Low level laser therapy for wound healing

Wendy L. Schneider and David Hailey

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This Health Technology Assessment Report has been prepared on the basis of available information of which the Foundation is aware from public literature and expert opinion and attempts to be current to the date of publication. It has been externally reviewed. Additional information and comments relative to the report are welcome and should be sent to:

Director, Health Technology Assessment
Alberta Heritage Foundation for Medical Research
3125 Manulife Place, 10180 - 101 Street
Edmonton, Alberta T5J 3S4
CANADA

Tel: 780-423-5727, Fax: 780-429-3509

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Summary

- Low level laser therapy (LLLT) has been used in the treatment of wounds. Issues related to use of the technology in this application are definition of standard protocols and evidence of effectiveness.
- Low level lasers most commonly used for wound treatment are the gallium arsenide (GaAs), gallium aluminum arsenide infrared semiconductor (GaAlAs) and the helium neon (HeNe) devices.
- Differences exist in the delivery of LLLT. Variables include pulse rate, duration of treatment, applicator placement (contact or non-contact), wavelengths and spot size.
- To date, neither Health Canada nor the U.S. Food and Drug Administration has approved low energy lasers for use in wound healing.
- A systematic review of the literature indicates that the efficacy of LLLT in this application is not established. There is no good scientific evidence to support its use.
- Any local use of LLLT in this application should be supported by empirical data from good quality studies of its efficacy and effectiveness.
- Other, possibly more promising alternative therapies should be considered as adjunct therapies to conventional wound healing practices.
Introduction

A request for information about the use of low level laser therapy (LLLT) to assist wound healing was received from the Capital Health Authority (CHA). This technology has been increasingly used within the Edmonton area, with somewhat different approaches being taken by individual operators. The concern was whether there was any scientific evidence to show the effectiveness of LLLT in accelerating the wound healing process. As well, the CHA was lacking formalized protocols that would detail dosage parameters and proper timing or sequencing of laser exposure to the various phases of wound healing.

There is controversy surrounding the use of LLLT in this application. This technology assessment focuses on the efficacy, effectiveness and safety of the approach in general terms and as it pertains to medical practice in Alberta. Economic aspects of LLLT used to accelerate wound healing are beyond the scope of this study.

The methodology used in the assessment is outlined in Appendix A. Only clinical studies were considered.

Low level laser therapy, also known as low intensity and low power therapy, is considered to work through a photochemical response to laser light that induces biochemical alterations in cells, leading to physiological changes. Several authors suggest that the laser radiation has a wavelength-dependent capability to alter cellular processes without significant heating \( (2, 10, 11, 20, 32) \). It is this characteristic that therapists make use of when applying low level laser therapy to accelerate wound healing. The cellular response to laser light coined the terms ‘photobiology’ and ‘biostimulation’ \( (11) \).

The clinical use and research in low energy lasers owe much of their popularity to work begun in Hungary and other eastern European countries in the mid-1960s. Accelerated wound healing was one of the first effects reported by early investigators. Early laser therapy reports were enthusiastic and anecdotal, but contained no clear mechanism of action.

Although laser therapy remains on the fringes of Canadian medicine, general interest has increased as determined by the increased volume of current literature available \( (25) \). A review article written in 1995 describes the controversial use of low intensity laser irradiation in clinical settings. Use of this therapy stems from the favourable results shown in laboratory studies. It is here that the scientific rationale of laser therapy first gave an impression of the influences that laser irradiation can have on cellular processes \( (2) \).
Description of LLLT technology

The types of laser therapy devices used for LLLT are shown in Table 1 and include the gallium arsenide, gallium aluminum arsenide infrared semiconductor lasers (GaAs and GaAlAs, respectively) and the helium neon laser (HeNe). Despite similarities of dose and a convergence in laser choice, significant differences persist between treatment approaches. These differences include pulse rate, applicator placement (contact or non-contact), and the use of a single wavelength or a combination of wavelengths. Also of potential importance are the irradiance (power/unit area), beam divergence, spot size, delivery (fiber optic, direct), polarity, and for pulsed devices, pulse duration and duty cycle. Reported individual treatment times range anywhere from 35 seconds to 20 minutes. Any protocol development of laser therapy should preferably include consideration of all these parameters as well as information about site preparation, technique and number of treatments (2, 10, 11).

The lasers listed in Table 1 are those most commonly used for LLLT. The therapy is often used in combination with other alternative therapies such as ultraviolet light, ultrasound or hyperbaric oxygen (see Table 2). The uses of concurrent therapies make it difficult to frame a definitive statement on the effects of laser therapy alone.

