

Until April 2006, the Canadian Agency for Drugs and Technologies in Health (CADTH) was known as the Canadian Coordinating Office for Health Technology Assessment (CCOHTA).

Publications can be requested from:

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

or download from CADTH's web site:
<http://www.cadth.ca>

Cite as: Foerster V, Murtagh J, Fiander M, *Pulsed dye laser therapy for port wine stains* [Technology Report number 78]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2007.

Production of this report is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon. The Canadian Agency for Drugs and Technologies in Health takes sole responsibility for the final form and content of this report. The views expressed herein do not necessarily represent the views of Health Canada or any provincial or territorial government.

Reproduction of this document for non-commercial purposes is permitted provided appropriate credit is given to CADTH.

CADTH is funded by Canadian federal, provincial, and territorial governments.

Legal Deposit – 2007
National Library of Canada
ISBN: 1-897257-82-1 (print)
ISBN: 1-897257-83-X (online)
I3008 – March 2007

PUBLICATIONS MAIL AGREEMENT NO. 40026386
RETURN UNDELIVERABLE CANADIAN ADDRESSES TO
CANADIAN AGENCY FOR DRUGS AND TECHNOLOGIES IN HEALTH
600-865 CARLING AVENUE
OTTAWA ON K1S 5S8

Canadian Agency for Drugs and Technologies in Health

Pulsed Dye Laser Therapy for Port Wine Stains

Vicki Foerster, MD MSc CCFP

James Murtagh, MHA CHE

Michelle Fiander, MA MLIS¹

March 2007

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



Health technology assessment (HTA) agencies face the challenge of providing quality assessments of medical technologies in a timely manner to support decision making. Ideally, all important deliberations would be supported by comprehensive health technology assessment reports, but the urgency of some decisions often requires a more immediate response.

The Health Technology Inquiry Service (HTIS) provides Canadian health care decision makers with health technology assessment information, based on the best available evidence, in a quick and efficient manner. Inquiries related to the assessment of health care technologies (drugs, devices, diagnostic tests, and surgical procedures) are accepted by the service. Information provided by the HTIS is tailored to meet the needs of decision makers, taking into account the urgency, importance, and potential impact of the request.

Consultations with the requestor of this HTIS assessment indicated that a review of the literature would be beneficial. The research question and selection criteria were developed in consultation with the requestor. The literature search was carried out by an information specialist using a standardized search strategy. The review of evidence was conducted by one internal HTIS reviewer. The draft report was internally reviewed and externally peer-reviewed by two or more peer reviewers. All comments were reviewed internally to ensure they were addressed appropriately.

Reviewers

CADTH takes sole responsibility for the final form and content of this bulletin. The statements and conclusions in this bulletin are those of CADTH and not of the reviewers:

Charles Lynde, MD FRCPC,
Assistant Professor, University of Toronto
University Health Network, Toronto Western Division
Toronto ON

Jerry K.L.Tan, BSc, MD, FRCPC
Adjunct Professor
Department of Medicine, University of Western Ontario
London ON

Mariusz Sapijaszko, MD, FRCPC(Dermatology), Fellow American Academy of Cosmetic Surgery
Clinical Assistant Professor, Division of Dermatology, Department of Medicine, University of Alberta
Director, Western Canada Dermatology Institute
Edmonton AB

The Health Technology Inquiry Service (HTIS) is an information service for those involved in planning and providing health care in Canada. HTIS responses are based on a limited literature search and are not comprehensive, systematic reviews. The intent is to provide a list of sources and a summary of the best evidence on the topic that CADTH could identify using all reasonable efforts within the time allowed. HTIS responses should be considered along with other types of information and health care considerations. The information included in this response is not intended to replace professional medical advice, nor should it be construed as a recommendation for or against the use of a particular health technology. Readers are also cautioned that a lack of good quality evidence does not necessarily mean a lack of effectiveness particularly in the case of new and emerging health technologies, for which little information can be found, but which may in future prove to be effective. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete, and up to date, CADTH does not make any guarantee to that effect. CADTH is not liable for any loss or damages resulting from use of the information in the report.

Copyright: This report contains CADTH copyright material. It may be copied and used for non-commercial purposes, provided that attribution is given to CADTH.

Links: This report may contain links to other information available on the web sites of third parties on the Internet. CADTH does not have control over the content of such sites. Use of third party sites is governed by the owners' own terms and conditions.

TABLE OF CONTENTS

ABBREVIATIONS	V
1 CONTEXT AND POLICY ISSUES.....	1
2 RESEARCH QUESTIONS.....	2
3 METHODS	2
4 SUMMARY OF FINDINGS	3
4.1 Quasi-systematic reviews.....	3
4.2 Clinical studies	4
4.3 Economics and costs	6
4.4 Limitations of evidence.....	6
4.5 Limitations of current review.....	7
5 CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING.....	7
6 REFERENCES.....	8
APPENDIX 1: DETAILS OF INCLUDED CLINICAL STUDIES	11

ABBREVIATIONS

AE	adverse events
HTA	health technology assessment
IPL	intense pulsed light
MD	medical doctor
Nd:YAG	neodymium:yttrium-aluminum garnet
PDL	pulsed dye laser
PWS	port wine stain
SR	systematic review

Title: Pulsed Dye Laser Therapy for Port Wine Stains

Date: January 30, 2007

1 CONTEXT AND POLICY ISSUES

Port wine stains (PWS), which are the most common type of capillary vascular malformations, are congenital, occurring in three to five of every 1,000 births. Gender distribution is equal.¹⁻³ Although they are benign, these lesions can be disfiguring. Most (80% to 90%) occur in the head and neck, starting as flat pink to red lesions that may darken to a deeper shade of red or blue, sometimes becoming thicker and more nodular as a child grows to adulthood. They do not spontaneously resolve.¹⁻⁵ In rare cases, PWS are associated with other vascular, soft tissue, and neurological findings as part of the Sturge-Weber or Klippel-Trenaunay syndromes.⁵

A PWS results from an abnormal network of dilated blood vessels in the dermis, lying 100 μm to 1,000 μm below the skin's surface. The overlying epidermis is normal. The diameters of the blood vessels vary from 10 μm to 300 μm .⁴ The pathogenesis is unclear, but the condition could be due to a deficiency in the autonomic innervation of vessels, so that these vessels dilate progressively through life.^{6,7}

