputy Head for the Department of Ophthalmology at Queen's University. He provided expert advice and review for the clinical and economic sections of the report.

Irene Pan is a research assistant at the University of Ottawa Eye Institute. She was a clinical reviewer and contributed to writing the clinical review.

Jason Blair is a resident in Ophthalmology at the University of Ottawa Eye Institute. He was a clinical reviewer and contributed to writing the clinical review.

David Vollman is a resident in Ophthalmology in the School of Medicine at Washington University. He provided programming for the economic model as well as clinical expertise.

Andra Morrison is an information specialist at CADTH. She was responsible for designing and executing the literature search strategies, writing the methods section and associated appendix on literature searching, and verifying and formatting bibliographic references.

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Conflict of Interest

In 2005, Chris Skedgel received a research contract from Pfizer Belgium.

Peter Kertes has received honoraria from Novartis, Pfizer, Alcon, and Genentech. He has also received research funding from Novartis, Pfizer, Allergan, OXiGENE, and Alimera. Dr. Kertes has been reimbursed for travel expenses from Novartis, Pfizer, Alcon, and Bausch & Lomb.

Steve Kymes has consulting agreements with Allergan and Pfizer to provide advice on model development and development of manuscripts related to the cost-effectiveness of treatment of

glaucoma and, specifically from Pfizer, for research on glaucoma incidence and the burden of disease.

Allan Cruess received occasional honoraria for lectures given under sponsorship from Novartis, Pfizer, and Alcon.

Sanjay Sharma has provided consultancy for Amgen, Pfizer, Novartis, and Genentech.

None of the other authors or reviewers declared any conflict of interest.

Management of Neovascular Age-related Macular Degeneration: Systematic Drug Class Review and Economic Evaluation

Technologies

Single and combination therapy with photodynamic therapy using verteporfin (V-PDT); anti-vascular endothelial growth factor (anti-VEGF) therapies, including pegaptanib, ranibizumab, and bevacizumab; and steroids or analogues, anecortave acetate and triamcinolone.

Condition

Adults 40 years of age or older with neovascular age-related macular degeneration (AMD).

Issue

The recent emergence of several pharmacologic therapies for AMD has led to uncertainty regarding the impact of single and combination therapies as well as the optimal timing of therapy and the impact of re-treatment.

Methods and Results

Eighteen articles describing nine unique randomized trials, one controlled trial, and five case series were identified through a systematic literature review. Two cost-utility analyses in adults 40 years of age and older from the perspective of the Canadian public health care system and a patient lifetime time horizon were conducted. Pegaptanib, ranibizumab, and V-PDT were compared for predominantly classic lesions, and pegaptanib and ranibizumab were compared for all neovascular lesions. An analysis of budget impact and ethical and psychosocial issues was also conducted.

Implications for Decision Making

- **Uncertainty still remains.** No direct evidence demonstrating the effect of timing or re-treatment on health was found. There was insufficient evidence to suggest whether combination therapy (or which combinations) is better than monotherapy. Evidence for bevacizumab's effectiveness is less compelling than other anti-VEGF agents.
- **Pegaptanib or ranibizumab represent optimal treatment strategies.** Pegaptanib is the least costly strategy, and ranibizumab would be likely to be the most cost-effective strategy for those willing to pay more than an additional \$59,000/quality-adjusted life year. These results are most sensitive to the cost of ranibizumab therapy and change in visual acuity. At its current price, bevacizumab is likely to be the most cost-effective strategy if it is more effective than V-PDT.
- **Access, equity, and legal issues remain.** Access is of issue in Canada and the UK as existing systems are over extended in meeting resource needs to achieve early referral, diagnosis, and treatment within an effective therapeutic window. Equity issues are encountered as patients incur the costs of treatment at private clinics. Continued off-label use of bevacizumab raises ethical, legal, equity, and policy implications.

This summary is based on a comprehensive health technology assessment available from CADTH's web site (www.cadth.ca):
Brown A, Hodge W, Cruess A, Blackhouse G, Hopkins R, McGahan L, Sharma S, Pan I, Blair J, Vollman D, Morrison A.
Management of Neovascular Age-related Macular Degeneration: Systematic Drug Class Review and Economic Evaluation.

EXECUTIVE SUMMARY

The Issue

Age-related macular degeneration (AMD) has been identified as a major cause of vision loss in the elderly. Verteporfin plus photodynamic therapy (V-PDT) as well as pegaptanib have been approved in Canada for the treatment of AMD.

With the emergence of alternative treatments, including bevacizumab, ranibizumab, triamcinolone, and anecortave acetate, a variety of treatment strategies is available to specialist physicians. These include the use of single and combination therapy and treatment of different lesion subtypes of AMD. There is uncertainty as to whether the timing of initiation of therapy or re-treatment decisions are important factors for delivering optimal care. Those who administer funds for the care of AMD patients need to know how various AMD treatment strategies will impact the health system.

Objective

The objective of this report is to assess the impact of the pharmaceutical management of neovascular age-related macular degeneration by answering the following research questions:

- What is the clinical evidence on the relative effectiveness of pegaptanib, bevacizumab, ranibizumab, triamcinolone, anecortave acetate, or placebo (either alone or in combination) versus V-PDT in neovascular AMD?
- What is the relative cost-effectiveness of the various forms of pharmaceutical management of neovascular AMD?
- What is the evidence regarding the timing for the initiation of therapy for the comparisons listed above?
- What is the evidence regarding re-treatment with a different regimen in persons who did not have satisfactory clinical response to a particular regimen?

Clinical Review

Methods: We obtained published literature by searching MedLine, EMBASE, BIOSIS Previews, CINAHL, PubMed, and the Cochrane Library. Two reviewers systematically applied selection criteria and independently assessed quality and extracted data. A meta-analysis was conducted.

Results: Ranibizumab showed statistically significant improvement in visual acuity [in terms of loss of less than 15 letters or gain of at least 15 letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale] relative to V-PDT. Compared with V-PDT, ranibizumab improved vision by an increase of 4.9 to 11.3 letters on the ETDRS scale on average at 12 months post-treatment. Other vision outcomes involving vision loss also favoured ranibizumab over V-PDT. When examining lesion characteristics, ranibizumab-treated eyes showed a smaller increase in lesion size over V-PDT as well as an increase in lesion shrinkage over V-PDT. The only trial that compared anecortave acetate and V-PDT showed that both failed to improve visual acuity in patients. With the exception of the FOCUS trial, no RCTs compared the efficacy and safety of combination anti-vascular endothelial growth factor (anti-VEGF) therapies versus V-PDT. Although long-term studies are lacking, current studies suggest that ranibizumab is well tolerated concerning systemic adverse events. Local adverse events that were compared with V-PDT included post-injection increases in intraocular pressure and cataract formation, endophthalmitis, retinal detachment, retinal tears, and

vitreous hemorrhages. Regarding the quality of the nine RCTs included for review, the mean Jadad score was 2.89, of a maximum of five.

Economic Analysis

Methods: We reviewed the economic literature and performed an economic evaluation in TreeAge Pro by TreeAge Software Inc. using a micro-simulation approach with a decision-analytic Markov model.

Results: The findings and design approaches varied for the 12 studies included in the economic review. The primary economic study found that, from a provincial health provider perspective, treatment with pegaptanib dominated V-PDT for treatment of patients with predominantly classic lesions. Treatment with ranibizumab cost \$56,382/quality-adjusted life year (QALY) when compared with treatment with pegaptanib for predominantly classic lesions, and \$56,194/QALY for treatment of patients with any CNV lesion (predominantly classic, minimally classic, or occult). The results were found to be sensitive to the visual acuity outcomes, the cost of ranibizumab, and the utility loss associated with visual impairment.

Health Services Impact

The number of neovascular AMD patients in Canada is about 183,000 or 1.16% of Canadians aged 40 or older. New pharmaceutical management options have added considerably to the logistical complexity of treatment for neovascular AMD patients. New assessment procedures and repeat injections are adding to the workload of ophthalmology clinics, with increased numbers of patients being referred for therapy for which higher expectations are associated. In particular, continued off-label use of bevacizumab raises ethical, legal, and policy implications.

Conclusions

The review of clinical evidence found that, with the exception of trials comparing ranibizumab with V-PDT, there was a significant lack of trials comparing the other anti-VEGF agents in general. There is only one RCT that looked at the efficacy and safety of anecortave acetate compared with V-PDT. However, although results have shown seemingly effective visual acuity improvement with bevacizumab, this was based only on three poor quality RCTs. Whether generalizations from ranibizumab to bevacizumab can be made is not clear from the evidence identified.

Six non-RCT studies suggest the combination therapies analyzed are effective. These combination therapies are typically a combination of V-PDT and anti-VEGF therapies. However, inferences regarding relative efficacy cannot be made from these study designs. Conclusions drawn by these studies need to be confirmed by results of future larger-scale randomized controlled trials.

Overall, the efficacy of anti-VEGF therapies over V-PDT is well supported by RCTs. What remains unclear is whether combination therapy (and which combinations) are superior or merely equal to monotherapy. Furthermore the efficacy of one anti-VEGF agent compared with another is also unclear and this has very important practical and economic implications. The scant nature of the evidence does not allow us to draw conclusions regarding optimal timing of initiation of therapy and re-treatment.

Between V-PDT, pegaptanib, and ranibizumab, only ranibizumab demonstrated a reversal of the degenerative process for neovascular CNV, on average. The primary economic evaluation found that

the premium for using ranibizumab would not be considered cost-effective using a willingness-to-pay threshold of \$50,000. A 3.5% reduction in the price of ranibizumab would be required to achieve that. Alternately, this might be achieved by reducing the frequency of treatment below that used in the clinical trials. However evidence for the impact this might have on effectiveness is lacking. Using bevacizumab as a substitute for ranibizumab could be more effective and less costly than either V-PDT or pegaptanib. However, currently there is limited clinical trial evidence on the efficacy and safety of bevacizumab in the treatment of AMD.

ABBREVIATIONS

AMD	age-related macular degeneration
Anti-VEGF	anti-vascular endothelial growth factor or vascular endothelial growth factor inhibitor
CI	confidence interval
CNV	choroidal neovascularization
ETDRS	Early Treatment Diabetic Retinopathy Study
ICER	incremental cost-effectiveness ratio
IOP	intra-ocular pressure
IVT or IVTA	intravitreal triamcinolone
LogMAR	logarithm of the minimum angle of resolution
MI	myocardial infarction
NEI	National Eye Institute
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NV-AMD	neovascular AMD
OCCP	Ontario Case Costing Project (also called the “Ontario Case Costing Initiative”)
OHIP	Ontario Health Insurance Plan
PC	predominantly classic
PDT	photodynamic therapy
QALY	quality-adjusted life year
RCT	randomized controlled trial
RR	relative risk
TAP study	treatment of age-related macular degeneration with photodynamic therapy study
VA	visual acuity
VIP study	verteporfin in photodynamic therapy study
V-PDT	verteporfin (Visudyne [®]) plus photodynamic therapy
WMD	weighted mean difference

GLOSSARY

Classic CNV: Angiographic findings in which the CNV appears as an area of bright, well demarcated hyperfluorescence. (See also Predominantly classic CNV, Minimally classic CNV, and Occult CNV.)

Choroid: The layer in the eyeball between the retina and the sclera. It contains blood vessels and a pigment that absorbs excess light to prevent blurring of the vision.

Choroidal neovascularization (CNV): Blood vessels that grow through the choroidal membrane and enter the subretinal pigment epithelial and/or subretinal spaces.

Cost-effectiveness acceptability curve: A graph that shows the probability that an intervention is more cost-effective than its comparator, at various threshold values for willingness to pay for an additional quality-adjusted life year.

Extrafoveal CNV: CNV that comes no closer than 200 microns to the centre of the foveal zone.

Fibrovascular retinal pigment epithelial detachment: A form of occult CNV with areas of irregular elevation of retinal pigment epithelium associated with stippled hyperfluorescence.

Fovea: A pinpoint, depressed area of the central retina. It is the retinal area with the greatest visual acuity. It normally lacks retinal blood vessels.

Juxtafoveal CNV: Well-demarcated CNV that is between 1 and 199 microns from the centre of the foveal zone but does not reach its centre.

Macula: The fovea plus the surrounding area on the retina.

Macular degeneration: A leading cause of blindness in the elderly. It may also occur in children and young adults as a hereditary disease. Reading and driving abilities are the major loss. Although patients may be “legally blind” they are usually still able to get around quite well. In the “wet” or neovascular form of macular degeneration (the focus of this report), there is a leaking neovascular membrane in the choroid.

Minimally classic CNV: Area of CNV occupying <50% of the entire lesion area. Usually progresses at a slower rate of vision loss than classic CNV but faster than occult. (See also Classic CNV, Predominantly classic CNV, and Occult CNV.)

Occult CNV: Angiographic findings characterized by a fibrovascular retinal pigment epithelial detachment and/or late leakage of an undetermined source. Of the forms of neovascular age-related macular degeneration, it progresses at the slowest rate of vision loss. (See also Classic CNV, Predominantly classic CNV, and Minimally classic CNV.)

Photodynamic therapy (PDT): A treatment for age-related macular degeneration. A photosensitive dye (verteporfin) is given intravenously and accumulates in the neovascular membrane of the choroid. The PDT laser then activates the dye, thrombosing the membrane.

Predominantly classic (PC) CNV: Area of CNV occupying $\geq 50\%$ of the entire lesion area. This is the most aggressive form of neovascular age-related macular degeneration, leading to faster vision loss than the other subtypes. (See also Classic CNV, Predominantly classic CNV, and Minimally classic CNV.)

Pro re nata: As needed.

Snellen value: Visual acuity can be measured using the Snellen eye chart. Patients are asked to identify letters of standard sizes at a specified distance. A visual acuity measurement of 6/60, for example, indicates the smallest letter identified by the patient at a distance of six meters could be seen by a healthy eye at 60 metres.

Subfoveal CNV: CNV that underlies the centre of the foveal zone.

Treatment of Age-related Macular Degeneration with Photodynamic Therapy Study Group (TAP study group): Usually refers to reports by the TAP study group reporting on a prospective, randomized multicentre clinical trial sponsored by QLT Inc., Vancouver, British Columbia, and Novartis Ophthalmics, Bulach, Switzerland.

Vital dye: The process of staining living tissue by injecting a dye into it.

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1 INTRODUCTION

1.1 Disease or Condition

Age-related macular degeneration (AMD) is the leading cause of visual loss in people over 50 years of age in North America. AMD is also the leading cause of registered visual impairment in Canada. Over the next 25 years, the increase in numbers of blind individuals aged 40 years of age and older is expected to be greatest for age-related macular degeneration (111%), but it will also be substantial for open angle glaucoma (105%) and diabetes (85%).¹

The interface of retinal photoreceptors, retinal pigment epithelium, and choroid has a unique metabolism in the body, based on the diurnal renewal of photo-receptor outer segments. This tissue interface is highly susceptible to oxidative damage because of its exceedingly high oxygen demand, lifelong exposure to light, and the presence of highly unsaturated fatty acids in photoreceptor phospholipid cellular membranes. There is also evidence for a genetic predisposition for the development of the age-related macular changes leading to AMD.²

There are two main types of AMD: “dry” (atrophic) and “wet” (exudative). The dry form is more common (85% of cases) but usually causes less severe visual impairment. Over 100,000 Canadians have the neovascular or “wet” form of AMD, a proliferative retinopathy, which leads more rapidly to more severe vision loss and which is responsible for 90% of severe visual loss in AMD. The hallmark of “wet” AMD is choroidal neovascularization, characterized by the growth of abnormal new blood vessels, arising from the choroid, leading to subretinal fluid, blood, and lipid exudation, culminating in the destruction of macular vision through the formation of disciform fibrovascular scarring.³

Neovascular AMD is the condition of interest for this review. It was originally classified by the proximity of the leading edge of the lesion to the centre of the macula (the fovea): extrafoveal, juxtafoveal, and subfoveal. Neovascular AMD may also be subdivided angiographically using the vital dye sodium fluorescein injected intravenously: classic, predominantly classic, minimally classic, and pure occult (see glossary for brief descriptions of each). The choroidal neovascular lesion of AMD can be further studied angiographically using another intravenous vital dye, indocyanine green (ICG), especially with high speed scanning laser technology. This helps to better delineate new vessels of choroidal neovascularization (CNV) in the presence of subretinal blood, lipid, and turbid fluid. About 40% of neovascular AMD are of the classic subtype, while about 60% are of the occult subtypes (AC, unpublished observations, 2008).