Table 1: Low level lasers in clinical use for wound healing

<table>
<thead>
<tr>
<th>Laser type</th>
<th>Wavelength</th>
<th>Indications treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helium neon (HeNe)</td>
<td>632.8 nm</td>
<td>soft tissue wounds, arthritis</td>
</tr>
<tr>
<td>Gallium arsenide (GaAs)</td>
<td>904 nm</td>
<td>soft tissue wounds</td>
</tr>
<tr>
<td>Gallium aluminum arsenide (GaAlAs)</td>
<td>820, 830 nm</td>
<td>soft tissue wounds</td>
</tr>
</tbody>
</table>

Regulatory considerations

The Health Protection Branch in Canada and the Food and Drug Administration (FDA) in the U.S. were contacted about regulatory status for low level lasers used for wound healing.

Health Canada

In Canada, low level lasers are regulated as Class 2 or Class 3(a) devices under standards such as those written by the Canadian Standards Association (CSA), the American National Standards Institute (ANSI) and Underwriters Laboratories (UL). Such standards address laser safety in health care facilities, medical electrical equipment, and safety of diagnostic and therapeutic laser equipment. In Canada, lasers have not been approved for use in wound healing. Health Canada Device Licensing staff request a Device Evaluation Division
Opinion before licensing a device for a novel indication such as promoting wound healing. The Regulations state that clinical data are required in support of efficacy prior to licensing. They also define the requirements for carrying out clinical trials in Canada.

**U.S. Food and Drug Administration**

In the United States, medical lasers must have premarket approval or premarket clearance from the FDA prior to marketing for any claimed human indication, unless specifically exempted by the FDA. To date, the FDA has approved no biostimulation laser therapy devices for humans; therefore, it is illegal in the U.S. to make any claims of clinical effectiveness. The Office of Compliance has issued notifications and warnings to firms suspected of illegally marketing these devices with claims of effectiveness. Low level laser units cannot be introduced into commerce legally for human treatment, unless via an Investigational Device Exemption or with Institutional Review Board approval.

Although there appear to be no safety concerns regarding low level lasers, they have not received regulatory approval from Health Canada or the FDA as a therapy to accelerate wound healing.

**Evidence of efficacy and effectiveness**

**Best evidence**

The Cochrane Wound Group Trials Register identified four RCTs of laser therapy pertaining to treatment of venous leg ulcers (3, 7, 10, 21, 22). Each of the studies contained very small numbers of participants with group sizes varying between 15 to 23. All patients were deemed to have venous leg ulceration, though none of the trials reported the diagnostic criteria. The results of the studies suggested that there were no improvements in the healing rate of venous ulcers with the use of low level laser therapy. The only suggestion of therapeutic benefit was shown in one small RCT where a combination of laser and infrared light led to an improvement in the healing rates of venous ulcers (3). The Cochrane Review stated that more research is needed before a clear direction for medical practice is identified (10).

In the literature search undertaken for the present assessment, a further six primary studies of LLLT effectiveness for wound healing were identified (14, 15, 20, 24, 28, 30) and are summarized in Table 2. They include a non-randomized controlled prospective study, two randomized controlled trials, a prospective comparative study and two non-controlled clinical series. Although two of these investigations had the potential to provide a good level of scientific evidence, the numbers of subjects were small and/or variables were uncontrolled.
<table>
<thead>
<tr>
<th>Study</th>
<th>Patient characteristics</th>
<th>Therapy</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gogia et al. (14)</td>
<td>n=12</td>
<td>Both groups: sterile whirlpool with Betadine® at 100°F, followed by sterile saline wet-to-dry dressings covered with gauze and cotton mesh wrapping. Experimental group also received HeNe laser at 632.8 nm and 1 mW power output, energy density of 2 J/cm² before dressings were applied. Both groups were administered to once daily, five days per week for 20 trmts. Time duration of each laser session not given.</td>
<td>Overall healing of the wound area was slightly greater in the control group as compared to the experimental group. There was no significantly accelerated healing of the lower leg/foot ulcers treated with HeNe laser. The findings of this study failed to show an enhanced rate of wound healing with HeNe laser stimulation. Further controlled clinical studies on a large number of patients are needed to warrant the clinical efficacy of low-energy lasers in enhancing wound healing in humans. Poor level of scientific evidence, very small patient sample*.</td>
<td></td>
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<td>1992</td>
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<tr>
<td>Telfer et al (30)</td>
<td>n=12</td>
<td>Patients were treated with low energy photon therapy (LEPT) as an add-on modality to conventional treatment. LEPT administered with a micro-processor-controlled device to provide adequate laser parameters.  - 22 red-head provided 6mW power, dose 4-6 J/cm²  - 7 infrared-head provided 12 mW power, dose 4 J/cm². Time duration of each laser session not given. Outpatients treated 3X/wk, inpatients 5X/wk. Number of trmts appeared to depend on ulcer size and healing rate depended on number of sessions rather than on the total course duration.</td>
<td>Thirteen ulcers (87%) completely healed, two decreased in size by 75%. Smallest ulcer healed after 5 sessions, a larger, 3-cm ulcer healed after 25 sessions. One ulcer (9-cm X 2-cm) required two courses, separated by one month, of 30 sessions each.</td>
<td>Abstract only. Authors state that based on this pilot study a double blind study will be initiated.</td>
</tr>
<tr>
<td>Clinical series</td>
<td></td>
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<tr>
<td>[to define and obtain technical data in order to conduct future double-blind, placebo-controlled study, see Gupta et al. (15)]</td>
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<td>1993</td>
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### Table 2: Studies of LLLT on open wounds, con’t