Commonly reported sequelae of PWS are stigmatization, sadness, stress, and low self esteem.^{1,8,9} The negative effects can have repercussions for parents and for affected children and adolescents, particularly those aged 10 to 20 years.⁹ As a result, treatment is not just cosmetic, but reconstructive as well.¹

In attempts to remove or lighten PWS, many types of therapy have been tried, including cosmetic make-up, skin excision, skin grafting, radiation, dermabrasion, cryosurgery, tattooing with skin-tone colours, and electrotherapy.^{1,4,10} Satisfactory results were not obtained from these interventions. Beginning in the 1980s,

alternatives such as laser therapy were pursued.¹¹

The term "laser" stands for light amplification by stimulated emission of radiation. The effect of laser light on tissue is a function of the type of tissue, wavelength (nm) of the laser, the power used, and whether the light is pulsed or continuous.¹² Different target tissues selectively absorb different light wavelengths, so that specific lasers must be chosen for specific types of treatment. Ideally, light can be focused onto a tissue target where it becomes heat and causes local destruction (known as photothermolysis), while sparing adjacent healthy tissue.¹³

Various types of lasers have been tested, but the most successful for the management of PWS, which was introduced in 1985, has been the flashlamp-pumped pulsed dye laser (PDL) that emits a pulsed beam of yellow light at 585 nm and selectively targets hemoglobin.¹ For PWS, the target tissue is the hemoglobin in the blood vessels that form a vascular lesion. PDL light causes agglutination of erythrocytes, thrombus formation, and eventual destruction of a blood vessel.¹⁴ The objective is to reduce the number and size of these vessels.¹⁵

Because the vessels are of various sizes and depths in the skin, different laser wavelengths and pulse durations have been tried. Initially, continuous-wave argon lasers with absorption peaks of 488 nm to 514 nm were used to target hemoglobin, but unacceptable rates of scarring and pigmentation arose because these wavelengths also allow absorption by melanin. A search for superior laser therapies ensued.

Changing the pulse duration and spot size varies the laser's penetration into the dermis. Deep penetration is required to target the larger calibre and more deeply seated vessels forming a PWS. Care must be taken in delicate areas (periorbital regions) and those that scar readily (anterior chest, neck).¹³ Clinicians may test small areas of a PWS first to determine the clinical response obtained from various PDL settings or types of technologies.¹⁵

Despite some success achieved with the 585 nm PDL laser, clearance of a PWS is not generally achieved, with up to 30% of lesions being resistant to treatment.^{7,16} Laser penetration is decreased in more darkly pigmented people, and this may result in less satisfactory results. These challenges have led to a continuing quest for alternatives including second-generation and third-generation PDLs; exploration of combinations of types of therapy; and the addition of cooling sprays to protect epidermal tissue, reduce pain, and prevent pigmentary changes.^{15,17} Several studies have explored the newer laser alternatives and their use in defined populations, particularly people of Asian descent.

Health Canada reviews medical devices to assess their safety, effectiveness, and quality before they are authorized for sale. The only PDL approved for marketing in Canada is the Candela PDL Dermatologic Laser with Dynamic Cooling Device known as the VBeam[®] (Candela Corporation, Wayland, MA), which has been assigned a Class III designation. A licence for the device was initially granted in May 2001, with device modifications subsequently approved.¹⁸ In the US, the Food and Drug Administration has approved the Candela “family” of PDLs for benign cutaneous vascular lesions such as PWS, telangiectasia, rosacea, and hemangioma; and benign cutaneous lesions such as warts, scars, striae, and psoriasis.^{19,20}

The VBeam, which has been described as the newest PDL technology, uses a wavelength of 595 nm and extended pulse durations from 450 to 1,500 μ s. It is 20 times more powerful and 18 times faster than the original PDL, and lighter in weight at 400 pounds (versus the original models that weighed 1,000 pounds).²¹ According to the manufacturer’s web site, the VBeam eliminates post-treatment purpura (a form of bruising). Its long duration of action means that power can be delivered at a lower peak energy to coagulate rather than destroy the targeted blood vessels.²² Some purpura in response to treatment is desirable, however, because less benefit has been observed when purpura is minimized.^{3,4,13}

The ability of a 595 nm laser to penetrate deeper into the skin means that this technology is useful for specific types of PWS,²¹ although 585 nm PDL technology is often called the treatment of choice for PWS.^{4,12,23} Alternative technologies have been investigated for the treatment of PWS including the CO₂ laser, the copper vapour laser, intense pulsed light (IPL) devices, and neodymium:yttrium-aluminum garnet (Nd:YAG) lasers.^{4,11} Some authors comment that these technologies may result in higher side effect rates than PDL. Therefore, they may not be used as solitary therapies, although they may be combined with or used after PDL to enhance clearance rates.^{13,15,17}

Ongoing research is focused on PDL innovations including changes in wavelength, pulse duration, light dosage, and degree of skin cooling.^{3,13,24} Individualized treatment is becoming desirable. PDL therapy produces good results in a limited population of patients with PWS, but finding an appropriate PWS treatment protocol has become more complicated as manufacturers introduce devices that allow operators to vary treatment parameters.²⁴

Provincial insurers have queried the procedure’s clinical benefit as they note significant growth in the pressure to fund this therapy for lesions such as PWS.

2 RESEARCH QUESTIONS

1. Is PDL therapy clinically effective in the management of PWS?
2. Does effectiveness vary according to clinical situations or patient groups?
3. Is PDL therapy for PWS cost-effective?

3 METHODS

A literature search was conducted by an information specialist using health technology assessment (HTA) resources including MEDLINE[®], EMBASE[®], BIOSIS Previews[®], The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD)

databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search.

Because the technology has been in use for decades, it is the topic of a large body of literature. Consequently, the literature search was limited to articles published in English between 2000 and November 2006. The results of the literature search were reviewed, and articles that reported on the use of PDL for PWS were selected, evaluated, and summarized. The draft report was internally reviewed and then externally reviewed by peer reviewers. Subsequent changes to the report were reviewed internally to ensure that reviewers' comments had been appropriately addressed.