Recurrence of choroidal neovascularization remains a vexing problem in the treatment of neovascular AMD, dating from the original National Eye Institute (NEI) sponsored clinical trials in the US of the Macular Photocoagulation Study (MPS) Group⁴ and the Medical Research Council (MRC) sponsored trials of the Canadian Ophthalmology Study Group (COSG)⁵, both studies that evaluated thermal laser therapy for CNV. Recurrence occurred in excess of 50% of the cases. In recent clinical trials of vascular endothelial growth factor inhibitor (anti-VEGF) therapies designed for FDA requirements, there have been no stopping rules, but persistence and recurrence of CNV was still observed. Newer trials now being carried out are designed to determine stopping rules and maintenance of therapy guidelines, taking into account the underlying propensity for CNV lesions to recur.

1.2 The Technology

Photodynamic therapy (PDT) using verteporfin (V-PDT) (Visudyne[®], Novartis Ophthalmics) has been a mainstay of therapy for neovascular AMD, especially in eyes with classic subfoveal CNV. Verteporfin has been approved in Canada for treatment of AMD since 2000.⁶ Reimbursement of verteporfin in Ontario, Saskatchewan, and Newfoundland is limited to classic neovascular AMD, while other Canadian provinces and territories fund independent of lesion type. However, occult subtypes of CNV often convert to classic CNV with follow-up if left untreated. Pegaptanib (Macugen[®], Pfizer) has been approved in Canada for AMD since 2005.⁷ Pegaptanib is an anti-VEGF aptamer that binds VEGF 165, the main pathological isoform. Newer anti-VEGF therapies are emerging, specifically ranibizumab [Lucentis[®], Genentech (US)/Novartis Ophthalmics (Canada)], bevacizumab [Avastin[®], Genentech (US)/Roche (Canada)], as well as a new steroid analogue given as a juxtasclear depot injection, anecortave acetate (Retaane[®], Alcon).

Ranibizumab was approved in Canada for neovascular AMD in June 2007.⁸ Anecortave acetate is not approved for use in Canada. It has been approved for use in AMD treatment in Australia. Bevacizumab has been approved in Canada for treatment of metastatic colorectal cancer.⁹ Its use in ophthalmology is off-label, using doses intravitreally many times lower than anti-cancer doses. A trend towards increased use of ranibizumab and bevacizumab is occurring in some parts of the world, including Canada.¹⁰

Therapies may be used individually (monotherapy) or in combination. V-PDT may be used in combination with pegaptanib, ranibizumab, and/or bevacizumab. Triple therapy combinations refer to use of the aforementioned combinations with the off-label use of the steroid intravitreal triamcinolone (Kenalog[®], Westwood-Squib, and generic triamcinolone, Sandoz). Combination therapy protocols are investigational, and there is interest in their efficacy and cost-effectiveness. Furthermore, based on clinical experience it is expected that V-PDT treatment frequency will decrease when combination therapy is used. It is also possible that anecortave acetate (Retaane, Alcon) or newer steroid technologies will replace triamcinolone in some combination therapies.^{11,12}

Table 1 summarizes the formulary status of AMD drugs in Canadian jurisdictions. Currently, verteporfin has a limited formulary listing in Nova Scotia and the Non-Insured Health Benefits Program, and pegaptanib is not listed on any of the formularies. As of January 2008, an application to fund ranibizumab has been submitted to the Common Drug Review. Bevacizumab has been approved in Canada for the treatment of metastatic colorectal cancer and is also being used off-label for AMD. At the dose required for AMD treatment, it is a much cheaper alternative to ranibizumab.

2 THE ISSUE

AMD has been identified as a major cause of vision loss in the elderly. V-PDT as well as pegaptanib have been approved in Canada for the treatment of AMD.

With the emergence of alternative treatments, including bevacizumab, ranibizumab, triamcinolone, and anecortave acetate, a variety of treatment strategies are available to specialist physicians. These include the use of single and combination therapy and treatment of different lesion subtypes of AMD. There is uncertainty as to whether the timing of initiation of therapy and re-treatment

decisions are important factors for delivering optimal care. Those who administer funds for the care of AMD patients need to know how various AMD treatment strategies will impact the health system.

Table 1: Formulary status of AMD drugs in Canadian jurisdictions

Publicly Funded Drug Plans	AMD Drugs Available in Canada					
	verteporfin	pegaptanib	ranibizumab	bevacizumab	Triamcinolone injection	Triamcinolone acetonide (generic injectable)
Alberta	Not listed	Not listed on any formulary	Not listed	Not listed on any formulary	B	B
British Columbia	Not listed		Not listed		B	B
NIHB	R		Not listed		B	B
Manitoba	Not listed		Not listed		B	B
New Brunswick	Not listed		Not listed		Not listed	Not listed
Newfoundland and Labrador	Not listed		Not listed		B	B
Nova Scotia	R		Not listed		B	B
Ontario	Not listed		L		B	B
Quebec	Not listed		L		Not reported	Not reported
Saskatchewan	Not listed		Not listed		B	B

Sources: National Prescription Drug Utilization Information System (NPDUIS) Database, Canadian Institute for Health Information, Ottawa ON (October 2007). Quebec Communiqué sur la liste de Médicaments (Nov 2007); Ontario Drug Benefit Formulary Edition 40 (Mar 2008). Data was reported only for provinces for which data were available. Anecortave acetate is not approved for treatment of AMD in Canada.

AMD=age-related macular degeneration; B=benefit, no justification required for reimbursement; L=limited, requires that specific criteria be met for reimbursement (automated process); NIHB=Non-Insured Health Benefits; R=restricted, requires formal request to drug program for reimbursement (case-by-case review).

3 OBJECTIVE

The objective of this report is to assess the impact of the pharmaceutical management of neovascular age-related macular degeneration by answering the following research questions:

- What is the clinical evidence on the relative effectiveness of pegaptanib, bevacizumab, ranibizumab, triamcinolone, anecortave acetate, or placebo (either alone or in combination) versus V-PDT in neovascular AMD?
- What is the relative cost-effectiveness of the various forms of pharmaceutical management of neovascular AMD?
- What is the evidence regarding the timing for the initiation of therapy for the comparisons listed above?
- What is the evidence regarding re-treatment with a different regimen in persons who did not have satisfactory clinical response to a particular regimen?

4 CLINICAL REVIEW

4.1 Methods

For the clinical and economic sections of the report, a protocol was written a priori and followed throughout the review process.

4.1.1 Literature search strategy

A literature search was conducted for the clinical review, which was developed by the information specialist (AM*) with input from the project team. Prior to running the search, it was internally peer reviewed by another CADTH information specialist.

The following bibliographic databases were searched through the OVID interface: MedLine (1950-present; In-Process & Other Non-Indexed Citations), EMBASE (1980-present), BIOSIS Previews (1985-1989 and 1989-present), CINAHL (1982-present); PubMed; and the Cochrane Library. Controlled vocabulary and keywords used in the search included terms for age-related macular degeneration and the drugs of interest in this project: verteporfin, bevacizumab, pegaptanib, ranibizumab, and anecortave acetate and their brand names. Triamcinolone was intentionally left out of the literature search strategy, because it is used only in combination with other AMD treatments, so relevant articles about triamcinolone would be captured through the search of the other interventions. Methodological filters were applied to limit retrieval to clinical controlled trials, comparative studies, observational studies, meta-analyses, and systematic reviews. See Appendix 1 for the detailed search strategy.

In addition to the literature search for the clinical review, two supplemental searches were carried out. The first search aimed to find literature regarding the timing of the initiation of therapy and the potential impact on the progression of the disease. The second search was limited to systematic reviews and randomized controlled trials of bevacizumab, pegaptanib, ranibizumab, and anecortave acetate.

There were no language restrictions; papers of interest in languages other than English were listed as “language other than English paper; awaiting translation.” OVID AutoAlerts were set up to send monthly updates with any new literature. Monthly updates were also performed in PubMed and Cochrane Library databases and searched for relevant articles until November 2, 2007.

Grey literature (literature that is not commercially published) was identified by searching the web sites of health technology assessment and related agencies, professional associations, and other specialized databases. Google and other Internet search engines were used to search for additional web-based materials and information. These searches were supplemented by searching the bibliographies and abstracts of key papers and conference proceedings and through contacts with appropriate experts and agencies.

* Initials of persons refer to team members. The full names can be found in the list of co-authors or the list of acknowledgements in the front section of the report.

4.1.2 Selection criteria and methodology

Studies that were included met the following criteria:

- Study design: randomized controlled trial (RCT).
- Population: adults 40 years of age or more with neovascular age-related macular degeneration (AMD). We selected 40 years of age as a threshold to be consistent with Canadian epidemiologic data on prevalence, which included this age range.¹
- Interventions and comparators: comparison of V-PDT with pegaptanib, bevacizumab, ranibizumab, anecortave acetate, placebo, or clinically relevant combinations; also intravitreal triamcinolone, if in combination with one or more of the others.
- Outcomes: Primary outcome — a measure of visual acuity convertible to utility values. Secondary outcomes — quality of life indicators, size of the lesion before/after by either fluorescein angiography or optical coherence topography; as well as adverse events and other harm information.

Once the search results were obtained, two reviewers (IP and JB) independently performed an initial screening of citations (titles, abstracts, and keywords) using the selection criteria. Conflicts regarding the screening decision between the two reviewers were resolved by discussion and consensus. The articles described in the citations considered relevant by both reviewers according to the selection criteria were obtained for the next level of screening.

Next, two reviewers (IP and JB) independently applied the selection criteria to the full-text articles. Only the most recent report of duplicate reports published by the same site or study group was incorporated into the evidence synthesis.

Due to the low number of studies identified after screening and the fact that only two were combination therapy,^{12,13} the first criterion was relaxed to obtain non-RCT clinical studies that met the other criteria.¹⁴ The study designs included non-randomized controlled studies as well as non-experimental designs such as case series.

4.1.3 Data extraction strategy

A data extraction form was designed a priori to document and tabulate all relevant information available in the selected studies (see Appendix 1A). Two reviewers (IP, JB) extracted data from the selected studies. Differences between reviewers were resolved by discussion and consensus. In cases when a consensus was not achieved, a third reviewer was involved to provide a decision.

4.1.4 Strategy for quality assessment

Two reviewers (IP, JB) assessed study quality using the criteria proposed by Jadad,¹⁵ on a scale of 0 to 5 in increasing order of quality. Adequacy of allocation concealment was evaluated as “Adequate,” “Inadequate,” or “Unclear” according to the method proposed by Schulz and Grimes.¹⁶ Quality scores were not considered in the meta-analysis but were intended to be used for interpretation and drawing conclusions.

4.1.5 Data analysis methods

For measures of visual acuity, other efficacy, and safety measures, continuous outcomes were summarized as the weighted mean difference (WMD) and 95% confidence interval (CI). Binary outcomes were summarized as the relative risk (RR) and 95% CI where possible. For ordinal variables, such as ETDRS scale performance, we calculated a WMD, without the associated p-value, when trial level descriptions of variance were unavailable. Meta-analysis and forest plots were generated for other outcomes when there were counts of event rates, with Review Manager software generating measures of variance using binomial methods, or if mean and standard deviations were reported for continuous measures. We sought to meta-analyze between-treatment differences by lesion subtype and measure inconsistency between trials using an I^2 quantity. We also planned to assess the potential for publication bias using a funnel plot and visual inspection.

For both the clinical and economic analyses, efficacy data were used as proxy for effectiveness. We recognize that results achieved in these RCTs are generally more optimistic than those in everyday practice.

Comparative study results were presented in subgroups, first with the ranibizumab studies^{13,17} with a subgroup summary, followed by the one anecortave acetate study,¹⁸ followed by an overall measure. Software for data analysis was Review Manager Version 4.2 for Windows and Microsoft Excel 2002 for Windows XP.

Results of the evidence synthesis were compared with existing reviews in the literature.

Non-RCT studies were not included for the meta-analysis because of concerns regarding validity,¹⁹ but their results were summarized (Appendix 2). These studies were used as sources of information on combination therapies.

4.2 Results

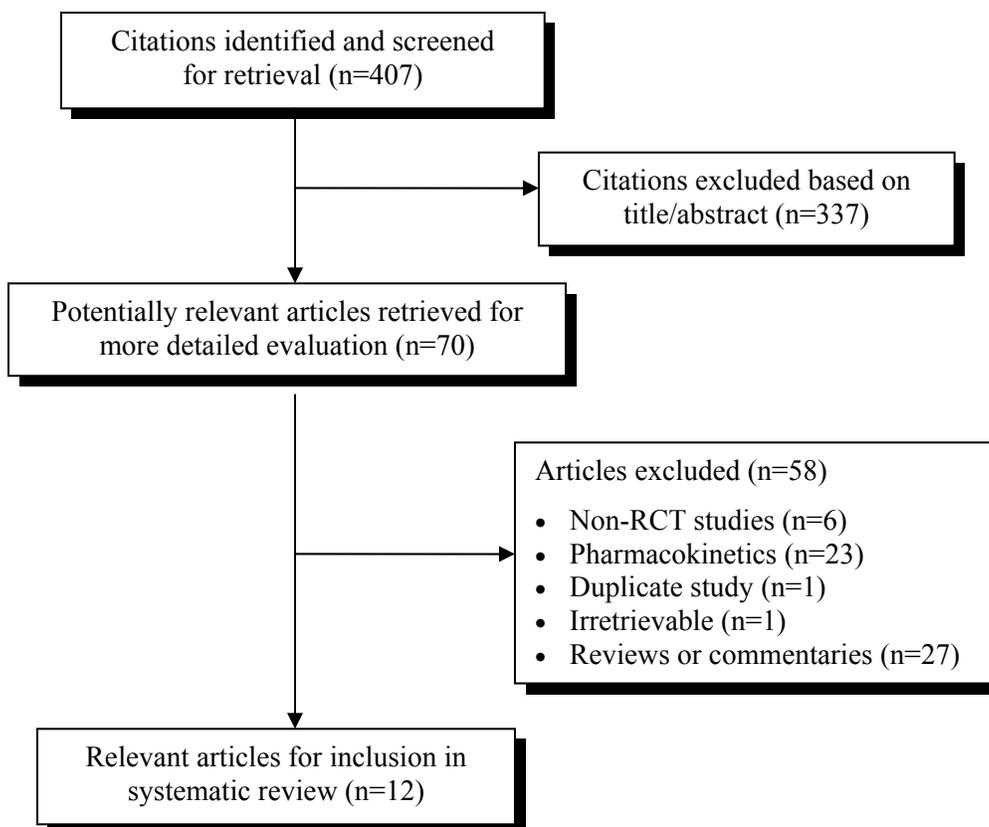
4.2.1 Quantity and quality of evidence available

The systematic literature search resulted in a return of 407 citations, of which nine^{13,17,18,20-25} met the selection criteria after the initial search results were returned (Appendix 1B). Altogether, these articles reported six unique randomized controlled trials^{13,17,18,20,23,24} of 1,915 subjects with an average age ranging from 72.7 to 77.7 years. Of the nine reports, seven^{13,17,18,20,22-24} were original articles and two^{21,25} were abstracts identified in the grey literature. The mean and median Jadad scores for the nine studies are 2.89 and 3 respectively. Six of the nine articles do not report their methods of allocation concealment (Appendix 1B).

Three additional RCTs,^{12,26,27} all involving bevacizumab compared with V-PDT, were selected from our literature search updates after the main literature search had been completed (Appendix 1B). This brought the total number of included RCTs to 12 (Figure 1). The three bevacizumab papers could not be meta-analyzed, because of the nature of their outcome measures. One²⁶ will be described separately, because its control group was V-PDT with triamcinolone rather than V-PDT alone. The mean Jadad score for two of the bevacizumab studies^{12,27} was 2.5. The quality of the third article²⁶ could not be assessed due to lack of information in the methods section.

Six non-RCT studies were also identified. They met all selection criteria except the RCT requirement.^{11,28-32}

Figure 1: Selected articles for clinical review



RCT=randomized controlled trial.

4.2.2 Trial characteristics

Detailed trial characteristics are summarized in Appendix 1B.

The Treatment of Age-related Macular Degeneration with Photodynamic Therapy & the Verteporfin in Photodynamic Therapy (TAP & VIP) Study Groups' Report 1²⁰ was an investigation of V-PDT versus Placebo-PDT alone; Kaiser²² was a substudy of this study. VIP Study Group's Report 2²³ reported their two-year results of comparing V-PDT to PDT alone. Michels *et al.*'s study²⁴ aimed to determine the effect of early V-PDT re-treatment. Heier *et al.* (the FOCUS Study Group)¹³ compared the combination therapy of V-PDT and ranibizumab to V-PDT alone; Antoszyk *et al.*²⁵ was its substudy. Brown *et al.*¹⁷ compared ranibizumab with V-PDT. Its substudy by Bressler *et al.*²¹ reported data on quality of life specifically. Slakter *et al.*¹⁸ presented the only RCT that compared the efficacy of anecortave acetate with V-PDT. Hahn *et al.*²⁶ compared bevacizumab with V-PDT combined with triamcinolone. Bashshur *et al.*²⁷ compared the efficacy of bevacizumab with that of V-PDT. Lazic and Gabric¹² compared bevacizumab, as well as a combined bevacizumab plus V-PDT therapy, with V-PDT.

In the studies that compared ranibizumab or anecortave acetate with V-PDT^{13,17}, subgroup analysis based on study quality or type of lesions (classic or occult) was not possible because of the low number of studies or lack of reported outcomes. The study quality was low (Jadad score=2) for the two ranibizumab studies^{13,17} and slightly higher for the anecortave acetate study¹⁸ (Jadad score=3). In all of these studies, the adequacy of allocation concealment was unclear. There was not sufficient evidence to produce summary measures of the treatment effects on classic or occult lesions. Only one study reported the results of classic and occult lesions separately, and that study reported the benefits of V-PDT over PDT alone.²⁰ One study¹⁷ did report the change in the size of lesion for all lesions, which included predominately classic lesions; and, in addition, the study provided results on classic lesions only.

Characteristics of the six non-RCTs that reported clinical results on combination therapies^{11,28-32} are summarized in Appendix 2.

4.2.3 Data analyses and synthesis

For the studies that had controls or comparative groups,^{13,17} baseline characteristics [age in years, percentage of females, Visual Acuity Score (Early Treatment Diabetic Retinopathy Study) as measured by the number of letters, and baseline lesion size] are presented in Appendices 3a and 3b.

The primary efficacy outcome measured at 12 months is the change in the numbers of letters of the Early Treatment Diabetic Retinopathy Study (ETDRS) score. We used ETDRS, as this is the preferred measure used in trials where vision is the primary outcome. This has been seen in all major studies concerning macular degeneration including the ANCHOR,²¹ MARINA,³³ VISION,³⁴ and FOCUS¹³ trials. The primary outcome was visual acuity, defined as the number of letters on the ETDRS scale, which uses ordinal variables. Three studies reported this primary outcome.^{13,17,18} In addition, because the three studies did not report measures of dispersion around their primary endpoint, meta-analysis, forest plots, and statistical tests were not possible for the change in the number of letters readable on the ETDRS scale.

Because measures of variance could not be reported for ETDRS outcomes (due to a lack of trial-level descriptions of dispersion),³⁵ we calculated a WMD without the associated p-value. For the ETDRS, this represented a change in the number of letters of the intervention and the control groups.

We sought to examine between trial inconsistencies using the I^2 quantity, but there were too few studies to provide a reliable interpretation of this measure. Similarly, we did not produce funnel plots, because we felt the low number of studies would make a visual inspection of asymmetry unreliable.³⁶

Other visual measures include the percentage of patients who have avoided a loss of more than 15 letters and the percentage of patients who have gained more than 15 letters. Secondary visual acuity measures include the percentage of patients with severe vision loss as defined as a loss of more than 30 letters (for ranibizumab intervention)^{13,17} or for the percentage of patients with loss of more than four letters lines (20 letters) (for anecortave acetate intervention).¹⁸ Lesion characteristics were also captured. The other measures include the size of the lesion, the size of classic lesions, and the size of leakage area, all in optic disc areas units [1 optic disc unit=2.54 mm²].

Adverse events were classified into ocular and general adverse events. The ocular adverse events captured are the percentage of patients with retinal detachment, endophthalmitis, intraocular

inflammation, vitreous hemorrhage, post-injection intra-ocular pressure (IOP) ≥ 30 mm Hg, and cataract formation. The general adverse events include death, myocardial infarction (MI), stroke, and cerebral infarction.

Finally, quality of life was presented in a study by Bressler²¹ by using the National Eye Institute Visual Function Questionnaire (NEI VFQ-25) scale. The subscales for near activities, distant activities, and vision-related dependencies were also reported.

a) Baseline characteristics of study patients

The baseline characteristics of the patients in the primary studies that compared intervention groups (ranibizumab or anecortave acetate) with the control group (V-PDT)^{13,17,18} are presented in Appendices 3a and 3b. The age of the patients in both the intervention and the V-PDT group are similar (intervention 76.3 years; V-PDT 76.8 years). There were slightly more females in the V-PDT group (V-PDT 53.0%, intervention 50.7%) with the exception of one study,¹³ where more females received the intervention. The baseline visual acuity score as measured by ETDRS was similar between the intervention and the V-PDT group (intervention 47.5 letters; V-PDT 46.9 letters) with generally more letters readable in the intervention cohorts except for one study,¹³ where the number of letters readable was higher in the V-PDT group. The baseline lesion size as measured by the number of optic disc units was similar in both groups (intervention 1.7, V-PDT 1.7). No measures of dispersion were provided and no statistical tests for difference can be generated for differences in baseline characteristics.

For the two bevacizumab studies with a V-PDT comparator group (Lazic and Gabric¹² and Bashshur *et al.*²⁷), the age of the patients in both the intervention and V-PDT group are similar (intervention 75.7 years; V-PDT 75.4 years). There was an overall similar percentage of females in the intervention (65%) and V-PDT (64%) groups; but in Bashshur *et al.*,²⁷ more females received the intervention (bevacizumab 56% female, V-PDT 43% female). The baseline visual acuity score was measured with the logMAR score by Lazic and Gabric,¹² showing a similar score between the intervention and V-PDT groups (bevacizumab plus V-PDT combination 1.062; bevacizumab 1.090; V-PDT 1.106). Bashshur *et al.*²⁷ reported Snellen scores, which were similar between bevacizumab (20/119) and V-PDT (20/108). Both studies reported similar baseline retinal thickness in micrometers (intervention groups 352.5 μm , V-PDT 352.0 μm). No measures of dispersion were provided, so statistical tests for differences in baseline characteristics were not conducted. (Appendix 3)

b) Efficacy

The primary efficacy outcome reported was the Visual Acuity Score, which was the number of letters readable on the ETDRS scale (Appendices 7 and 8). The net benefit (WMD) with ranibizumab is larger than with anecortave acetate. In ranibizumab studies, the gain in the number of letters was positive, while for anecortave acetate, there was a loss in the number of letters. With monthly ranibizumab, there was a gain of between 4.9 and 11.3 letters at 12 months, and for the V-PDT group there was a loss in the number of letters between 8.2 and 9.5. The overall weighted difference was a net benefit of 18.0 letters for ranibizumab. Not enough information was available to infer statistical significance. With anecortave acetate, there was a significant drop in letters with anecortave acetate and a very large drop with the V-PDT group; in other words, it resulted in a severe vision loss in both treatment groups rather than an improvement (see Appendix 5). The net benefit of the anecortave acetate intervention over the V-PDT group is much smaller.

The results of the Bashshur *et al.*²⁷ and Lazic and Gabric¹² bevacizumab studies could not be pooled, because their primary outcome was different. One used the change in logMAR score and the other reported changes in the Snellen scores (Appendix 1B).

Two common efficacy outcomes reported were the significant vision loss (loss of <15 letters) and significant vision gain (≥ 15 letters), and these are reported in the forest plots in Appendices 7 and 8. The ranibizumab intervention was more beneficial compared with V-PDT in avoiding significant vision loss at 12 months, having a 45% higher risk of avoiding loss (RR=0.59; 95% CI=0.53 to 0.75; $p < 0.00001$). The overall benefit can be described only for patients who received monthly doses of ranibizumab. Patients who received ranibizumab were six times more likely to have significant vision gain than V-PDT (RR=0.16; 95% CI=0.10 to 0.25; $p < 0.00001$).

Other visual acuity measures reported include severe vision loss, described by >30 letters lost in ranibizumab studies or more than four lines (20 letters) in the anecortave acetate study (Appendix 15). There is a benefit relative to V-PDT of avoiding severe vision loss when patients are assigned to the ranibizumab intervention. The risk of severe vision loss is 5% of the risk that patients are exposed to with V-PDT (RR=0.05; 95% CI=0.01 to 0.21; $p < 0.00001$). In the anecortave acetate intervention group there was no statistical benefit of anecortave acetate over V-PDT.

c) Lesion characteristics

The change in the size of the lesion was different for ranibizumab versus the V-PDT group, and ranibizumab was more successful than the V-PDT group in slowing the gain in lesion size for all lesions (Appendix 16). No information on lesion characteristics was provided for anecortave acetate interventions. For the ranibizumab intervention, the mean reduction in lesion size was 2.14 units more than the V-PDT group^{13,17} (WMD= -2.13; 95% CI= -2.46 to -1.80; $p < 0.00001$). In one study,¹⁷ the efficacy of lesion size reduction was reported separately for classic lesions only (Appendix 11). For classic lesions only,¹⁷ there was a benefit in reducing the classic lesion size by 1.10 optic disc units (WMD= -1.10; 95% CI= -1.40 to -0.80; $p < 0.00001$). The size of the leakage area was also decreased more in ranibizumab intervention groups, while the area increased in V-PDT groups^{13,17} (WMD= -2.14; 95% CI= -2.52 to -1.76; $p < 0.00001$) (Appendix 12).

d) Retinal thickness

Lazic¹² reported the decrease in the thickness of the retina. With combination therapy of bevacizumab plus V-PDT, the decrease in the thickness in the intervention group was higher at one month and at three months than the decrease in retinal thickness in the V-PDT group (one month: combination -64.5 μm , V-PDT: -53.6 μm , net benefit -10.9 μm ; three months combination -59.6 μm , V-PDT -50.5 μm , net benefit -9.1 μm).

e) Harm

Several adverse outcomes were reported, and these adverse events were subdivided into ocular adverse events and general (systemic) adverse events (Appendices 13 to 16.6). Most of the adverse events were reported in ranibizumab studies,^{13,17} and the lone adverse event reported by the anecortave acetate study¹⁸ was mortality.

The intervention group showed a statistical increase in the risk of increased post-injection intra-ocular pressure (IOP) ≥ 30 mm Hg in ranibizumab relative to V-PDT (RR=2.04; 95% CI=1.04 to 4.00; $p=0.04$) (Appendix 16A).

There was also an increase in the percentage of patients who had cataract formation in the ranibizumab intervention group relative to the control group (RR=1.68; 95% CI=0.99 to 2.86; p=0.05) (Appendix 16B). There were no statistical differences in the rate of general (systemic) adverse events between the intervention and V-PDT groups. Also, the rate of mortality was not statistically different for the intervention versus V-PDT groups, and no differences existed in the benefit of the intervention over V-PDT group for ranibizumab and anecortave acetate in terms of mortality.

In the bevacizumab study by Lazic and Gabric,¹² the adverse events that were reported included the rates of retinal detachment, cataract progression, and the tearing (detachment) of pigment epithelial. The rate of these events was zero in the V-PDT control groups. For the combination bevacizumab plus V-PDT group and the bevacizumab group, the rate of retinal detachment over the three month study period was 7.7% and 14.8% respectively. The rates of cataract progression for the combination intervention and bevacizumab intervention were 5.8% and 7.4% respectively. The rate of pigment epithelial tears was zero in the combination group and 5.6% in the bevacizumab group.

f) Quality of life

Quality of life was measured in one ranibizumab study²¹ by the National Eye Institute Visual Function Questionnaire, which is a scale from 0 to 100. Patients who had the intervention had a higher level of improvement in scores for the overall score as well as sub-scores in near activities, distant activities, and vision-related dependencies (Appendix 12). The magnitude of the effect was higher in the patients who received monthly 0.5 mg ranibizumab than those who received monthly 0.3 mg. No information was provided for anecortave acetate. Not enough information (i.e., standard deviations) was available to pool the results.

g) Combination therapy

As mentioned in Section 4.1.2, only two eligible RCTs^{12,13} reported clinical outcomes of a combination therapy. Therefore, the six non-RCTs that met the other criteria are summarized here, as well as in Appendix 2, to present a more substantial knowledge base on combination therapy.

Chan *et al.*³⁰ compared the benefit of combined intravitreal triamcinolone (IVTA) and V-PDT with V-PDT alone in the treatment of AMD. By one year, improvement in the best-corrected visual acuity for the combination therapy group was significantly larger than in the monotherapy group. A smaller proportion of combination therapy group subjects developed moderate vision loss as well (p=0.009). It was concluded that V-PDT with IVTA is a superior treatment option to V-PDT alone in terms of preventing visual loss and stabilization of vision for both predominantly classic and occult with no classic CNV subjects.

Similarly, Liggett *et al.*²⁸ reported their six-month results of a combination therapy of high-dose IVTA and V-PDT with the addition of pegaptanib sodium injection in a retrospective, interventional case series study. All 22 eyes received the combination therapy, but 13 eyes had previously been treated with IVTA and V-PDT. Results indicated that the newly treated group presented a significant improvement in visual acuity. Therefore, Liggett *et al.* concluded that the triple combination therapy demonstrated improvement and stabilization in visual acuity, especially when used as first-line therapy.

A different triple combination therapy was used to treat CNV secondary to AMD. In their prospective, non-comparative study, Augustin *et al.*³¹ evaluated the efficacy and safety of combining

V-PDT, bevacizumab, and dexamethasone. They followed the subjects for an average of 40 weeks and observed significant increase in visual acuity with no occurrence of serious adverse events.

Dhalla *et al.*²⁹ also reported positive results of treating CNV with a combination therapy of V-PDT and bevacizumab. In their retrospective case series of 24 eyes, subjects were followed for seven months. Patient visual acuity and re-treatment rate were assessed. The authors reported a high (83%) indication of stabilization of visual acuity, and 67% had improved in visual acuity. Also, 63% of the subjects needed only one single combination therapy for CNV resolution. In addition, there was no serious adverse events observed, suggesting high tolerance to the combination therapy.

Ladas *et al.*³² also studied a combination of V-PDT and bevacizumab, this time in a neovascular AMD (NV-AMD) patient group with serous pigment epithelium detachment. They found that at nine months follow-up, four out of the six patients had improved visual acuity and had decreased central retinal thickness.

Ahmadih *et al.*¹¹ studied a combined therapy of V-PDT, intravitreal bevacizumab, and intravitreal triamcinolone in treating NV-AMD. Fifteen of the 17 subjects had improved visual acuity by 24 weeks of follow-up. The rest were not responsive to the combination treatment in terms of visual acuity. Significant decrease in central macular thickness occurred at six weeks and then stabilized.