4 SUMMARY OF FINDINGS

The literature search resulted in 137 citations, of which 40 were deemed to be relevant. These were reviewed in full text. The 40 articles included 27 clinical studies, 10 reviews, two quasi-systematic reviews, and one quality of life analysis.

4.1 Quasi-systematic reviews

No rigorous systematic reviews (SRs) or HTAs were located, although two "quasi" SRs were retrieved. In both cases, the authors implied that their reports were SRs or HTAs, although neither is comprehensive or systematic:

- De Borgie *et al.*,¹
 - These authors from The Netherlands examined the introduction of PDL for the management of facial PWS in children. They were concerned that PDL had emerged without a systematic evaluation of the associated costs and benefits.
 - The 10 studies that were reviewed were published between 1989 and 1998, with sample sizes ranging from 12 to 134 children (age range three months to 17 years). The methods for identifying or selecting studies were not described. An evidence table including clinical outcomes was provided. Overall clearance rates of

>50% were reported for 73% to 100% of the children in the study.

- The burden of illness was found to be significant (particularly the psychosocial impact). The authors concluded that PDL treatment of facial PWS in children is justifiable for two reasons: prevention of psychological morbidity and improvements in health status. They observed that children should be treated as young as possible to avoid the disturbances observed between ages 10 and 20 years.
- The safety and efficacy of PDL were examined as were the factors associated with negative patient outcomes (vessels that were large or deep).
- No cost-effectiveness studies were located.
- The authors concluded that the use of 585 nm PDL was a benefit in the treatment of facial PWS among children, but that the introduction and diffusion of the technology had occurred in an uncontrolled manner without the benefit of iterative HTA processes, and as a result, "the field was not prepared to use the technique properly."
- Smit *et al.*,¹²
 - These authors from the Netherlands examined four indications for PDL: PWS, telangiectasia, scars, and hemangiomas.
 - The authors located 123 trials of which 71 (58%) reported on PDL for the management of PWS. Among the 71 trials, 54% were prospective, 34% were based on objective measurements, and 24% were controlled. Of the 123 trials, 44 (36%) were selected for inclusion in the review, but neither the number of trials included per clinical condition nor the selection criteria were reported (aside from a preference for larger, controlled, prospective trials based on objective measurements). This lack of detail suggests that a rigorous SR was not completed or was inaccurately reported.
 - The location of a PWS was predictive for outcome (lesions on the forehead, lateral

face, and neck responded more favourably than those on the central face, lip, chin, dermatome V2 of the face, and the extremities). Although complete clearance was rare (data were not provided), most patients were satisfied with the outcomes. Although the age at treatment did not influence the degree of lesion lightening, early treatment maximized the psychological benefit.

4.2 Clinical studies

Despite the promising number of studies retrieved, many enrolled small numbers of patients. An analysis of the 27 clinical studies led to the exclusion of 14, based on small samples sizes ($n < 50$). This was done to manage the amount of material presented in this rapid review.

The 13 included case series are reported in Table 1 and described in Appendix 1, according to the following groups: 585 nm laser studies (six),^{6,14,25-28} 595 nm laser studies (two),^{29,30} comparative studies (three),^{7,10,31} and studies examining psychological outcomes (two).^{5,8}

Of the 13 included studies, five were prospective case series.^{7,25,27,29,30} The remaining eight were retrospective analyses conducted through chart review or survey.^{5,6,8,10,14,26,28,31}

Efficacy was determined to be lightening of PWS colour (versus changes in thickness, size, or texture), thus rendering the lesion less visible.⁵ With respect to efficacy, most of the patients in the included studies had results that were categorized as good or excellent, although there were also patients in the majority of studies with minimal responses.

In the five non-comparative case series that examined efficacy,^{14,25-27,30} good or excellent results were obtained in 56% to 90% of patients, whereas poor results occurred in 1% to 20% (1% to 7% in studies where the PWS was limited to the face or neck, versus lesions of the trunk that are more resistant). Four of these studies focused on Asian patients.^{14,26,27,30} These studies were a result of earlier research that had shown a decreased likelihood of response in those with

more skin pigment (due to absorption of the laser energy by melanin). Two studies^{26,27} showed high rates of good to excellent response in these patients, although the remaining two^{14,30} had lower response rates (56% and 67%).

Impressions of benefit varied between patients and treating dermatologists in a study that compared impressions of outcomes.²⁷ The dermatologists awarded more favourable scores than did the patients. The main response was in lightening of PWS colour; the texture, size, and height were less likely to respond, a change that was also observed by other researchers.⁵

Patients generally received multiple treatments (three to seven) that were administered at six- to 12-week intervals over ≥ 1 year. Treatments for adults were generally performed without anesthetic or with the use of topical anesthetic cream. For children, a general anesthetic was more common.

Adverse events (AEs) were mentioned in eight studies,^{7,10,14,25,27,29-31} but the topic was not addressed in the remaining five.^{5,6,8,26,28} AEs were seen as mild and not a deterrent to treatment. Purpura was common and perhaps accepted as the norm, because it was often not described. The same applied to swelling, crusting, and weeping of the lesion, which was explored by Loffeld *et al.*,²⁹ who examined patient-reported morbidity. Less common but consistently present (when AEs were reported) were increases or decreases in pigmentation, although these consistently resolved within months. Permanent AEs such as scarring or hyper- or hypo-pigmentation (side effects of earlier types of technologies) were not reported in any of the studies.

Recurrence rates were studied by three groups:^{6,8,28}

- Michel *et al.*,²⁸ in a retrospective survey of 320 patients in Germany (46% response rate), found that 16% of patients had re-darkening of their PWS after 585 nm PDL treatment. The recurrence rate did not increase with length of follow-up. No children under age 10 ($n=19$) experienced a recurrence, suggesting to the authors that treatment at a young age may be beneficial.

Table 1: List of included studies				
Author	Study Location	Design (all case series or surveys)	Patient Group	Outcome of Interest*
585 nm PDL				
Goh <i>et al.</i> ²⁷	Singapore	prospective	94 Asian patients with PWS of face or neck	efficacy
Michel <i>et al.</i> ²⁸	Germany	retrospective	147 patients surveyed 1+ year post-treatment	recurrence rate
Namba <i>et al.</i> ²⁶	Japan	retrospective	543 treated Asian patients	efficacy
Wang <i>et al.</i> ¹⁴	China	retrospective	194 patients, 95% with PWS of face or neck	efficacy
Bernstein <i>et al.</i> ²⁵	US	prospective	95 consecutive patients (104 areas)	efficacy
Soueid & Waters ⁶	England	retrospective	94 of 110 (85%) children	recurrence rate
595 nm with cooling				
Loffeld <i>et al.</i> ²⁹	England	prospective	51 consecutive patients	patient-reported morbidity
Asahina <i>et al.</i> ³⁰	Japan	prospective	66 of 77 consecutive adult Asian patients	efficacy
Comparisons				
Scherer <i>et al.</i> ⁷	Germany	prospective; 585 versus long-pulsed	62 patients with untreated PWS	efficacy from each wavelength
Chang <i>et al.</i> ³¹	US	retrospective; 585 versus 595	64 Asian patients with PWS of face or neck	efficacy from each wavelength
Verna <i>et al.</i> ¹⁰	Italy	retrospective; 585 versus argon	108 patients with PWS of face from group of 203	efficacy from each technology
Mental health outcomes				
Troilius <i>et al.</i> ⁸	Sweden	retrospective	147 patients treated months to 8 years earlier with PDL (wavelength unspecified)	multiple mental health outcomes
Hansen <i>et al.</i> ⁵	US	retrospective	55 patients treated mean of 7 years earlier with 585 nm PDL	mental health outcomes; some clinical outcomes

*See Appendix 1 for specific outcome measures.

- Troilius *et al.* in Sweden⁸ primarily measured psychosocial reactions to the treatment of PWS, but in their survey they also enquired about recurrence rates. Recurrence was reported by 32 of 122 patients (26%), occurring from months to eight years after completion of treatment (50% of patients had been treated with the less successful pre-PDL therapies).
- In England, Soueid and Waters⁶ examined recurrence rates through a retrospective audit of children treated at one centre from 1997 to 2000. Of the 94 children included in the data analysis, 15 (16%) experienced recurrence a mean of 31 months after treatment completion. The authors explain this as an inability of current laser therapies to eradicate large or deep vessels, thus allowing a lesion to recur. These authors

urge continuing investigation for new types of treatment to ensure eradication of the vessels causing PSW, because otherwise “most or all of treated PWS [will] eventually re-emerge.”

4.3 Economics and costs

To assess quality of life and the personal value that a treatment has for patients, Schiffner *et al.* from Germany³² performed willingness-to-pay and time trade-off analyses through a survey of 36 patients treated with PDL for PWS of the face; 25 patients (69%) completed the survey. After treatment, patients were willing to pay an average of 12% of their monthly income and to devote 1.2 hours per day to an imaginary therapy that would relieve them of their complaints. The authors note that these data corresponded to figures from a survey of patients with psoriasis.

A survey of physicians at 34 laser centres in England³³ revealed that:

- 94% of the centres had PDL technology
- 95% of the physicians considered laser to be the best treatment for PWS (100% for children)
- 95% treated PWS of the head and neck (versus 53% treating the upper limb, 33% the trunk, and 30% the lower limb)
- 81% used general anesthesia at times, particularly for children
- 79% routinely cooled the skin before treatment
- 84% considered two to three months to be the optimal treatment interval.

In their review, De Borgie *et al.*¹ wished to analyze the cost-effectiveness studies of PDL for PWS, but no such studies were located. The authors note that, before a cost-effectiveness analysis can be completed, the clinical effectiveness of a technology must be established. PDL for PSW is complex because the optimal number of treatment sessions, length of each session, length of therapy in months, need for anesthesia, and point at which therapy is discontinued vary among patients.

In one reference to acquisition expense that was located, the typical purchase price was listed as US\$40,000 to US\$90,000.³⁴ The Candela Corp. 2005 annual report states that “most treatments of vascular lesions cost the patient between \$300 and \$800, depending on the length and the type of procedure.”³⁵ This cost is per treatment, and multiple treatments are usually required. Costs for training would be a consideration, although these were not mentioned by any authors. Costs would also be incurred for the delivery of general anesthesia if it is used (primarily for pediatric cases).

4.4 Limitations of evidence

Several studies of PDL for PWS published from 2000 to the present were identified in the literature search. According to narrative reviews on the topic, several studies were conducted before 2000. These were not pursued in an attempt to limit the literature to the most recent evidence available, so that this review could be provided to the requestor in the required timeframe. Despite reasonable numbers of studies, these were of weak design, being case series, retrospective surveys, or retrospective chart reviews.

The two studies^{23,36} that included randomization were both small (n=15) and therefore, were excluded from the detailed analysis. The first was a study from Germany³⁶ that compared 585 nm and 595 nm PDL and two pulse durations, randomizing the 15 enrolled patients to receive different treatments; 585 nm produced superior results. The second was a study from England²³ investigating the optimal gap in treatment time, randomizing the 15 enrolled patients to receive two-week or six-week treatment intervals. Patients receiving treatment every two weeks had better results without suffering more AEs, although the benefit was not quantified.

With a few exceptions, studies were small, analyzing the outcomes of <100 patients. The five studies with >100 patients^{8,10,14,26,28} were all retrospective, each research group reviewing the experience at only one institution. Three studies^{25,30,31} mentioned the use of blinded assessors where physicians analyzed efficacy

using pre- and post-treatment photographs. Common outcome measures were not used across studies, making comparisons difficult.

Subjective measurements (physicians' or patients' impressions of change) were generally used to determine the cosmetic outcomes of treatment. Currie and Monk in England³⁷ explored this issue, noting that for results from an analysis to be meaningful, "observers must be able to produce results that not only have a small inter-observer variability but are also reproducible." In the Currie and Monk study,³⁷ pre- and post-treatment photographs of the PWS of 20 patients were reviewed by six experts in laser therapy who were blinded to the patients' identities, the scores awarded by each physician-reviewer, and their previous scores. Little agreement was found, emphasizing the problems of using subjective analysis.

The weakness in the subjective assessment of outcomes has led to an exploration of objective measures to determine changes in lesion colour. Four studies^{16,38-40} used an objective measurement, often with traditional subjective measurement by physicians. All four studies were excluded from the detailed analysis because of small sample sizes.