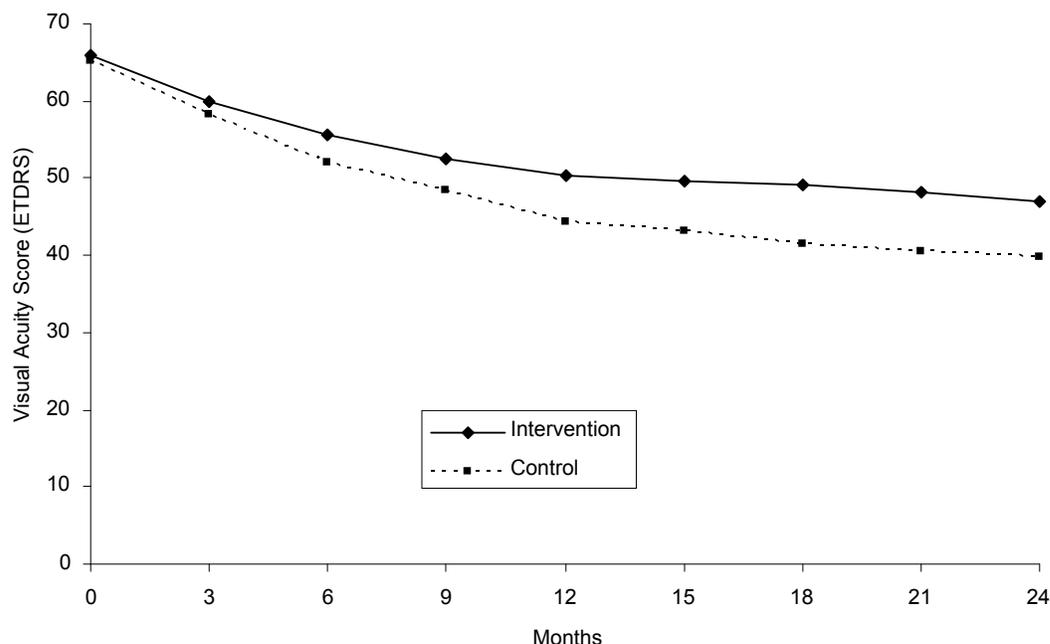
All in all, these six studies suggest the combination therapies analyzed are effective. However, they are not high quality evidence. Conclusions presented here need to be confirmed by results of future larger-scale randomized controlled trials.

4.2.4 Other analyses

The study by Hahn *et al.*²⁶ differed from the other bevacizumab RCTs^{12,27} in that the comparators were combination therapies of V-PDT plus triamcinolone. Thirty patients were randomized into three equally sized groups: 1) bevacizumab, 2) combination triamcinolone and V-PDT at standard light dosage, and 3) combination triamcinolone and V-PDT at reduced light dosage. The baseline characteristics were slightly different than the other bevacizumab studies, having a slightly higher age across comparator groups (ranging from 77.5 to 80 years old) and fewer females (ranging from 10% to 30%). The baseline ETDRS ranged from 43 to 54. At completion of the three-month study, the improvement in visual acuity was highest with the bevacizumab monotherapy group, with an improvement of 11.8 letters. The standard light-triamcinolone/V-PDT group declined on average 0.5 letters, and the reduced light-triamcinolone/V-PDT group declined by seven letters. Also, the bevacizumab monotherapy group had improved efficacy in reducing retinal thickness over standard light-triamcinolone and reduced light-triamcinolone: -138 μ m, -132 μ m, and -78 μ m respectively.

A study by Blinder *et al.*²⁰ reported the benefit of V-PDT versus PDT alone (Figure 2). The benefit is obtained within the first 18 months, and no difference is seen beyond that point. At 18 to 24 months, the difference between the two groups in this study appears to be converging. Longer term analysis may be helpful in determining long term effects.

Figure 2: Visual Acuity Score (ETDRS) — Verteporfin and PDT versus PDT alone



A study by Michels *et al.*²⁴ investigated the use of V-PDT on a periodic basis versus one-time V-PDT at baseline. The regimented treatment included V-PDT at zero, two, four, and six months, while the other group received V-PDT at time zero. After the initial treatment, the one-time group was inspected at three and six months and was given treatment if required. After six months, the patients in both groups were evaluated at nine and 12 months and received V-PDT if necessary for leakage. The difference in the change in ETDRS by the number of letters was not significant between the two groups at six months (intervention= -4.3, V-PDT= -6.1; $p=0.427$), or at 12 months (intervention= -8.5, V-PDT= -9.9; $p=0.589$). Similarly, the difference in the percentage of patients who lost more than 15 letters or gained more than 15 letters was not statistically significantly different. The percentage of patients who had severe vision loss of more than 30 letters was also not statistically different between the two groups, although the magnitude was large (intervention=10.5%, V-PDT=21.3%; $p=0.056$).

4.3 Discussion

Of the three primary studies^{13,17,18} that were included in the analysis, the differences in baseline characteristics between intervention (ranibizumab or anecortave acetate) and V-PDT were small for age, gender, ETDRS score, and lesion characteristics.

The ranibizumab intervention, in general, provided superior efficacy outcomes than anecortave acetate intervention versus the V-PDT group. The number of letters read on the ETDRS scale at 12 months was increased in the ranibizumab cohorts compared with baseline, while V-PDT cohorts experienced an average reduction in the number of readable letters. The anecortave acetate cohorts also experienced an average reduction in the number of letters read. Ranibizumab intervention was superior to V-PDT in avoiding significant vision loss and producing significant vision gain.

Ranibizumab also appears to eliminate severe vision loss, while patients who receive either anecortave acetate or V-PDT still risk severe vision loss.

The evidence indicates ranibizumab is also beneficial in changing lesion characteristics. With classic and occult lesions, ranibizumab prevents increases in lesion size while anecortave acetate and V-PDT cohorts still have increases in lesion size compared with baseline. For classic lesions only, compared with baseline, ranibizumab has the benefit of reducing lesion size while classic lesions increase in size with V-PDT. When looking at the size of the area of leakage, ranibizumab has the benefit of reducing the size of the leakage area compared with baseline, while it increases in size with V-PDT.

While ranibizumab provides increased efficacy outcomes, it also incurs more ocular adverse events such as post-injection IOP \geq 30 mm Hg and increased cataract formation. There was no difference in systemic adverse events or the risk of mortality between ranibizumab, anecortave acetate, or V-PDT. However, overall measures such as quality of life suggest that relative to V-PDT, patients who had ranibizumab report higher quality of life on overall measures as well as for subscales of near activities, distant activities, and vision-related dependencies.

In terms of study quality, there was an apparent difference between the three included RCTs that involved bevacizumab^{12,26,27} and the other nine RCTs.^{13,17,18,20-25} The mean Jadad score was 2.5 for the former and 2.89 for the latter. The bevacizumab studies also had a much smaller sample size (mean n=86) and shorter duration (mean study duration=4 months) than the other RCTs. It is clear that formal RCT methodology applied to bevacizumab outcomes is at an earlier stage compared with ranibizumab. Bevacizumab has been studied at the case series level and is extensively used in the Canadian marketplace off-label. With regard to RCT methodology, while early results with bevacizumab are encouraging, more rigorous study with this drug will be needed in order to better understand its efficacy and side-effect profile, especially compared with ranibizumab.

These findings are subject to certain limitations. The low yield of studies made subgroup analysis impossible for many analyses. Few studies reported the primary outcome of ETDRS visual acuity. Moreover, the studies that used ETDRS as the primary outcome did not report measures of dispersion around their primary endpoint. Thus, meta-analysis, forest plots, and statistical tests were not possible for the change in the number of letters readable on the ETDRS scale. In addition, a lack of studies made it impossible to make inferences regarding the relative benefit of anti-VEGF therapies other than ranibizumab.

We identified five meta-analyses,³⁷⁻⁴¹ in addition to a previous CADTH report,⁴² that examined the effectiveness of treatments for AMD. Among these, Wormald *et al.*³⁷ and TAP & VIP Study Groups³⁸ compared V-PDT with placebo. Three included studies^{20,22,23} of this review addressed the same clinical question; however, it was not the objective of this review to perform a meta-analysis comparing V-PDT with placebo. Nevertheless, results from all three studies agreed with Wormald *et al.*³⁷ and the TAP & VIP Study Groups³⁸ that V-PDT appears to be effective in preventing serious visual loss with few safety issues. However, Wormald *et al.* doubted the clinical significance of V-PDT's effect size.³⁷

Lynch and Cheng³⁹ and Ladewig *et al.*⁴⁰ made an attempt to summarize clinical evidence for the efficacy and safety of intravitreal bevacizumab in treating neovascular AMD. Our systematic review was able to identify two recent RCTs on bevacizumab versus V-PDT (Lazic and Gabric¹² and Bashshur *et al.*²⁷). Both favoured bevacizumab, supporting the uncontrolled clinical trial results that indicated a moderate benefit of intravitreal bevacizumab in neovascular AMD treatment. We also

identified and summarized four combination therapy studies involving bevacizumab (Ahmadiéh *et al.*,¹¹ Ladas *et al.*,³² Augustin *et al.*,³¹ Dhalla *et al.*²⁹), and they all support the benefit of intravitreal bevacizumab for AMD treatment in terms of increasing visual acuity with few or no adverse events observed.

Takeda *et al.*⁴¹ discussed the efficacy of pegaptanib and ranibizumab for NV-AMD treatment. In their meta-analysis, they included studies published by the VISION and MARINA study groups. These did not meet the inclusion criteria for our systematic review, as the anti-VEGF agents under study were not compared with V-PDT, the standard treatment for the purpose of our report. (It should be noted that data from the VISION and MARINA trials were used in our primary economic evaluation.) However, the ANCHOR and FOCUS study groups were included in their review for the efficacy of ranibizumab as well as in our review.^{13,17} Both Takeda *et al.*⁴¹ and our results are consistent in finding that ranibizumab is significantly superior to V-PDT alone in improving visual acuity in NV-AMD patients, with mild to moderate adverse events.

a) Timing for the initiation of therapy

The clinical review found no direct evidence on the timing for initiation of therapy. One study that remotely touched upon the issue of timing was done by Michel *et al.*²⁴ The authors compared the outcome of repeating V-PDT every two months with the standard regimen of repeating V-PDT every three months for the first six months of treatment. Results showed that more frequent repetition of V-PDT was not beneficial in terms of either visual acuity improvement or lesion size reduction. However, in a subgroup analysis, it was demonstrated that more frequent repetition of V-PDT improved the mean visual acuity at month 12 of follow-up for patients who had lesions <2,000 µm at baseline (p<0.002).

b) Re-treatment with a different regimen in persons who did not have satisfactory clinical response to a particular regimen

There is no evidence on re-treatment with a different regimen in any of the randomized controlled trials included in this review. However, one retrospective interventional case series done by Liggett *et al.*²⁸ recorded the outcome of using pegaptanib with V-PDT and intravitreal triamcinolone in *de novo* patients versus those who had previously received intravitreal triamcinolone and V-PDT. In this small study, the patients treated *de novo* did slightly better in terms of lines of vision gained, but it was not statistically significant (p=0.55).

Ongoing randomized controlled trials and HTA studies of AMD are summarized in Appendix 17. These trials range from combination therapy trials to classic parallel arm studies to long term open label studies with one agent.

5 ECONOMIC ANALYSIS

A review of existing economic evaluations was undertaken to understand previous estimates of cost-effectiveness, to look for relevant Canadian analyses, and to locate any relevant data for a primary economic evaluation.

5.1 Review of Economic Studies: Methods

The following bibliographic databases were searched through the OVID interface: MedLine (1950-present; In-Process & Other Non-Indexed Citations), EMBASE (1980-present), BIOSIS Previews (1985-1989 and 1989-present), CINAHL (1982-present), PubMed, Health Economic Evaluations Database (HEED), and the Cochrane Library. Controlled vocabulary and keywords used in the search included terms for age-related macular degeneration and the drugs of interest in this project: verteporfin, bevacizumab, pegaptanib, ranibizumab, and anecortave acetate and their brand names. An economic filter was used to limit retrieval to relevant economic records. See Appendix 1 for the detailed search strategy.

OVID AutoAlerts were set up to send monthly updates with any new economic literature. Monthly updates were also performed in PubMed, HEED, and Cochrane Library databases. The updates were searched for relevant articles until November 2, 2007. We obtained supplementary cost information for the economic model by contacting experts and researching administrative data bases.

An economic evaluation was included for review if it satisfied all of the following criteria:

- Study design: a full economic evaluation (study providing a summary measure of the trade-off between costs and consequences)
- Population: as in the clinical review, adults 40 years of age or older with neovascular AMD
- Interventions and comparators — comparison of V-PDT, pegaptanib, bevacizumab, ranibizumab, anecortave acetate, intravitreal triamcinolone, placebo, or clinically relevant combinations
- Primary outcome: outcome reported as an incremental measure of the implication of moving from the comparator to the intervention, for example, a summary measure such as the incremental cost-effectiveness ratio.

Two reviewers (AB and JP) applied the selection criteria to the title and abstract (if available) of literature obtained in the first phase of the literature search to identify its relevance to our objective. For articles rated as confirmed or undecided, we obtained full-text hard copies. In the second phase of the literature search two reviewers (AB and BD) applied the selection criteria to the full-text articles. If a study satisfied all the inclusion-exclusion criteria, it was included for review.

One reviewer (AB) used a data extraction sheet (Appendix 18) to extract the principal content of each included study. As the studies varied in terms of design, data collection, and analysis, no effort was made to pool the results quantitatively. Instead, each study was summarized, and a qualitative comparison was undertaken. Data extracted from included economic studies was checked by a second reviewer (GB).

Two reviewers (AB and AG) used a checklist developed for the *British Medical Journal (BMJ)* to assess the quality of the included economic evaluations.⁴³ This checklist is appropriate for full economic evaluations; that is, evaluations that present the costs and consequences of health interventions and a summary measure of the trade-off between the two. Implications of the quality assessment are summarized in the discussion (section 5.2.1). The checklist as well as the results of the quality assessment appears in Appendix 19 and 20b.

5.2 Review of Economic Studies: Results

The economic literature search identified 392 potentially relevant articles. After applying the inclusion criteria, 12 articles were included for review. Most of the articles compared V-PDT with placebo or best supportive care (Brown *et al.*,⁴⁴ Grenier,⁴⁵ Hopley *et al.*,⁴⁶ Larouche,⁴⁷ Meads,⁴⁸ Sharma *et al.*, 2001,⁴⁹ Smith *et al.*⁵⁰). One compared bevacizumab and ranibizumab in a threshold analysis (Raftery *et al.*⁵²). One compared anecortave acetate and V-PDT, also in a threshold analysis (Sharma *et al.*, 2005⁵³). Two compared pegaptanib with best supportive care or usual care (Javitt *et al.*,⁵⁴ Wolowacz *et al.*⁵¹). One compared pegaptanib with V-PDT and standard care (Earnshaw *et al.*⁵⁵).

Appendix 19 and Appendix 19 present the results for the quality assessment of the full economic evaluations using the *BMJ* checklist.⁴³ The *BMJ* checklist includes 35 questions under three headings: study design, data collection, and analysis and interpretation of results. Each question is answered with “yes,” “no,” or “not clear.” The “no” and “not clear” responses have been added together following an approach described by Jefferson *et al.*⁵⁶ The sum of the “no” and “not clear” answers indicates the extent to which issues were not handled. The lower the numerical score, the higher the implied quality. For 10 of the studies, the score was five or lower, suggesting relatively high quality evaluations (Brown *et al.*,⁴⁴ Earnshaw *et al.*,⁵⁵ Hopley *et al.*,⁴⁶ Javitt *et al.*,⁵⁴ Larouche,⁴⁷ Meads,⁴⁸ Sharma *et al.*, 2001,⁴⁹ Sharma *et al.*, 2005,⁵³ Smith *et al.*,⁵⁰ Wolowacz *et al.*⁵¹).

Table 2 summarizes the characteristics of the included economic evaluations, and Table 3 summarizes their results.

Table 2: Characteristics of economic evaluations included in the review						
Author	Industry Sponsorship	Study Perspective	Interventions and Comparators	Study Design	Location	Outcome and Sources
Brown <i>et al.</i> ⁴⁴	Yes	Third-party insurer	PDT with verteporfin Placebo	Cost-utility analysis	US	Cost per QALY Costs from US Medicare data Visual acuity from TAP study
Earnshaw <i>et al.</i> ⁵⁵	Not clear*	Public payer	Pegaptanib PDT with verteporfin and standard care	Cost-utility analysis and cost-effectiveness analysis	Canada	Cost per QALY and cost per vision year Costs from Québec and federal government and clinical experts Outcomes from VISION, VIP, and TAP studies
Grenier ⁴⁵	No	Societal	PDT with verteporfin Placebo	Cost-effectiveness analysis	Switzerland	Cost per vision year Costs from Swiss prices, taxes, and wages Vision-years derived from

Table 2: Characteristics of economic evaluations included in the review						
Author	Industry Sponsorship	Study Perspective	Interventions and Comparators	Study Design	Location	Outcome and Sources
						TAP study
Hopley <i>et al.</i> ⁴⁶	No	Third-party payer	PDT with verteporfin Placebo	Cost-utility analysis	Australia	Cost per QALY Costs from Australian Medicare Benefits Schedule Visual acuity from TAP study
Javitt <i>et al.</i> ⁵⁴	Yes	Third-party payer	Pegaptanib Usual care	Cost-utility analysis and cost-effectiveness analysis	US	Cost per QALY and cost per vision-year Costs from US published sources Outcomes from the VISION study
Larouche ⁴⁷	No	Societal	PDT with verteporfin No treatment	Cost-utility analysis	Québec, Canada	Cost per QALY Economic data from Institut Nazareth and Louis-Braille in Québec Visual acuity from TAP and VIP studies
Meads ⁴⁸	No	Direct costs to NHS and local and central government	PDT with verteporfin plus BSC BSC	Cost-utility analysis	UK	Cost per QALY Costs from UK sources Effectiveness measures from TAP study
Raftery <i>et al.</i> ⁵²	No	I Health care provider (NHS) II Government [†]	Bevacizumab (Avastin) Ranibizumab (Lucentis)	Cost-utility analysis with threshold analysis	UK	Cost per QALY simulations Becavizumab cost based on US price per injection Ranibizumab cost based on reducing US price of colon cancer drug based on reduced required dose Ranibizumab visual acuity and adverse effects

Table 2: Characteristics of economic evaluations included in the review						
Author	Industry Sponsorship	Study Perspective	Interventions and Comparators	Study Design	Location	Outcome and Sources
						data from licensing trial For bevacizumab, a range of visual acuity assumptions were used for simulation
Sharma, 2001 <i>et al.</i> ⁴⁹	No	For-profit third-party insurer	PDT with verteporfin Placebo	Cost-utility analysis	US	Cost per QALY Costs from US Medicare reimbursement data Visual acuity from TAP study
Sharma, 2005 <i>et al.</i> ⁵³	Yes	Societal	Anecortave acetate PDT with verteporfin	Cost-utility analysis with threshold analysis	US	Cost per QALY Efficacy data provided on a proprietary basis by Alcon Research Ltd. Costs from US Medicare data, literature, and personal communication
Smith <i>et al.</i> ⁵⁰	Yes	I PDT with verteporfin treatment costs II Government [‡]	PDT with verteporfin Placebo	Cost-utility analysis	UK	Cost per QALY Cost estimates from NICE's technology assessment report (Meads <i>et al.</i> ⁴⁸) Visual acuity from TAP study
Wolowicz <i>et al.</i> ⁵¹	Yes	Government	Pegaptanib BSC	Cost-utility analysis	UK	Cost per vision year saved and cost per QALY Costs from various UK sources Patient level data from VISION trials

*One author is listed as an employee of Pfizer and another works for an organization that has received funding from Pfizer.

[†]Includes NHS costs as well as personal social service costs.

[‡]Includes other NHS costs besides treatment costs plus personal social service costs.

BSC=best supportive care; NHS=National Health Service; NICE=National Institute for Clinical Excellence; PDT=photodynamic therapy; QALY=quality-adjusted life year; TAP study=treatment of age-related macular degeneration with photodynamic therapy study; VIP study=verteporfin in photodynamic therapy study.

Table 3: Results of economic evaluations included in review

Author	Currency, Year	Estimate of Cost-Effectiveness	Conclusions
Brown <i>et al.</i> ⁴⁴	US dollars, 2004	Cost per QALY was \$31,103 (range \$20,736 to \$62,207)	PDT with verteporfin is a very cost-effective treatment by conventional standards.
Earnshaw <i>et al.</i> ⁵⁵	Canadian dollars, 2004	Cost per QALY: \$49,052 relative to V-PDT \$59,039 relative to standard care Cost per vision year gained: \$20,401 relative to V-PDT \$21,559 relative to standard care	Pegaptanib is cost-effective for subfoveal wet AMD in elderly patients, regardless of lesion type, relative to PDT with verteporfin and to standard care.
Grenier ⁴⁵	Swiss francs, 1998	Costs per vision year for PDT with verteporfin: 14,907 CHF Costs per vision year placebo group: 21,047 Incremental cost per vision year saved by verteporfin therapy: 9,624 CHF	Verteporfin therapy is cost-effective.
Hopley <i>et al.</i> ⁴⁶	British pounds (some costs in Australian dollars), 2003	Reasonable initial visual acuity, £31,607 per QALY (range £25,285 to £37,928) Poor initial visual acuity, £63,214 per QALY (range £54,183 to £75,856)	For reasonable initial visual acuity PDT with verteporfin is moderately cost-effective. For poor initial visual acuity, it is relatively cost-ineffective.
Javitt <i>et al.</i> ⁵⁴	US dollars, 2006	Cost per QALY at respective stage of NV-AMD: Early: \$36,282 Moderate: \$58,280 Late: \$132,381 Cost per vision year gained: Early: \$15,279 Moderate: \$20,350 Late: \$57,230	For patients with subfoveal NV-AMD, pegaptanib treatment should be started as early as possible to maximize the clinical and economic benefits.
Larouche <i>et al.</i> ⁴⁷	Canadian dollars, currency year not stated	PC AMD: \$33,880 per QALY PC AMD and pure occult AMD: \$43,253 per QALY	Economic results are favourable for V-PDT treatment of PC AMD and pure occult AMD.
Meads ⁴⁸	British pounds, 2000	Cost per QALY between £182,188 and £151,179	PDT with verteporfin is unlikely to be cost-effective.
Raftery <i>et al.</i> ⁵²	US dollars, currency year not stated	For PC AMD, the efficacy of bevacizumab relative to ranibizumab would have to be about 40% for ranibizumab to meet the NICE threshold for cost-effectiveness (£30k per additional QALY) For MC/OC AMD, results are somewhat worse for ranibizumab	Ranibizumab is highly unlikely to be cost-effective relative to bevacizumab at current prices.
Sharma, 2001 <i>et al.</i> ⁴⁹	US dollars, September 1, 2000	For 20/40 vision, \$86,721 per QALY (two-year model) and \$43,547 per QALY (11-year model). For 20/200 vision, \$173,984 per QALY (two-year model) and \$87,197 per QALY (11-year model)	V-PDT is of modest to poor cost-effectiveness. It is of minimal cost-effectiveness for AMD patients with good visual acuity and is cost-ineffective for those presenting with poor visual acuity.

Table 3: Results of economic evaluations included in review

Author	Currency, Year	Estimate of Cost-Effectiveness	Conclusions
Sharma, 2005 <i>et al.</i> ⁵³	US dollars, currency year not stated	Relative to PDT with verteporfin, the associated ICERs and cost per 15 mg vial of anecortave acetate are: US\$100,000/QALY for US\$3,022 per 15 mg vial US\$50,000/QALY for US\$2,986 per 15 mg vial US\$20,000/QALY for US\$2,964 per 15 mg vial US\$0/QALY for US\$2,950 per 15 mg vial (indifference point between anecortave acetate and PDT with verteporfin)	A cost per 15 mg vial for anecortave acetate of \$2,986 would be associated with an ICER that is under most reimbursement agencies' cost-effectiveness thresholds.
Smith <i>et al.</i> ⁵⁰	British pounds, December 2000	Government perspective, two-year time horizon, cost per QALY estimates: £286,000 for starting VA 20/100 £76,000 for starting VA 20/40 Government perspective, five-year time horizon: £30,000 for starting VA 20/100 £9,000 for starting VA 20/40 Cost of treatment perspective, two-year time horizon: £412,000 for starting VA 20/100 £90,000 for starting VA 20/40 Cost of treatment perspective, five-year time horizon: £69,000 for starting VA 20/100 £38,000 for starting VA 20/40	From a broad government perspective, and a five-year time horizon, PDT with verteporfin may yield reasonable value for money.
Wolowacz <i>et al.</i> ⁵¹	British pounds, 2005	Cost per vision year saved £2,696 Overall cost per QALY £8,023 Cost per QALY for subgroups: £2,033 for <75 years £11,657 for ≥75 years £8,023 for starting VA 6/12 to 6/95 £6,664 for starting VA 6/12 to 6/60 £1,920 for starting VA 6/12 to 6/24	Pegaptanib likely to be cost-effective relative to best supportive care in all groups studied. This result is not contingent on stopping rules.

AMD=age-related macular degeneration; CHF=Swiss francs; ICER=incremental cost-effectiveness ratio; MC=minimally classic; MC/OC=minimally classic or occult; NICE=National Institute for Clinical Excellence; NV-AMD=neovascular AMD; PC=predominantly classic; PDT=photodynamic therapy; QALY=quality-adjusted life year; V-PDT=verteporfin (Visudyne) plus photodynamic therapy; VA=visual acuity.

The Brown study⁴⁴ assessed the value conferred by V-PDT and the cost-utility of V-PDT for classic subfoveal CNV associated with AMD in the US. The authors felt another study (Sharma, 2001⁴⁹) needed to be updated with new five-year data from the TAP study. However, this follow-up was open-label and uncontrolled, and 48% of the original patients continued to the end of the five years. The authors concluded that PDT with verteporfin is very cost-effective by conventional standards. This study was financially supported by Novartis.

The Earnshaw *et al.* study⁵⁵ examined the cost-effectiveness of pegaptanib versus V-PDT and versus standard care for the treatment of subfoveal wet AMD in patients aged ≥ 65 years in Canada. Standard care was defined as placebo or treatment with V-PDT if lesion subtype and/or size qualified for treatment as indicated in the product monograph. Using a Markov model, patients received two years of treatment, with lifetime follow-up. The authors concluded pegaptanib is cost-effective for subfoveal neovascular AMD in elderly patients, regardless of lesion subtype.

The Grenier study⁴⁵ examined the cost-effectiveness of PDT with verteporfin for AMD patients with predominantly classic subfoveal CNV in terms of vision-years. The setting was Switzerland. Use of cost per vision year as the outcome measure makes comparison of their results with the other included economic studies difficult. They concluded that the greater effectiveness of verteporfin therapy versus placebo compensated for the cost of the therapy, so verteporfin therapy was cost-effective. But it is not clear how they came to this conclusion, since they did not present a method to value an additional vision-year.

The aim of the Hopley *et al.* study⁴⁶ was to refine cost-effectiveness estimates of V-PDT treatment for the purpose of funding decisions in Australia. They concluded that V-PDT can be considered moderately cost-effective for predominantly classic AMD patients with reasonable initial visual acuity but is relatively cost-ineffective for those with poor initial visual acuity.

The approach taken in the Javitt *et al.* ⁵⁴ study was similar to that of Earnshaw *et al.*, ⁵⁵ except that pegaptanib was compared only with usual care. The setting was the US with patients aged ≥ 65 years. The focus was on examining differences for patients with early, moderate, and late subfoveal NV-AMD, defined respectively as visual acuity in the better-seeing eye of 20/40 to more than 20/80, 20/80 to more than 20/200, and 20/200 to more than 20/400. Usual care was defined as placebo or V-PDT, because at the time of the VISION trial, V-PDT was the only treatment for patients with NV-AMD. The trial design allowed use of V-PDT in both the experimental and the usual care arms at the discretion of the physician. The study found that health gains with pegaptanib were most pronounced in patients receiving early care. Also, on average patients treated early with either pegaptanib or usual care incurred lower lifetime direct costs than those treated later. The authors concluded treatment with pegaptanib should be started as early as possible to maximize the clinical and economic benefits. The study was financially supported by Pfizer.

The Larouche study⁴⁷ was a health technology assessment by Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS) for the Québec government. The study population was patients in Québec over age 55 in 2001 with predominantly classic CNV or pure occult subfoveal CNV. The perspective was described as societal, although the included costs were from a health care system perspective. They concluded that for a Québec cohort and eight-year time horizon the results of the economic analysis were favourable for the use of V-PDT in cases of predominantly classic or pure occult exudative neovascular AMD. The net annual budget impact was estimated at \$17.3 million including both incident and prevalent cases and \$300,000 for incident cases only.

The Meads study⁴⁸ was a health technology assessment commissioned by the National Health Services R&D HTA Programme in the UK. The study had a two-year time frame. They concluded that unless the costs of blindness are very high or the effectiveness is much higher than demonstrated in the TAP or VIP trials, V-PDT is unlikely to be a cost-effective alternative to best supportive care in terms of stabilizing visual acuity. It was estimated that if all people in the UK who present with CNV AMD were treated with V-PDT, it would cost £63.4 million in the first year and £130.6 million per year by the third year.

The Raftery *et al.* study⁵² compares the clinical and cost-effectiveness of ranibizumab with bevacizumab using published data supplemented by assumptions on relative efficacy and adverse effects. The study was from the UK but relied on US prices. As background to their study, the authors note there is no clinical trial evidence comparing the efficacy of bevacizumab versus placebo or bevacizumab versus ranibizumab for AMD. However bevacizumab is widely used off-label for AMD. Given that the price of bevacizumab is 1% to 3% that of ranibizumab (based on current US prices), the authors modelled how much more effective ranibizumab would need to be to meet the National Institute for Clinical Excellence's (NICE's) cost-effectiveness threshold of £30k per additional quality-adjusted life year (QALY). To do this, ranibizumab would need to be 2.5 times better in terms of visual acuity. The authors felt this was unlikely, given the similarity of the molecules and the (albeit limited) data available.

Sharma *et al.*, 2001⁴⁹ assessed the cost-effectiveness of V-PDT for the treatment of CNV in patients with disciform degeneration in one eye whose second and better-seeing eye develops visual loss secondary to predominantly classic subfoveal CNV. The setting was the US. The authors concluded that V-PDT is of minimal cost-effectiveness for AMD patients presenting with good visual acuity in their second and better-seeing eye and is cost-ineffective for those presenting with poor visual acuity. However, the results for the 11-year horizon model were better and approached cost-effective levels.

In the Sharma *et al.*, 2005 study⁵³ the authors conducted a series of threshold analyses to determine the cost at which anecortave acetate at 15 mg for depot suspension (Retaane) would reach cost-effective levels using a cost-utility model. The setting was the US. A societal perspective was taken, including direct medical costs as well as costs associated with the risk of falls, depression, and use of supportive services and rehabilitative devices. PDT with verteporfin was taken as standard practice. At the time of the analysis, a phase III clinical trial for Retaane was ongoing, so no market price was available. The study found no difference in quality of life between the patients treated with anecortave or the patients treated with V-PDT. The authors concluded that a cost for anecortave acetate of \$2,986 would be associated with an incremental cost-effectiveness ratio (ICER) that is less than most reimbursement agencies' cost-effectiveness thresholds. It is questionable whether the one-year time horizon spans the relevant costs and benefits. This study received financial support from Alcon.

The Smith *et al.* study⁵⁰ estimated the cost-effectiveness of PDT with verteporfin in the UK setting. Results were provided for two perspectives. The cost-of-treatment perspective included costs to the National Health Service (NHS) for V-PDT treatment. In addition to that, the government perspective included other NHS costs plus personal social service costs. Because PDT with verteporfin may diminish the rate at which individuals become blind (defined by the authors as <20/200), the government perspective incorporated possible cost offsets in medical and social care. The study found that from a broad government perspective, and a five-year time horizon, PDT with verteporfin may yield reasonable value for money. The study had three conclusions. First, early treatment (i.e., less severe stage of disease) with V-PDT has a better chance to be cost-effective versus treating more

advanced cases. Consideration should be given to early detection and treatment. Second, from a health care provider cost-of-therapy perspective, treating people at lower levels of visual acuity would probably not be considered cost-effective. Third, from a government perspective (including other NHS costs and social care costs) and a five-year horizon, V-PDT may provide value for money. The study was financially supported by Novartis.

The Wolowacz *et al.* study⁵¹ estimated the cost-effectiveness of pegaptanib relative to best supportive care in a UK setting. Pfizer provided financial support and contributed to the design and conduct of the study. The model reported on in the study was used to support submissions to NICE (preliminary consultation on pegaptanib and ranibizumab available,⁵⁷ formal guidance forthcoming) and the Scottish Medicines Consortium (SMC) advice on pegaptanib.⁵⁸ The study found pegaptanib likely to be cost-effective in all groups studied and marginally more cost-effective in younger patients and those with better pre-treatment visual acuity. Cost-effectiveness was not sensitive to precise rules for treatment discontinuation, but could be optimized by discontinuing treatment after one year if visual acuity has dropped more than six lines from pre-treatment or dropped below a Snellen visual acuity value of 6/95 at any time. The authors concluded clinical judgment and patient preference should be important determinants in decisions about stopping treatment.