- A computer image processing program was used to comparatively analyze lesion color in digitized photographs of PWS pre- and post-treatment.¹⁶
- A hand-held spectrophotometer with a microprocessor was used to compare pre- and post-treatment lesion colour.^{38,39}
- Objective experimental approaches were used to assess changes in lesion colour, including pre- and post-treatment comparisons of digital images, comparisons of spectrophotometric images, and histology analyses of skin biopsy samples post-treatment.⁴⁰

A relapse or re-darkening of PWS is not uncommon (from 16% to 26% in the studies presented). To measure the rate of recurrence, studies must be of sufficient length to allow this observation to be made. The four prospective studies that examined physician-assessed clinical outcomes^{7,25,27,30} reported follow-up

periods of four or six weeks after the last PDL therapy session — too short a time span to allow for recurrence to be tracked. Longer-term studies are needed.

4.5 Limitations of current review

The evidence on which this review is based was methodologically weak. This review was also limited by the time available for its production and by its need to be brief to enhance uptake and use. By design, this is not a full HTA and therefore, is limited in its scope and rigour. A more rigorous review would include all relevant studies without limitations being placed on publication date or language, or size of patient group. In a detailed HTA report, the quality of studies would be formally evaluated. In addition, cost and coverage data could be obtained from Canadian jurisdictions.

5 CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The studies located for this report were generally of poor quality, most being case series, retrospective reviews, or surveys involving small numbers of patients. Weaknesses were found in reported outcomes because measuring the physical and psychological benefits of PDL therapy is difficult.

Given these limitations, the literature suggests that PDL therapy is beneficial, particularly when compared with the alternatives (including no treatment). Success is greater when patients are treated during childhood or adolescence, and when visible PWS are targeted to limit stigmatization, particularly when related to school attendance. Patients vary in their response to PDL depending on factors such as skin and lesion types, and characteristics.

The elimination of PWS is rare. Some patients will be resistant to current therapies, thus

receiving no benefit and no satisfaction from them. The focus of therapy is to lighten the colour of a lesion, but its texture, height, and area may be unaffected.⁵ Retrospective reviews and surveys show re-darkening of the lesions in $\geq 16\%$ of patients. This number could be higher if follow-up duration is long enough. Studies show that patients can have high expectations and that their assessments of outcomes may be less favourable than those of treating physicians. For this reason, adequate education and counselling are important. Recurrence and resistance to treatment are stimulating the quest for more universally effective therapies.

All patients require multiple PDL sessions, although studies vary in terms of optimal numbers of sessions and length of treatment, and determination of the point at which to cease therapy. The studies in this review reported three to seven treatments at intervals of six- to 12-weeks, but one review mentions studies that have included 19 and 25 treatment sessions per patient.³³ The need for multiple treatments has cost implications. Although most evidence supports PDL for initial therapy, other devices such as Nd:YAG or IPL may be required in addition to PDL to treat residual or resistant PWS.

In summary, the complicating factors in the treatment of PWS include the subjective nature of outcome determination, the uncertainty about how much treatment is enough, the high expectations of patients, differing reactions of different skin types and lesions on different parts of the body, and the ethical difficulties involved in conducting studies of a more rigorous design, e.g., randomized controlled trials of adequate numbers and follow-up.

Coverage decisions regarding PDL therapy for PWS may confront payers with the need to assess the implications of discriminating among potential beneficiaries on the basis of age, ethnicity, or affected body part. It may be difficult to define treatment parameters given the variable characteristics of lesions and potential for recurrence. In addition, cost-effectiveness is unknown as that information is currently unavailable.

6 REFERENCES

1. De Borgie CA, Bossuyt PM, van der Horst CM, van Gemert MJ. Introduction of the flash-lamp pulsed-dye laser treatment of facial port-wine stains in childhood: a case of health care technology assessment. *Lasers Surg Med* 2001;28(2):182-9.
2. Lam SM, Williams EF, III. Practical considerations in the treatment of capillary vascular malformations, or port wine stains. *Facial Plast Surg* 2004;20(1):71-6.
3. Hamilton MM. Laser treatment of pigmented and vascular lesions in the office. *Facial Plastic Surg* 2004;20(1):63-9.
4. Kelly KM, Choi B, McFarlane S, Motosue A, Jung B, Khan MH, et al. Description and analysis of treatments for port-wine stain birthmarks. *Arch Facial Plastic Surg* 2005;7(5):287-94.
5. Hansen K, Kreiter CD, Rosenbaum M, Whitaker DC, Arpey CJ. Long-term psychological impact and perceived efficacy of pulsed-dye laser therapy for patients with port-wine stains. *Dermatol Surg* 2003;29(1):49-55.
6. Soueid A, Waters R. Re-emergence of port wine stains following treatment with flashlamp-pumped dye laser 585 nm. *Ann Plast Surg* 2006;57(3):260-3.
7. Scherer K, Lorenz S, Wimmershoff M, Landthaler M, Hohenleutner U. Both the flashlamp-pumped dye laser and the long-pulsed tunable dye laser can improve results in port-wine stain therapy. *Br J Dermatol* 2001;145(1):79-84.
8. Troilius A, Wrangsjö B, Ljunggren B. Patients with port-wine stains and their psychosocial reactions after photothermolytic treatment. *Dermatol Surg* 2000;26(3):190-6.
9. Weinstein JM, Chamlin SL. Quality of life in vascular anomalies. *Lymphatic Research & Biology* 2005;3(4):256-9.
10. Verna G, Pedrale R, Kefalas N, Fava F, Devalle L, Baglioni E, et al. Treatment of port-wine stains: A comparative study of the argon and pulsed dye laser based on our clinical experience. *Riv Ital Chir Plast* 2003;35(3-4):117-20.