5.2.1 Discussion

Of the 12 included economic evaluations (Brown *et al.*,⁴⁴ Earnshaw *et al.*,⁵⁵ Grenier,⁴⁵ Hopley *et al.*,⁴⁶ Javitt *et al.*,⁵⁴ Larouche,⁴⁷ Meads,⁴⁸ Raftery *et al.*,⁵² Sharma *et al.*, 2001,⁴⁹ Sharma *et al.*, 2005,⁵³ Smith *et al.*,⁵⁰ Wolowacz *et al.*⁵¹), seven examined V-PDT compared with placebo or best supportive care (Brown *et al.*,⁴⁴ Grenier,⁴⁵ Hopley *et al.*,⁴⁶ Larouche,⁴⁷ Meads,⁴⁸ Sharma *et al.*, 2001,⁴⁹ Smith *et al.*⁵⁰). Of these, four found results favourable for V-PDT (Brown *et al.*,⁴⁴ Grenier,⁴⁵ Larouche,⁴⁷ Smith *et al.*⁵⁰). Two found mixed results, suggesting moderate cost-effectiveness with V-PDT for those with reasonable initial visual acuity, but cost-ineffective for those with poor initial visual acuity (Hopley *et al.*,⁴⁶ Sharma *et al.*, 2001⁴⁹). The Meads⁴⁸ study concluded V-PDT was unlikely to be cost-effective relative to best supportive care. Differences in study design, perspective, and setting may partially account for some of the variance in results among the studies comparing V-PDT with no active treatment.

One study compared bevacizumab and ranibizumab (Raftery *et al.*⁵²), and one compared anecortave acetate and V-PDT (Sharma *et al.*, 2005⁵³). Raftery *et al.*⁵² found that ranibizumab is unlikely to be cost-effective relative to bevacizumab due to the large difference in relative prices at current levels. Sharma *et al.*, 2005⁵³ found anecortave acetate likely to be a cost-effective alternative relative to V-PDT. It should be noted that both of these studies were threshold analyses requiring assumptions about efficacy, but they used limited actual evidence of efficacy.

Three studies analyzed pegaptanib as the intervention, comparing it with best supportive care, usual care, or V-PDT (Earnshaw *et al.*,⁵⁵ Javitt *et al.*,⁵⁴ and Wolowacz *et al.*⁵¹). All three studies found results favourable to pegaptanib.

In terms of the quality assessment, two studies^{45,52} had *BMJ* checklist scores higher than five. Higher scores on the checklist suggest lower quality.^{43,56} These two studies are unique in that they have marked differences in study design relative to the others. The Grenier study⁴⁵ was the only cost-effectiveness analysis, expressing its outcomes in terms of cost per vision year gained. All the other studies were cost-utility analyses, using cost per QALY gained as their primary outcome measure. The Raftery *et al.* study⁵² used threshold analysis, asking the question: How much more effective

would ranibizumab have to be to overcome the price advantage of bevacizumab and meet the NICE threshold of £30k per additional QALY? This approach was taken because of the lack of RCT evidence on the effectiveness of bevacizumab.

Only two of the included economic studies reported on timing of initiation of therapy or re-treatment with another regimen.

a) Timing for the initiation of therapy

The studies by Javitt *et al.*⁵⁴ on pegaptanib and Smith *et al.*⁵⁰ on V-PDT came to the general conclusion that treatment with the drug should be started as early as possible to maximize the clinical and economic benefits.

b) Re-treatment with a different regimen in persons who did not have satisfactory clinical response to a particular regimen

The study by Wolowacz *et al.*⁵¹ on pegaptanib found that the results of the study were not contingent on stopping rules.

Five of the studies reported industry sponsorship (Brown *et al.*,⁴⁴ Javitt *et al.*,⁵⁴ Sharma *et al.*, 2005,⁵³ Smith *et al.*,⁵⁰ Wolowacz *et al.*⁵¹). Some evidence suggests studies funded by industry were more likely to report ratios below widely used willingness-to-pay thresholds.⁵⁹

For most studies, it may be impractical to make inferences regarding the economic impact on the Canadian health system, since the settings for the studies were varied. Four were set in the US (Brown *et al.*,⁴⁴ Javitt *et al.*,⁵⁴ Sharma *et al.*, 2001,⁴⁹ Sharma *et al.*, 2005⁵³), four in the UK (Meads,⁴⁸ Raftery *et al.*,⁵² Smith *et al.*,⁵⁰ Wolowacz *et al.*⁵¹), two in Canada (Larouche *et al.*,⁴⁷ and Earnshaw⁵⁵), and one each in Switzerland (Grenier⁴⁵) and Australia (Hopley *et al.*⁴⁶). Two of the economic evaluations were components of larger comprehensive health technology assessments sponsored by government agencies (Meads,⁴⁸ Larouche⁴⁷).

5.3 Primary Economic Evaluation: Methods

As none of the studies analyzed all the interventions of interest in this report in a Canadian setting, we undertook a primary economic evaluation for Canada.

5.3.1 Type of economic evaluation

We took a decision analytic approach and modelled a cost-utility analysis, conducting it as a microsimulation of a Markov model.⁶⁰ Microsimulation models are computer models that operate at the level of the individual behavioural entity; in this case, the patient. A hypothetical cohort of patients was followed throughout the study time horizon (in this case, the patient's expected life span), rather than an actual cohort of patients as would be the case in a clinical trial. A Markov model uses transition probabilities between health states for each cycle of the model. The microsimulation approach includes randomized individual patient characteristics and tracks the progress of individual patients through particular health states in terms of health outcomes and costs.^{61,62}

5.3.2 Target population

The target population was adults aged 40 or older with neovascular AMD. As mentioned in the clinical section, we selected 40 years of age as a threshold to be consistent with Canadian epidemiologic data on prevalence.¹

5.3.3 Comparators

For people with predominantly classic (PC) lesions, the comparators to ranibizumab were pegaptanib and V-PDT. For people with lesions of any subtype (including PC), the comparator to ranibizumab was pegaptanib. In each case, it was assumed that treatment was provided according to the schedule outlined in the clinical trials. For ranibizumab, this was administered once per month, and for pegaptanib it was every six weeks. People undergoing V-PDT were treated twice per year unless their visual acuity had progressed to “severe visual impairment” (i.e., worse than 6/33).

5.3.4 Perspective

The perspective was that of a provincial health system. Only direct medical costs relevant to a provincial health care provider were considered. Indirect costs accruing only to the patient were not included.

5.3.5 Time horizon

The time horizon of the model was the lifetime of the patients.

5.3.6 Modelling

Separate models were created for those with PC lesions and those with lesions of any subtype. A larger technical description of the model can be made available upon request to CADTH. The reason for this distinction was that V-PDT has been shown to be effective in slowing the progression of neovascular AMD in people with PC lesions but has not been shown in clinical trials to have similar efficacy in treatment of people with minimally classic or occult lesions. Therefore, our model for treatment of PC lesions compared treatment with V-PDT, pegaptanib, and ranibizumab. Our model that considered treatment of any lesion subtype (i.e., PC or minimally classic or occult) considered only pegaptanib and ranibizumab. Due to lack of clinical evidence on responsiveness to combination treatments, we did not model combinations of treatments such as pegaptanib plus V-PDT or ranibizumab.

The modelled cohort was a cross-sectional sample of patients with macular degeneration as presented in the ANCHOR¹⁷ and MARINA trials.³³ Comparison was made to the characteristics of participants included in the TAP trial,⁶³ and no significant differences were seen. Therefore, the distribution of age and baseline visual acuity of participants entered into the model reflected that seen in the former two trials. No adjustments were made in the model for race or gender, as there is no evidence that these factors affect either costs or QALYs. All analyses were based upon the assumption that visual acuity was based upon that found in the “better seeing eye,” as is customary in ophthalmology studies considering quality of life.

Most model parameters were taken from those estimated from the systematic review provided above. For ETDRS estimates, in order to enrich the sample and provide a more stable estimate for the microsimulation, the mean change along with the associated standard error was calculated from

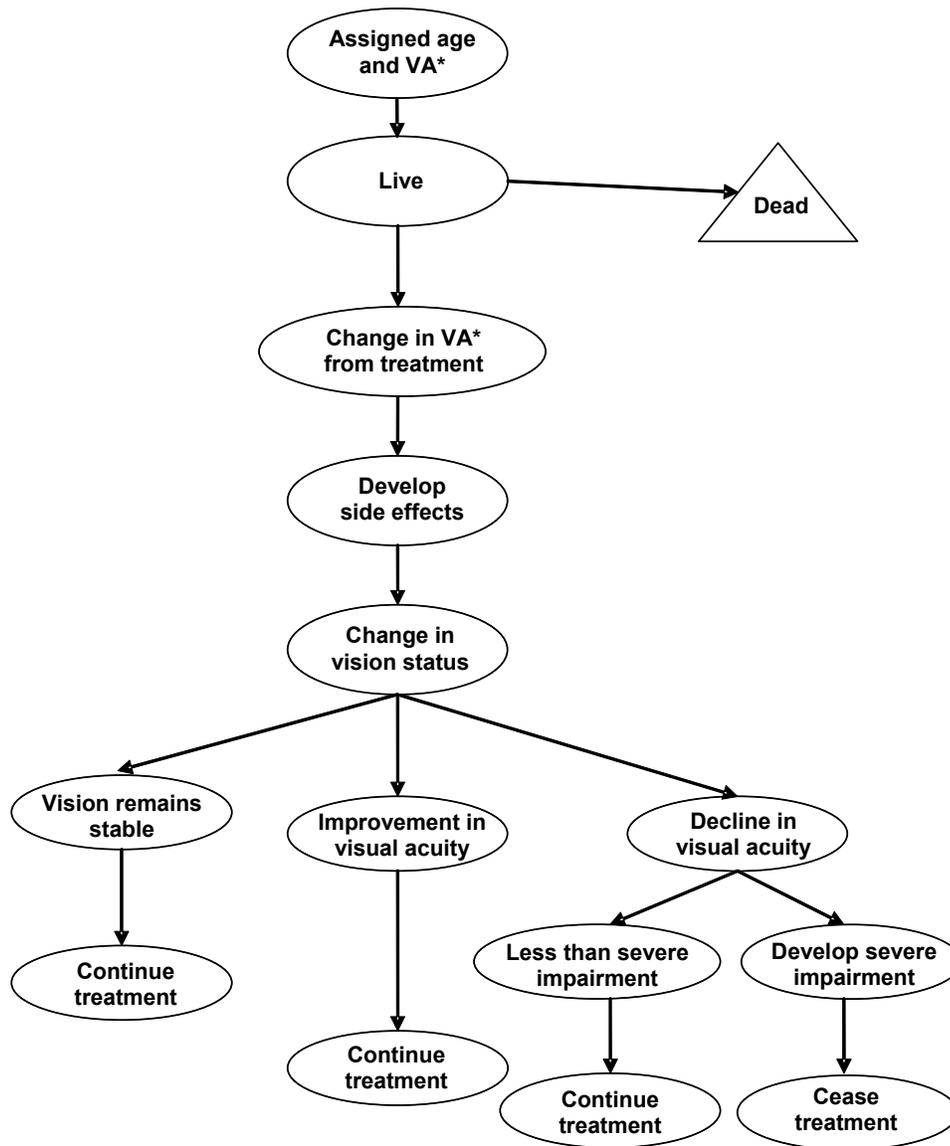
RCTs that included any of the treatment comparators included in the economic model. When data was available from multiple studies for a treatment group, data was pooled using a random effects meta-analysis. Estimates were made by evaluating the difference (treatment minus placebo) in ETDRS found in trials comparing an active treatment versus placebo. The difference between treatment and control was added to the pooled placebo efficacy of all trials to estimate the absolute change in ETDRS for each treatment. The results are provided below:

	ETDRS (standard error)
V-PDT	-9.97 (0.68)
Macugen	-3.27 (0.45)
Lucentis	10.23 (0.44)

The Markov model evaluated is illustrated as a schematic bubble diagram in Figure 3. Participants were randomly assigned an age and baseline visual acuity as they entered the model, based upon the distributions found in the ANCHOR trial¹⁷ (for PC lesions) and MARINA³³ (for all lesions). As there was limited information concerning the distribution characteristics a priori, we assumed a normal distribution for both parameters. Following treatment, participants were randomly assigned a response to treatment based on that found in the clinical trials reported above. Following treatment, participants faced simulated exposure to adverse events based upon rates seen in the clinical trials. Participants were then assigned to a health state based upon their visual acuity (VA). Those with VA better than 6/12 were assigned to “mild visual impairment,” those with VA worse than 6/12 but better than 6/30 were assigned to “moderate visual impairment,” and those worse than 6/33 were assigned to “severe visual impairment.” Costs were assigned to each health state based upon the degree of impairment. Cost of treatment and the utility for each stage were assigned at the point at which treatment occurred. Those who entered the “severe visual impairment” state after the first cycle were no longer treated. We assumed they did not respond to treatment, and further treatment was therefore not indicated. Those who were in the mild or moderate health states continued to be treated.

In order to achieve convergence, the model was evaluated by conducting 500 simulations, each consisting of 5,000 trials. The ICER is reported.

Figure 3: Bubble diagram of model for treatment of neovascular macular degeneration



*Visual acuity measured in letters correct at 2m.

5.3.7 Data considerations

The main clinical effectiveness outcome incorporated into the model is the change in visual acuity, defined as the number of letters correct at 2 m. This outcome was evaluated in the clinical review section of this report (Appendix 4). However, additional analysis was undertaken for the economic model. To ensure we had data on visual acuity change for all model comparators, an additional literature search and analysis was conducted. Mean visual acuity change for each model treatment comparator was estimated by pooling single arms of studies from identified studies. Pooling was done by means of random-effects meta-analysis.

In addition to visual acuity change, the model incorporated rates of adverse events (MI, stroke, retinal detachment, endophthalmitis, and intraocular inflammation). The rates of visual acuity change and adverse events along with their sources are provided in Appendix 20.

Various sources were used for unit costs of medications, procedures, and physician visits. The PPS Pharma Guide⁶⁴ (Ontario Edition, July 2007) was used to derive the unit costs for pegaptanib and bevacizumab. Unit costs for triamcinolone and cephalexin were based on the Ontario Drug Benefit Formulary reimbursement rate.⁶⁵ An Australian price for anecortave acetate was used since it is available there.⁶⁶

The costs for eye-related procedures (i.e., photodynamic therapy, cataract extraction, fluorescein angiography, etc.) were provided by a hospital participating in the Ontario Case Costing Project (OCCP). This hospital also provided the cost of an ophthalmology clinic visit. The physician costs applicable to the eye-related procedures were based on fee codes from the Ontario Health Insurance Plan (OHIP) schedule of benefits and fees. Appropriate fee codes for each procedure were determined through expert opinion of three ophthalmologists. The cost per general practitioner and specialist visit was also based on the OHIP schedule of benefits. The unit costs were combined with expert opinion on dosing regimens and treatment frequencies to derive the annual costs for each model comparator and for vision-related complications. The annual treatment cost for each comparator and for each vision-related complication is provided in Appendix 20.

Regardless of treatment, patients are assigned additional costs depending on whether they had severe or less than severe visual impairment during a given year. These “health state costs” may incorporate such things as government disability payments, specialized housing costs, and the costs of visual impairment aids. The annual visual impairment health state costs used in the model was based on a report by Canterbury Communications⁶⁷ on vision loss in Canada. This was the only Canadian source of vision loss costs that could be found. The annual costs of stroke and myocardial infarction were based on a recent Canadian longitudinal analysis of matched diabetic and non-diabetic patients.⁶⁸ The health state costs for visual impairment severity, MI, and stroke along with their sources are provided in Appendix 20.

The parameter values used in the model and their sources are listed in Appendix 20.

5.3.8 Valuing outcomes

Utilities were calculated based upon the formula developed by Sharma.⁶⁹

$$\text{Equation 1: conversion of visual acuity to utility score} \\ \text{Utility} = 0.374 \times (\text{visual acuity in better-seeing eye}) + 0.514$$

This approach values health outcomes based upon patients’ opinions. While Sharma included a multivariate version of the formula in his report, the only significant variable in the model was visual acuity. Therefore we relied on the univariate version with visual acuity only to estimate utilities.