11. Laser treatment for skin problems. *Drug & Therapeutics Bulletin* 2004;42(10):73-6.
12. Smit JM, Bauland CG, Wijnberg DS, Spauwen PHM. Pulsed dye laser treatment, a review of indications and outcome based on published trials. *Br J Plast Surg* 2005;58(7):981-7.
13. Rothfleisch JE, Kosann MK, Levine VJ, Ashinoff R. Laser treatment of congenital and acquired vascular lesions. A review. *Dermatol Clin* 2002;20(1):1-18.
14. Wang H, Wang J, Jin H, Wen S, Jiang G. Flashlamp-pumped pulsed dye laser in treatment of port-wine stains 36. *Chin Med Sci J* 2001;16(1):56-8.
15. Lanigan SW, Taibjee SM. Recent advances in laser treatment of port-wine stains. *Br J Dermatol* 2004;151(3):527-33.
16. Yong-Gee SA, Kurwa HA, Barlow RJ. Objective assessment of port-wine stains following treatment with the 585 nm pulsed dye laser. *Australas J Dermatol* 2001;42(4):243-6.
17. Loo WJ, Lanigan SW. Recent advances in laser therapy for the treatment of cutaneous vascular disorders. *Lasers Med Sci* 2002;17(1):9-12.
18. *Medical devices active license listing* [database online]. Ottawa: Medical Devices Bureau, Therapeutic Products Directorate, Health Canada; 2006. Available: <http://www.mdall.ca/> (accessed 2006 Nov 21).
19. *Pulsed Dye Laser Treatment*. [Clinical Policy Bulletins no. 0559]. Hartford (CT): Aetna; 2006 Oct 13. Available: http://www.aetna.com/cpb/medical/data/500_599/0559.html (accessed 2006 Dec 8).
20. Center for Devices and Radiological Health, U.S. Food and Drug Administration. *510(k) summary: Candela family of pulsed dye lasers pigmented lesion handpiece accessory (K051359)*. Rockville (MD): The Center; 2005 Jul 13. Available: <http://www.fda.gov/cdrh/pdf5/K051359.pdf> (accessed 2006 Dec 11).
21. Dover JS. Perspectives on innovations in pulsed dye laser development. In: [*Vbeam studies and publications*]. Wayland (MA): Candela Corporation; 2003. Clinical paper no. 3. Available: <http://www.candelalaser.com/files/docs/ClinicalPapers/0920-15-0035.pdf>.
22. Vbeam highlights. In: *Candela Corporation* [Web site]. Wayland (MA): Candela Corporation; 2006. Available: <http://www.candelalaser.com/products/index.cfm?task=vbeam> (accessed 2006 Dec 11).
23. Tomson N, Lim SP, Abdullah A, Lanigan SW. The treatment of port-wine stains with the pulsed-dye laser at 2-week and 6-week intervals: a comparative study. *Br J Dermatol* 2006;154(4):676-9.
24. Kono T, Groff WF, Sakurai H. Treatment of port wine stains with the pulse dye laser. *Ann Plast Surg* 2006;56(4):460-3.
25. Bernstein EF, Brown DB. Efficacy of the 1.5 millisecond pulse-duration, 585 nm, pulsed-dye laser for treating port-wine stains. *Lasers Surg Med* 2005;36(5):341-6.
26. Namba Y, Mae O, Ao M. The treatment of port wine stains with a dye laser: a study of 644 patients. *Scand J Plast Reconstr Surg Hand Surg* 2001;35(2):197-202.
27. Goh CL. Flashlamp-pumped pulsed dye laser (585nm) for the treatment of portwine stains. A study of treatment outcome in 94 Asian patients in Singapore. *Singapore Med J* 2000;41(1):24-8.
28. Michel S, Landthaler M, Hohenleutner U. Recurrence of port-wine stains after treatment with the flashlamp-pumped pulsed dye laser. *Br J Dermatol* 2000;143(6):1230-4.
29. Loffeld A, Zaki I, Abdullah A, Lanigan S. Study of patient-reported morbidity following V-beam pulsed-dye laser treatment of port wine stains. *Lasers Med Sci* 2005;20(3-4):114-6.
30. Asahina A, Watanabe T, Kishi A, Hattori N, Shirai A, Kagami S, et al. Evaluation of the treatment of port-wine stains with the 595-nm long pulsed dye laser: a large prospective study in adult Japanese patients. *J Am Acad Dermatol* 2006;54(3):487-93.
31. Chang CJ, Kelly KM, Van Gemert MJC, Nelson JS. Comparing the effectiveness of 585-nm vs. 595-nm wavelength pulsed dye laser treatment of port wine stains in conjunction with cryogen spray cooling. *Lasers Surg Med* 2002;31(5):352-8.

32. Schiffner R, Brunnberg S, Hohenleutner U, Stolz W, Landthaler M. Willingness to pay and time trade-off: useful utility indicators for the assessment of quality of life and patient satisfaction in patients with port wine stains. *Br J Dermatol* 2002;146(3):440-7.
33. Mahendran R, Sheehan-Dare RA. Survey of the practices of laser users in the UK in the treatment of port wine stains. *J Dermatolog Treat* 2004;15(2):112-7.
34. Lasers, dye, dermatologic [UMDNS #18-206]. In: *ECRI Sourcebase* [database online]. Plymouth Meeting (PA): ECRI; 2006.
35. *Candela: annual report 2005*. Wayland (MA): Candela Corporation; 2005 Oct. Available: <http://www.candelalaser.com/about/annReport2005.pdf> (accessed 2006 Dec 11).
36. Greve B, Raulin C. Prospective study of port wine stain treatment with dye laser: comparison of two wavelengths (585 nm vs. 595 nm) and two pulse durations (0.5 milliseconds vs. 20 milliseconds). *Lasers Surg Med* 2004;34(2):168-73.
37. Currie CL, Monk BE. Can the response of port-wine stains to laser treatment be reliably assessed using subjective methods? *Br J Dermatol* 2000;143(2):360-4.
38. Bernstein EF. High-energy 595 nm pulsed dye laser improves refractory port-wine stains. *Dermatol Surg* 2006;32(1):26-33.
39. Chiu CH, Chan HH, Ho WS, Yeung CK, Nelson JS. Prospective study of pulsed dye laser in conjunction with cryogen spray cooling for treatment of port wine stains in Chinese patients. *Dermatol Surg* 2003;29(9):909-15.
40. Yang MU, Yaroslavsky AN, Farinelli WA, Flotte TJ, Rius-Diaz F, Tsao SS, et al. Long-pulsed neodymium:yttrium-aluminum-garnet laser treatment for port-wine stains. *J Am Acad Dermatol* 2005;52(3:Pt:1):t-90.

APPENDIX 1: DETAILS OF INCLUDED CLINICAL STUDIES

Author; Study Design;	Intervention	Patient Group	Outcome Measures	Results and AEs	Conclusions
585 nm PDL					
Goh <i>et al.</i> ; ²⁷ prospective case series; ≥1 year follow-up	585 nm PDL (Candela Corp.) at 8 to 12-week intervals under topical anesthesia	n=94 Asian patients in Singapore with PWS of face or neck; 78% female; mean age 26.4 years (range 1 to 58)	efficacy: improvement as per opinions of patient and treating MD (dermatologist); mean number of laser treatments required	improvement % (as per patient versus MD): excellent=22 versus 36; good=61 versus 50; fair=10 versus 13; same=6 versus 1; mean number of treatments=4; AEs were transient mild pigmentation and residual erythema; no scarring	>80% of patients had good or excellent response; patients had higher expectations than MDs; macular and lighter coloured lesions responded better than papular, nodular, or dark lesions
Michel <i>et al.</i> ; ²⁸ retrospective case series; ≥1 year follow-up	585 nm PDL (Candela Corp.) at 6 to 8-week intervals	147 treated patients responding to survey ≥1 year after treatment completion (survey response 46%); 61% female; mean age at treatment end 28 years (range 3 to 73); response rate excellent 8%, good 40%, moderate 41%, poor 11%	recurrence rate: influence of age on recurrence rate; mean number of laser treatments; mean years of treatment required	16% had partial PWS re-darkening, mostly those with purple lesions initially; those treated at younger age had fewer recurrences (mean age 21 versus 29, p=0.016), age <10 (n=19)=no recurrences; mean number of treatments=6.9± 5.0; years of treatment=1.7±1.1	PWS recurrences occurred in 16% of patients but recurrence did not occur when patients treated under age 10 and mean age in non-recurrence group was younger than in recurrence group
Namba <i>et al.</i> ; ²⁶ retrospective case series; ≥1 year follow-up	585 nm PDL (Candela Corp.); topical anesthesia for children, none for adults	543 treated Asian patients ≥1 year after treatment completion; mean age at treatment start 21 years (range 3 months to 93 years); >50% of lesions on face; >25% had previous therapy (various)	efficacy by PWS location, as sum of improvement assessed by patient and MD; factors affecting therapy's efficacy; mean number of laser treatments	efficacy (excellent, good, poor): PWS of face 52, 39, 9; PWS of trunk 39, 51, 10; PWS of extremities 12, 68, 20; more treatments for large lesions and patients with previous treatments; PWS location affected outcome; younger patients had better results; mean number of treatments=6 PWS for face, 9 upper extremities	improvement common but not complete and affected by PWS location (benefits for face>extremities>trunk); lesion size; patient age; and prior treatment experience
Wang <i>et al.</i> ; ¹⁴ retrospective case series	585 nm PDL (Synosure Corp.), 4 to 12-week intervals; topical anesthesia as needed	194 consecutive Asian patients; 63% female; mean age 26 years (range 1 month to 60 years); 90 children, 104 adults; 95% lesions on head and neck; mean lesion size 42 cm ²	efficacy: determined by comparing lesion lightening to pre-treatment photo; mean number of laser treatments	improvement excellent 8%, good 48%, fair 37%, poor, 7%; mean number of treatments=3.6; AEs include pigmentation in 3% (transient)	good or excellent responses found in 56% of patients with low rate of AEs

Author; Study Design;	Intervention	Patient Group	Outcome Measures	Results and AEs	Conclusions
Bernstein <i>et al.</i> ; ²⁵ prospective case series	585 nm PDL with cryogen cooling spray (Candela Corp.), 6- to 10-week intervals; pulse interval 1.5 μ s (versus prior devices that used 0.4 μ s)	95 consecutive patients (104 distinct areas); mean age 34 years (range 9 to 74); PWS location head and neck 65%, extremities 30%, trunk 5%; 20% had failed previous treatment with earlier laser technologies	efficacy: pre- and post-treatment photos subjectively estimated by blinded MD and by dermal spectrometer (degree of erythema); mean number of laser treatments	subjective assessment: 66% mean improvement (range 15% to 100%); \geq 50%, 88%; \geq 75%, 43%; \geq 90%, 16%; 100%; 5%; spectrometer reading showed 69% decrease in erythema across treatment group; mean number of treatments=3.7 for previously untreated; 4 for previously treated	authors concluded that response to PDL (longer pulse duration than previous) satisfactory, including results for previously unresponsive lesions
Soueid and Waters; ⁶ retrospective case series	585 nm PDL every 4.8 months on average (mean number of sessions 6.2)	n=94 of 110 (85%) children receiving PDL for PWS between 1997 and 2000 (16 excluded because of lack of follow-up, records)	recurrence rate	15 (16%) patients had PWS re-darkening and commenced treatment again; for these children, age range at start of initial treatment 7 months to 15 years; 10 females, 5 males; 14 Caucasian, 1 Asian; 14 PWS on face or head (13 on cheek); gap between initial and re-treatment 17 to 59 months (mean 31 months)	proportion of PDL-treated PWS will recur, possibly because of failure to eliminate all affected vessels initially, therefore, long-term follow-up recommended
595 nm PDL with cooling					
Loffeld <i>et al.</i> ; ²⁹ prospective case series, questionnaire-based	595 nm PDL with cooling (V-beam; Candela Corp.); general anesthesia for children; topical for some adults	51 consecutive patients; 70% female; mean age 30 years (range 1 to 67); PWS on face 74%	patient-reported morbidity	reported AEs of bruising 94% (up to 27 days, median 8 days); swelling 80% (up to 14 days, median 2 days); crusting 47% (up to 36 days, median 5 days); weeping 12% (up to 2 days, median 2 days)	results compared with previous study of 585 nm PDL; 595 nm appeared to be tolerated better, although detailed data comparisons not possible
Asahina <i>et al.</i> ; ³⁰ prospective case series	595 nm PDL with cooling (V-beam; Candela Corp.); 8-week intervals \times 4; topical anesthesia as needed	n=66 of 77 consecutive adult patients (10 did not complete study, although not because of AEs); 71% female; mean age 39 years (range 20 to 73); PWS on face or neck 53%	efficacy: pre- and post-treatment photos subjectively assessed; factors influencing efficacy	after 4 treatments, rating of improvement: excellent 15%; good 52%; fair 29%; poor 5%; improvement lower for pink or purple PWS (versus red), and lesion on leg (versus face, trunk, or arm); factors not predictive included sex, age, lesion size, skin type, presence of lesion hypertrophy; AEs included transient purpura (76%), mild pigment changes (6% to 17%)	authors concluded that procedure well tolerated and efficacy acceptable