One complication in making these estimates is that, while it is not specified in Sharma’s report, it is reasonable to assume that the visual acuity estimate used in his model was taken at the standard test distance (i.e., 6 m), while the initial visual acuity used in our estimates is based upon the testing done in the ANCHOR¹⁷ and MARINA³³ trials, which were both at 2 m. Therefore, to make the conversion from 2 m to 6 m, it was necessary to subtract 24 letters from the 2 m distance prior to conversion of

the ETDRS score to the decimal equivalent required for the Sharma formula. See below for this conversion:

$$\text{Equation 2: conversion of letters correct at 2 m to LogMAR score at 6 m} \\ (45 - (\text{letters correct} - 24)) \times 0.02$$

5.3.9 Discount rate

All costs and health outcomes were discounted at a base rate of 5% per year, and a sensitivity analysis was carried out at a 3% and at a 0% rate, as indicated in the CADTH economic guidelines.⁷⁰

5.3.10 Variability and uncertainty

The precision of the estimates was tested using one-way sensitivity analyses of all variables to determine at what change in the value of a parameter the cost-effectiveness decision is changed. For this we used a widely used willingness to pay of \$50,000 per QALY.⁷¹

As a measure of dispersion, the overall model was tested using second order Monte Carlo simulation to produce cost-effectiveness acceptability curves.⁷² In constructing the Monte Carlo simulation, all clinical variables were parameterized as distributions, as were most cost variables. However the cost of treatment was treated as a constant exogenous variable, as was utility gained, due to the difficulties of introducing uncertainty into the above formula.

5.4 Primary Economic Evaluation: Results

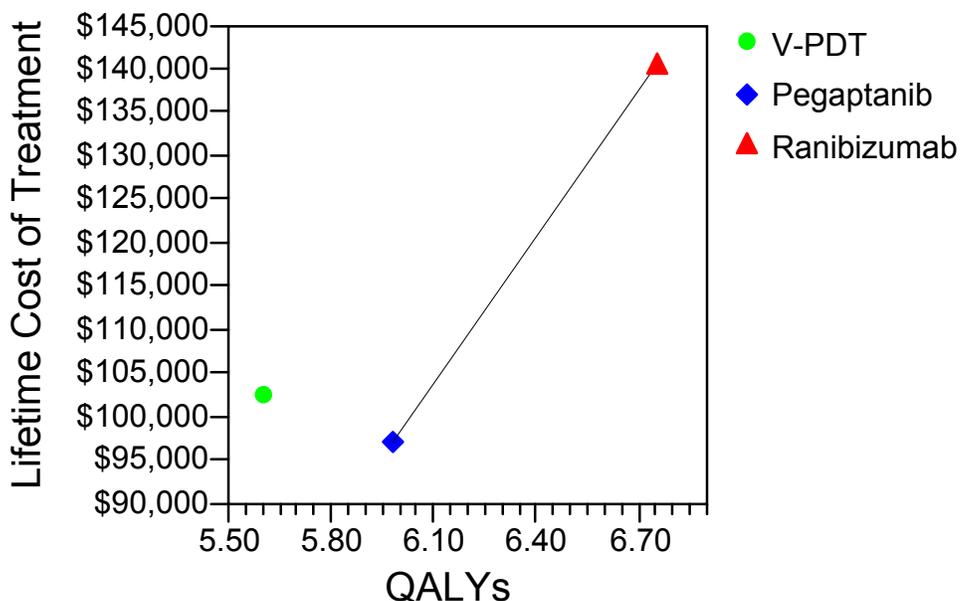
5.4.1 Analysis and results

The participants in the simulation lived for nine years on average, and the maximum was 45 years. Our ICER results are presented in Tables 4 and 5. Table 4 provides a comparison of the three therapies considered for treatment of predominantly classic lesions. Table 5 provides a comparison of pegaptanib and ranibizumab in the treatment of all lesions (i.e., lesions of any of the subtypes).

Strategy	Total Cost	Total Effectiveness (QALYs)	Incremental Cost	Incremental Effectiveness (QALYs)	Incremental Cost-Effectiveness Ratio (Cost/QALYs)
Treat with pegaptanib (Macugen)	\$96,975	5.98			
Treat with PDT with verteporfin	\$102,472	5.60	\$5,497	-0.37	Dominated
Treat with ranibizumab (Lucentis)	\$140,706	6.75	\$43,731	0.78	\$56,382

PDT=photodynamic therapy; QALYs=quality-adjusted life years.

Figure 4: Comparison of ranibizumab, pegaptanib, and V-PDT for treatment of persons with predominantly classic lesions



QALYs=quality-adjusted life years; V-PDT=photodynamic therapy with verteporfin.

In Table 4 and Figure 4, we see that for treatment of PC lesions, pegaptanib is the least expensive option, and V-PDT the least efficacious. Treatment with V-PDT is marginally more expensive and less efficacious than pegaptanib, meaning that treatment with pegaptanib dominates V-PDT.

Table 4 details the components of the ICER for ranibizumab when compared with V-PDT. Here we find that the improved efficacy of ranibizumab results in an average gain of 0.78 QALYs for people with PC lesions after discounting over their remaining lifetime. However, this gain comes at a cost of \$43,731, resulting in an ICER of \$56,382 per QALY when compared with pegaptanib.

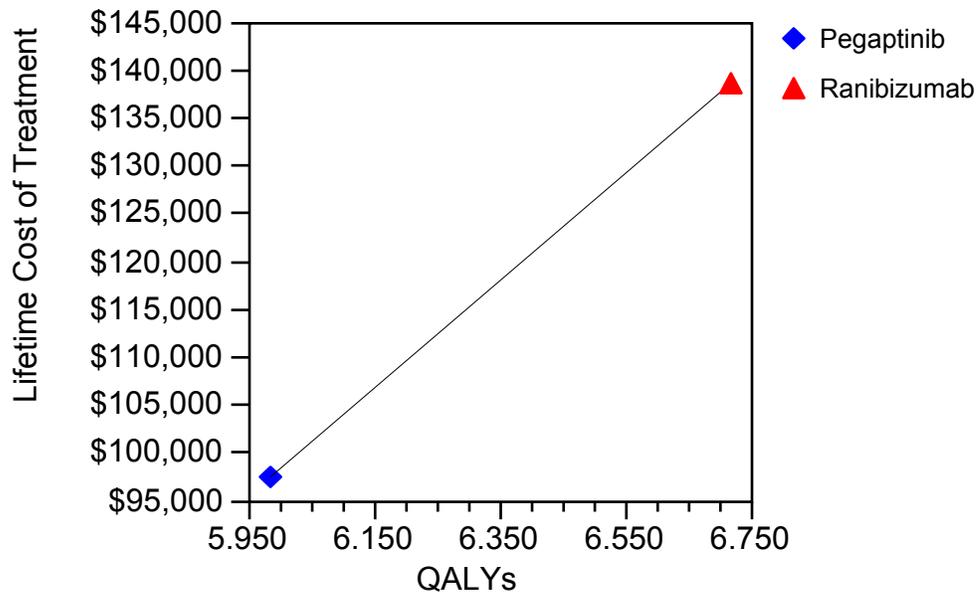
In Table 5 and Figure 5 we describe results for the treatment of lesions of all subtypes using ranibizumab and pegaptanib. The superior efficacy of ranibizumab again results in a gain in lifetime QALYs, here 0.73. This gain comes at a cost of \$41,163, resulting in an ICER of \$56,194.

Table 5: Comparison of the cost-effectiveness of strategies for treatment of persons with all neovascular lesions

Strategy	Total Cost	Total Effectiveness (QALYs)	Incremental Cost	Incremental Effectiveness (QALYs)	Incremental Cost-Effectiveness Ratio (Cost/QALYs)
Treat with pegaptanib (Macugen)	\$97,569	5.98			
Treat with ranibizumab (Lucentis)	\$138,733	6.72	\$41,163	0.73	\$56,194

QALYs=quality-adjusted life years.

Figure 5: Comparison of ranibizumab and pegaptanib for treatment of persons with all neovascular lesions



QALYs=quality-adjusted life years.

5.4.2 Sensitivity analyses

The results of our sensitivity analyses are provided in Table 6. While all variables in the model were tested across the entire clinically relevant range, only the cost of ranibizumab and the change in visual acuity were found to result in a change in the cost-effectiveness decision (i.e., resulted in an ICER for ranibizumab versus the comparator of a willingness to pay less than \$50,000 per QALY). As V-PDT was dominated by pegaptanib, we report the results of sensitivity analyses only for ranibizumab versus pegaptanib.

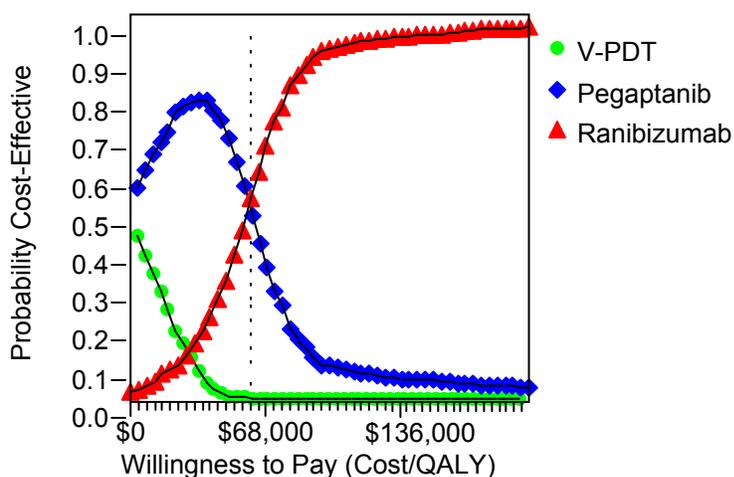
For treatment of PC lesions, the cost of ranibizumab must be less than \$20,500, or a reduction in annual cost of treatment of \$663 (5% base case discount rate), to meet a willingness to pay of \$50,000/QALY. Alternatively, if it were shown that treatment with ranibizumab resulted in an additional improvement of 0.5 letters correct (to 10.73) over 10.23 letters, then treatment with ranibizumab would meet that standard. Finally, if the improvement in utility associated with a decimal unit improvement in vision was 0.41 instead of 0.37, then ranibizumab would also meet that standard.

The cost-effectiveness acceptability curves for people with PC lesions and those with lesions of any subtype are provided in Figures 6 and 7. In Figure 6, we see that a policy for treatment of PC lesions with ranibizumab has the highest probability of being the most cost-effective strategy at a willingness-to-pay threshold greater than \$59,000/QALY (the vertical line). At a willingness-to-pay threshold of \$78,000, ranibizumab is the most cost-effective strategy in over 80% of the simulations. Only at the lowest willingness to pay (below \$10,000/QALY) is V-PDT the most cost-effective strategy in 30% or more of the simulations.

Table 6: Sensitivity analysis for comparison of ranibizumab and pegaptanib				
Variable	Base Case	Threshold Value that Makes Ranibizumab Cost-Effective at \$50,000/QALY		
		0%	3%	5%
Discount rate		0%	3%	5%
Annual cost of ranibizumab treatment	\$21,163	\$19,800	\$20,300	\$20,500
Change in visual acuity due to ranibizumab treatment (letters correct)	10.23±0.44	11.28	10.95	10.73
Utility associated with vision (coefficient for Equation 1)	0.37	0.43	0.42	0.41

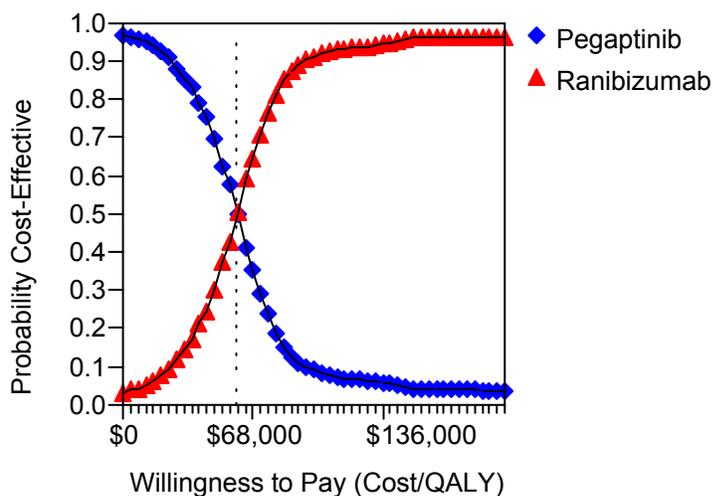
QALY=quality-adjusted life year.

Figure 6: Cost-effectiveness acceptability curves for the treatment of PC lesions



PC=predominantly classic; QALY=quality-adjusted life year; V-PDT=photodynamic therapy with verteporfin.

Figure 7: Cost-effectiveness acceptability curves for the treatment of all lesions



QALY=quality-adjusted life year.

Figure 7 provides a similar narrative for treatment of all lesions. Here we see that at a willingness to pay of \$50,000/QALY or less, pegaptanib provides more net benefit than does ranibizumab in nearly 65% of the simulations. It is only at a willingness to pay in excess of \$59,000 that treatment with ranibizumab has a higher probability of being cost-effective compared with pegaptanib (i.e., the most cost-effective strategy in over 50% of simulations). However, at a willingness to pay in excess of \$78,000/QALY, ranibizumab is cost-effective in over 80% of simulations.

5.4.3 Discussion

Of the three treatments analyzed for treatment of neovascular macular degeneration — PDT with verteporfin, pegaptanib, and ranibizumab — only ranibizumab demonstrated a reversal of the degenerative process. However, our analyses indicate that the premium required for this medication marginally exceeds cost-effectiveness based on a willingness to pay of \$50,000 per QALY. This could be achieved if the price of ranibizumab was reduced by 3.5% from \$1,575 per dose.

A second possible approach to reducing the cost of treatment by ranibizumab would be to reduce the frequency of treatment. As a 3.1% reduction in the total cost of treatment is required at a willingness to pay of \$50,000 per QALY, this could be achieved by reducing the number of treatments per year below the 12 used in the ANCHOR¹⁷ and MARINA³³ trials. While there have been some anecdotal reports supporting less frequent treatment, good quality clinical evidence suggesting benefit can be maintained with such a strategy is lacking. Therefore we were required to assume a monthly dosage schedule for the model. Should new clinical evidence be brought to light, this issue might be revisited. A summary of how many retinal specialists are in practice using pro re nata dosing schedules has been previously reported.⁷³

As we noted in Table 6, the cost-effectiveness decision is sensitive to the utility estimates upon which effectiveness (as measured by QALYs) is based. Relatively small changes in the coefficient defining the relationship between visual acuity as measured in decimal units (see Equation 1), influence the cost-effectiveness decision. Indeed, for someone with 20/100 vision at baseline, a change in utility of 0.01 units over that gained in the base case would result in treatment with ranibizumab being considered to be cost-effective at \$50,000 per QALY. This being the case, it should be recognized that this utility algorithm, while having undergone the rigors of peer review, has not been widely validated in other studies.

Another issue that merits discussion is the role of bevacizumab (Avastin) in the treatment of macular degeneration. Bevacizumab is a drug that many clinicians have argued has similar clinical performance to ranibizumab in treatment of choroidal neovascular disease, as they share similar molecular properties.⁷⁴⁻⁷⁶ However, it is considerably less expensive than ranibizumab. While our systematic review did not identify strong clinical evidence concerning the efficacy of bevacizumab, we conducted an analysis of the cost-effectiveness of treatment of macular degeneration, making the assumption that the clinical performance of bevacizumab would be similar to that of ranibizumab. The results for lifetime costs are provided in Table 7 for treatment of predominantly classic lesions. With this approach, the annual cost of treatment with bevacizumab was \$2,461, or 12% of the cost of treatment with ranibizumab. Our results show that bevacizumab would dominate either pegaptanib or V-PDT for treatment of PC lesions. Similar results were found for treatment of all lesions, so bevacizumab would also dominate ranibizumab for this application.

As it might be argued that bevacizumab might have inferior clinical performance, or more severe adverse events, compared with ranibizumab, we performed sensitivity analyses to evaluate how

much weaker the performance of bevacizumab would have to be in order for ranibizumab to meet standards of cost-effectiveness. We found that use of bevacizumab must generate less than 4.21 QALYs for ranibizumab to meet the \$50,000/QALY willingness-to-pay threshold if both treatments are included in the evaluation. This would imply that bevacizumab would be less efficacious than either pegaptanib or V-PDT. As this is highly unlikely, it would seem that if bevacizumab were found to be an appropriate agent for treatment of choroidal neovascular disease, it would be unlikely that ranibizumab would be considered to be an effective medication for this purpose. In this finding we support work by Raftery⁵² *et al.* that found the efficacy of bevacizumab would need to be less than half of that of ranibizumab to justify the cost premium for the latter medication. It should be recognized, however, that bevacizumab has not been approved for intravitreal injection in Canada and that there is currently no compelling clinical evidence concerning its efficacy or adverse events in the treatment of retinal disease.

Table 7: Comparison of the cost-effectiveness of strategies for treatment of persons with predominantly classic lesions

Strategy	Lifetime Cost	Total Effectiveness (QALYs)	Incremental Cost	Incremental Effectiveness (QALYs)	Incremental Cost-Effectiveness Ratio (Cost/QALYs)
Treat with bevacizumab (Avastin)	\$13,433	6.73			
Treat with pegaptanib (Macugen)	\$97,356	5.99	\$83,922	-0.75	Dominated
Treat with PDT with verteporfin	\$103,743	5.61	\$90,309	-1.13	Dominated

PDT=photodynamic therapy; QALYs=quality-adjusted life years.

Another strategy that has also received some attention is the use of combinations of ranibizumab and other treatments. For instance, some have speculated that V-PDT might be used to induce a better, longer lasting response to ranibizumab, and thus require fewer treatments. Alternatively, treatment might be started with ranibizumab and once response is gained, it would be maintained by pegaptanib. Either of these might present a cost-saving option (and thus meet standards of cost-effectiveness), but again, in the absence of strong clinical evidence to support evaluation, it would be premature to consider these options.

In this model, we did not explicitly consider the role of intravitreal steroids such as triamcinolone (Kenalog) to augment the treatment with V-PDT. However, it is our understanding that the primary purpose of these treatments is to reduce adverse events. As the rate of adverse events was not found to change the cost-effectiveness decision, and the price of the medication is nominal, it was felt that while these medications have important clinical utility, their role in the cost-effectiveness decision may be nominal. This may change if evidence comes out that they reduce the number of V-PDT treatments needed.

6 HEALTH SERVICES IMPACT

6.1 Population Impact

Table 8 illustrates the impact of AMD on the Canadian population in 2006.¹ We estimate the number of neovascular AMD patients in Canada at 183,000, comprising 1.16% of Canadians aged 40 or older.

Type of AMD	Population	Prevalence (percentage of Canadians aged 40 and older)
Drusen \leq 125 μ m	965,000	6.14%
Advanced	253,000	1.61%
Total AMD	1,218,000	7.75%
Total neovascular AMD*	183,000	1.16%

*Taking 15% as the proportion of AMD that is “wet” or neovascular AMD.³
AMD=age-related macular degeneration.

There is a scarcity of data on the economic burden of AMD in Canada. A US study estimated the cost at US\$575 million for 2006, including costs to the health care system and patients.⁷⁷ The cost of support services for patients with AMD in the UK has been estimated at £6,455 in the first year of blindness and £6,295 in subsequent years.⁵¹

6.2 Budget Impact

Recognizing that not all the treatments examined in this review are currently available or widely used for neovascular AMD, Table 9 shows the potential drug cost impact of each intervention. We estimate annual drug cost per patient, as well as annual drug cost for all neovascular AMD patients if that intervention was used exclusively. This assumes the existing health infrastructure and human resources have the capacity to treat 40,000 patients per year.

6.3 Planning and Implementation Issues

In the verteporfin-PDT era, patients typically were referred to a specialty centre for consultation by a retina specialist and subjected to fluorescein angiography and clinical stereoscopic fundus examination, after which a decision was taken to perform verteporfin-PDT therapy or not. The process was repeated every two to three months (three months according to protocol) with a decision to re-treat based on leakage detected by fluorescein angiography alone.

Anti-VEGF therapy has added considerably to the logistical complexity of timely delivery of ongoing care, access to initial assessment, and follow-up care for AMD. Now, in addition to the above, the initial assessment includes optical coherence tomography repeated every four to six weeks to determine if intravitreal drug injection should occur based on a variety of criteria, including subretinal or intraretinal fluid, retinal thickening, or leakage detected angiographically in addition to stereoscopic macular assessment. Repeat injections are adding a tremendous burden to already busy clinics, with increasing numbers of patients being referred for therapy for which higher expectations are associated. The volumes of injections are causing logistical problems in many clinics and must be performed aseptically if the endophthalmitis rate is to be kept to acceptably low levels.

Table 9: Budget impact comparisons of neovascular AMD treatments

Intervention	Drug Cost per Treatment (\$)	Number of Treatments per Year	Annual Drug Cost per Patient (\$)	Annual Drug Cost for All Neovascular AMD Patients (\$)
V-PDT*	1,800.00	2	3,600	144,000,000
pegaptanib	995.00 ⁶⁴	8.7 (once every six weeks)	8,657	346,280,000
ranibizumab	1,575.00	12 (once a month)	18,900	756,000,000
bevacizumab [†]	21.43 ⁶⁴	12 (once a month)	257	10,280,000
anecortave acetate monotherapy [‡]	1,735.22	2 ⁵³	3,470	138,800,000
triamcinolone (combination therapy only)	Kenalog 6.82 ⁶⁵	2 (V-PDT)	14	560,000
		8.7 (pegaptanib)	59	2,360,000
		12 (ranibizumab or bevacizumab)	82	3,280,000
	Generic 4.77 ⁶⁵	2 (V-PDT)	10	400,000
		8.7 (pegaptanib)	41	1,640,000
		12 (ranibizumab or bevacizumab)	57	2,280,000

*Verteporfin drug cost only. Does not include the cost of photodynamic therapy. Verteporfin plus photodynamic therapy (excluding physician cost) is \$2,946.22.

[†]Based on one 4 mL vial of bevacizumab at \$600 and 28 doses available from the vial.

[‡]Anecortave acetate is approved for AMD in Australia. Conversion rate: 1 Australian dollar=0.87 Canadian dollars (Aus\$1,985.38).⁶⁶ AMD=age-related macular degeneration.

The fee for injection varies greatly across the country, which may pose a problem for uptake of appropriate new therapies by clinicians in some provinces. Instead of the traditional practice of selling the drug through pharmacies, physicians are selling the drug made up by compounding pharmacies in the case of bevacizumab, while in the case of ranibizumab the option exists for physicians to be the purveyor of wholesale-priced drugs as well, ostensibly to lower the price to patients. This involvement by physicians in selling products as well as providing services is already raising alarm in certain health jurisdictions, not only from the point of view of protecting the safety of the drug supply, but also because of the possibility of great inequity of pricing. Prices charged to patients vary across different jurisdictions as well as within jurisdictions. Therefore coherent health policy direction in this area of new health technology is greatly needed.

Regarding the research questions relating to timing of initiation of therapy and re-treatment with a different regimen, the scant nature of the evidence does not allow us to draw conclusions on this.

6.4 ETHICAL AND PSYCHOSOCIAL ISSUES

6.4.1 Methods

Given that ethical and psychosocial issues were not a separate objective of this report, a formal literature search was not conducted for this section. LM and AB reviewed literature search results from the clinical and economic reviews for information regarding informed consent, service availability, equity, knowledge and training, psychological impact, social and family context, and effect of cognitive or physical factors on treatment eligibility.

Papers included in the clinical and economic reviews were searched for relevant information based on a data extraction form established a priori. One reviewer (LM) extracted information regarding

ethical and psychosocial issues related to the pharmacologic management of AMD, while AB verified accuracy. Any discrepancies were resolved by consensus.

6.4.2 Results

Of the papers selected for the clinical and economic reviews, five publications met the criteria for ethical or psychosocial content.^{20,23,47,48,52} Two articles from the clinical review provided content regarding ethical issues,^{20,23} and one review provided content regarding psychosocial issues.⁴⁸ An article identified in the economic review and two systematic reviews provided content regarding equity and access.^{47,48,52}

Ethical issues associated with the VIP and TAP trials were commented on in two articles that assessed inclusion criteria for possible biases of lesion size and visual acuity at baseline compared with natural history of visual acuity loss in different lesion compositions.^{20,23} These clinical trials suggest that treating smaller rather than larger neovascular lesions, regardless of lesion composition, likely results in better visual acuity.^{20,23} The authors suggest that there may be a duty to withhold verteporfin therapy for patients with large lesions presenting with good visual acuity, unless a recent history of vision loss is established.²⁰

Ethical issues arise when drugs that hold potential benefits for AMD patients are not accessible due to cost or availability for use by indication. Ranibizumab is licensed for AMD treatment at a price of \$1,575 per injection, while bevacizumab is used globally as a low-cost off-label alternative.⁵² This has ethical implications, since there is currently no clinical trial evidence of the efficacy of bevacizumab in treating AMD compared with placebo or ranibizumab. While Genentech owns both drugs in the United States, the company does not plan to seek approval of bevacizumab for AMD. The authors of this study suggest that continued off-label use of bevacizumab raises ethical, legal, and policy questions, as prescribers may feel compelled to use the more expensive licensed drug.⁵² While, in the United Kingdom, NICE plans to issue guidance on ranibizumab compared with supportive care, and on V-PDT late in 2007, bevacizumab has been omitted from their appraisal because it is not licensed for AMD in the UK. The authors suggest that a recommendation in favour of ranibizumab would make recruitment for a head-to-head comparison trial of ranibizumab versus bevacizumab challenging.⁵²

Access and equity issues may arise in the pharmacological management of AMD due to limited availability of personnel and resources. In 2002, the number of patients eligible for V-PDT exceeded the number of AMD treatments administered in Québec, according to a systematic review.⁴⁷ While 33 retinologists were able to administer V-PDT, only 15 did so in 2002.⁴⁷ Each retinologist performed between 40 and 50 PDT treatments per month or 7,400 treatments per year. In 2003, one hospital reduced its verteporfin budget by approximately 60% and sent less complex cases of AMD to private clinics. Despite hospital savings, patients incurred additional costs as physicians usually bill for medications and co-pay for drugs at a pharmacy depending on the category insured.⁴⁷ The review suggests that AMD patients can not always access V-PDT in a reasonable time frame due to organizational problems and that delayed diagnosis and treatment may result in further loss of vision or less effective treatment.

Similar access and equity issues exist in the United Kingdom where there were approximately 150 to 200 retinal specialists in 2003.⁴⁸ Existing facilities may not be able to accommodate early AMD assessment and treatment of referrals from primary care networks due to limited resources, according to one systematic review.⁴⁸ Extra resources are needed to manage increased referral, diagnosis, and

treatment. The review highlights issues of equity. Firstly, interventions in older persons have historically been considered a less favourable investment than those affecting younger persons, because of perceptions that health benefits are less likely to occur in older individuals.⁴⁸ The authors caution that care must be taken to ensure this perception does not preclude the decision on whether the benefits are worth the costs of verteporfin therapy. Secondly, the report cites some evidence to suggest inequitable access may exist because much of this therapy is privately funded.⁴⁸

There are inherent psychosocial issues associated with access to AMD treatment and the potential for vision loss associated with delayed diagnosis, assessment, and treatment. The burden of care on individuals, partners, and families is great, and treatments that reduce this burden or improve quality of life or independence are welcomed.⁴⁸ A summary of the key ethical and psychosocial issues associated with pharmacological management of AMD is presented in Table 10, and a more detailed summary appears in Appendix 21.

Table 10: Summary of results for ethical and psychosocial issues	
Author	Key Issue
Blinder <i>et al.</i> , 2003 ²⁰ Arnold <i>et al.</i> , 2001 ²³	For patients with large lesions presenting with good visual acuity, there may be a duty to withhold verteporfin therapy unless a recent history of vision loss is established. ^{20,23}
Raftery <i>et al.</i> , 2007 ⁵²	Continued off-label use of bevacizumab raises ethical, legal, and policy issues. The burden of care on individuals, partners, and families is great, and treatments that reduce this burden or improve quality of life or independence are welcome. ⁵²
AETMIS, 2005 ⁴⁷	Organizational problems prevent patients from accessing V-PDT within a reasonable time frame. Sending patients to private clinics when hospital budgets are cut may lead to equity issues. ⁴⁷
NHS, 2003 ⁴⁸	Existing facilities may not be able to accommodate early AMD assessment and treatment of referrals from primary care networks due to limited resources. Equity issues exist when health benefits are perceived as being less likely to occur in older individuals. Inequitable access may exist because much therapy is privately funded. The burden of care on individuals and their families is great, and treatments that reduce this burden or improve quality of life or independence are welcomed. ⁴⁸

6.4.3 Discussion

The review of clinical and economic papers brought forward limited information regarding ethical and psychosocial issues related to pharmacological management of AMD. Ethical issues are encountered in selecting patients who would benefit from therapy. Patients must be provided sufficient information regarding limitations in the current evidence to ensure informed consent to therapy. There may be a duty to withhold therapy for patients with large lesions presenting with good visual acuity unless they have experienced recent vision loss. Access is of issue in Canada and the United Kingdom as existing systems are over-extended in meeting resource needs to achieve early referral, diagnosis, and treatment within an effective therapeutic window. Equity issues are encountered as patients incur the costs of treatment at private clinics. Continued off-label use of bevacizumab raises ethical, legal, equity, and policy implications.

7 CONCLUSIONS

The review of clinical evidence found that, with the exception of trials comparing ranibizumab with V-PDT, there was a significant lack of trials comparing the other anti-VEGF agents in general. There is only one RCT that looked at the efficacy and safety of anecortave acetate compared with V-PDT. However, although results have shown seemingly effective visual acuity improvement with bevacizumab, this was based only on three poorer quality RCTs. Whether generalizations from ranibizumab to bevacizumab can be made is not clear from the evidence identified.

Ranibizumab showed statistically significant improvement in visual acuity (in terms of loss of less than 15 letters or gain of at least 15 letters on the ETDRS scale) relative to baseline and to V-PDT. Compared with V-PDT, ranibizumab improved vision by an increase of 4.9 to 11.3 letters on the ETDRS scale on average at 12 months post-treatment. Other vision outcomes involving vision loss also favoured ranibizumab over V-PDT. When examining lesion characteristics, ranibizumab-treated eyes showed a smaller increase in lesion size over V-PDT as well as an increase in lesion shrinkage over V-PDT. The only trial that compared anecortave acetate and V-PDT showed that both failed to improve visual acuity in patients. Although long-term studies are lacking, current studies suggest that ranibizumab does not produce significant additional systemic adverse events. Local adverse events that were compared with V-PDT included post-injection increases in intraocular pressure and cataract formation, endophthalmitis, retinal detachment, retinal tears, and vitreous hemorrhages.

Six non-RCT studies suggest the combination therapies analyzed are effective. These combination therapies are typically a combination of V-PDT and anti-VEGF therapies. However, inferences regarding relative efficacy cannot be made from these study designs. Conclusions drawn by these studies need to be confirmed by results of future larger-scale randomized controlled trials.

Overall, the efficacy of anti-VEGF therapies over V-PDT is well supported by RCTs. What remains unclear is whether combination therapy (and which combinations) are superior or merely equal to monotherapy. Furthermore, the efficacy of one anti-VEGF agent compared with another is also unclear, and this has very important practical and economic implications. The scant nature of the evidence does not allow us to draw conclusions regarding optimal timing of initiation of therapy and re-treatment.

Between V-PDT, pegaptanib, and ranibizumab, only ranibizumab demonstrated a reversal of the degenerative process for neovascular CNV, on average. The primary economic evaluation found that the premium for using ranibizumab would not be considered cost-effective using a willingness to pay threshold of \$50,000. A 3.5% reduction in the price of ranibizumab would be required to achieve that. Alternately, this might be achieved by reducing the frequency of treatment below that used in the clinical trials. However evidence for the impact this might have on effectiveness is lacking. Using bevacizumab as a substitute for ranibizumab could be more effective and less costly than either V-PDT or pegaptanib. However, there is currently limited clinical trial evidence on the efficacy and safety of bevacizumab in the treatment of AMD.

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APPENDICES

**Available from CADTH's web site
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