Author; Study Design;	Intervention	Patient Group	Outcome Measures	Results and AEs	Conclusions
Comparisons					
Scherer <i>et al.</i> , ⁷ prospective case series	585 nm PDL versus long-pulsed PDL (585 to 600 nm) with cooling (both Candela Corp.); 1 treatment; all possible wavelengths used on same lesion in different test areas	62 patients with untreated PWS; age range 2 to 65 years (no other details provided)	efficacy at each wavelength (585 nm versus long-pulsed PDL at 585, 590, 595, and 600 nm) assessed by 2 MDs 6 weeks after treatment	best response achieved 585 nm, 12 patients (19%); long-pulsed PDL 585 nm, 13 patients (21%); 590 nm 3 (5%); 595 nm 8 (13%); 600 nm 6 (10%); no difference 20 (32%), including no response in 7; AEs: hyper-pigmentation or atrophy equal (13 of 14 patients)	objective was to determine whether wavelengths >585 nm effective for PWS; increased efficacy occurred for long-pulsed PDL in some PWS (possibly because of targeting larger vessels) without increase in AEs
Chang <i>et al.</i> , ³¹ retrospective case series; ≥1 year follow-up	585 nm (32 patients) versus 595 nm (32 patients) PDL, with cooling (Candela Corp.); 1 to 6 treatments, 6 months to 3 years (mean 1 year)	64 Asian patients with PWS of face or neck; 66% female; age range 6 months to 64 years; study groups similar in age, sex, PWS severity, and number of treatments	efficacy 585 nm versus 595 nm: pre- and post-treatment photos subjectively assessed by 3 blinded non-treating plastic surgeons; outcome measure “blanching score” of poor=1 to excellent=4	mean blanching score for patients treated with 585 better (2.90±0.96) versus 595 nm (2.34±1.08), p<0.001; score of 2.9 corresponds to good (51% to 75% blanching); AEs: transient hyper-pigmentation resolving by 1 year reported in 14 (44%) of 585 nm group and 12 (38%) of 595 nm group; no permanent AEs reported	traditional PDL wavelength (585 nm) led to better results than longer 595 nm wavelength
Verna <i>et al.</i> , ¹⁰ retrospective case series; ≥1 year follow-up	Argon laser at 458 to 514 nm continuous beam (up to 1999) for mean of 4.6 sessions; PDL 585 nm (Candela Corp.) for mean of 7.8 sessions	108 patients with PWS of face from group of 203; 57% female; mean age 30 years (range 16 to 55); 95 patients of 203 excluded based on: type or location of lesion, previous therapy, drop-out, age <15 years; argon 89 patients; PDL 19 patients	efficacy: pre- and post-treatment digital photos evaluated using colorimetric table	good to excellent results overall: argon 31%; 585 nm PDL 53%; for patients with PWS classified as “dark”: argon 50%; 585 nm PDL 36%; AEs: transient hyper-pigmentation for 3 to 6 months	585 nm PDL outperformed older Argon laser technology except in treating dark PWS
Mental Health Outcomes					
Troilius <i>et al.</i> , ⁸ retrospective survey; follow-up several months to 8 years	PDL, wavelength unspecified (probably 585 nm), 6- to 12-week intervals	147 patients of 163 surveyed months to years post-treatment, (90% response rate) who had been treated 4 to 9 times with PDL until clear or lack of response; 62% female; median age 22 years (range	mental health outcomes pre-treatment (by recall) and post-treatment: multiple, e.g., self-esteem, social relationships, making friends, school or education, contact with opposite sex, employment	self-esteem: 45% thought they had lower self-esteem than unaffected peers; this improved post-treatment (p<0.001); social relationships: problems reported for 30% pre-treatment and 25% post-treatment; making friends: problems reported for 30% pre-treatment and	not all psychological parameters improved after PDL treatment of PWS; general response better when patients treated at younger age; important for patients to have realistic expectations of treatment results because complete clearance of PWS

Author; Study Design;	Intervention	Patient Group	Outcome Measures	Results and AEs	Conclusions
		2 to 74); PWS on face or neck 73%; previous treatment 50%	opportunities	25% post-treatment; school or education: problems reported for 33% pre-treatment; improvement post-treatment (p<0.008); contact with opposite sex age >12: problems reported for 53% pre-treatment; improvement post-treatment (p<0.001); employment opportunities: problems reported for 17% pre-treatment; no change post-treatment	often not achieved
Hansen <i>et al.</i> , ⁵ retrospective case series; follow-up mean 7 years (SD= 3.03; range 1 to 11 years)	585 nm PDL, 8- to 12-week intervals for 6 to 8 treatment sessions	n=55 (49% response rate for 109 of 164 patients who could be contacted); 62% female; mean age 29 years (range 7 to 81) at time of survey; PWS on face or neck 73%; previous treatment 50%	mental health outcomes post-treatment: worry about PWS appearance, ease of making friends, different treatment by others, overall satisfaction, would recommend to others; clinical outcomes assessed: changes in PWS characteristics including colour, texture, height, area	mental health outcomes: worry about appearance of PWS, 62% worried less, 31% no change, 7% worried more; making friends, 20% improved, 61% neutral, 19% not improved; treatment by others, 57% improved, 24% neutral, 19% not improved; satisfaction, 48% satisfied, 28% neutral, 24% not satisfied; would recommend: overall score 7.42 out of 10 (where 10 is top recommendation); clinical outcomes for PWS: colour, 62% improved, 19% no change, 19% worse; texture, 11% improved, 81% no change, 8% worse; height, 14% improved, 76% no change, 10% worse; area, 34% improved, 56% no change, 10% worse	most patients had improvement in colour of their PWS although not in PWS texture, height, or area; most tended to worry less about the PWS, felt satisfied or neutral, and would recommend treatment to others