<table>
<thead>
<tr>
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<th>Therapy</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nussbaum et al. (24) RCT 1994</td>
<td>n=20 (pressure ulcers in spinal cord injury (SCI) patients) Control group: n=9 Age: 036 y US/UVC group: n=5 Age: 042.2 y Laser group: n=6 Age: 042 y</td>
<td>Control group: All patients received wound cleansing 2X daily using Hygeol (1:20), and (moist) Jelonet dressings. US/UVC group: US applied to skin surrounding wound for 5 min per 5 cm² of wound area, frequency of 3 MHz and a SATA intensity of 0.2 W/cm² (1:4 pulse ratio). US treatment was alternated daily for 5 days/wk with UVC applied using a cold-quartz lamp. Time and distance of UVC treatment was dependent on wound surface appearance. Laser group: Treatment was applied 3X/wk in contact, probe centered over the wound using a 820 nm diode and 30 superluminous diodes at λ,660, 880 and 950 nm, 120 mW/cm², pulse repetition rate at 5,000 pps, energy density at 4J/cm² for 35 s, 3X per week.</td>
<td>Four patients did not complete the study (1 laser, 1 control, 2 elected to have surgery to repair wounds). Healing rate was not equal under the treatment conditions used. There was a significant difference in rate of healing between the laser and US/UVC groups. There was no significant difference between the control group and the other 2 groups. Laser treatment had no benefit for wound healing in SCI patients. Three patients showed deterioration, judged by an increase in ulcer size. Deterioration was also recorded for 1 control group patient and one US/UVC patient.</td>
<td>Authors point out a limitation of this study; it did not compare outcomes of combining wound care with placebo US or laser treatment. Because the US/UVC regimen involves daily treatment, a placebo effect should be considered in further work, and the combined regimen should be compared with either UVC or US. As well, these methods need to be tested on other patient populations and should be extended to a larger number of patients in a placebo-controlled trial. Fair level of scientific evidence, small patient sample and uncontrolled variables.</td>
</tr>
<tr>
<td>Shuttleworth et al. (28) Prospective comparative study of laser and conventional wound therapies (non-randomized) 1997</td>
<td>n=14 Age: 076.3 y Control group: n=8, 1 diabetic patient Laser group: n=6, 2 diabetic patients. (Three patients ultimately received both laser and conventional treatment during the trial.) Leg ulcers caused by a variety of conditions. Study period: 15 wks/patient</td>
<td>Control group: Conventional wound care and dressings in accordance with the local wound management policy. [On ethical grounds patients could not be restricted to only one treatment method.] Laser group: Each laser therapy session was a maximum of 4 min. using a 46-cluster probe and 2 sources of low-power laser: HeNe at λ,632.8 nm and infrared laser at λ,904 nm, 4 J/cm². Patients received treatment and dressings twice a week.</td>
<td>Control group: All patients showed improvement. Laser group: Three patients showed improvement or healed and three deteriorated.</td>
<td>The results of this study neither support nor refute the use of low-power laser therapy in wound management. Further studies should incorporate a larger sample size and actively control or eliminate variables such as the size of wounds. Laser therapy should not be recommended for use in routine wound treatment until more specific evidence is available. Fair to poor level of scientific evidence, very small patient sample.</td>
</tr>
</tbody>
</table>
Table 2: Studies of LLLT on open wounds, con’t

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Landau (20) Non-controlled clinical series 1998</td>
<td>n=50 (patients had chronic diabetic foot ulcers and had not responded to conventional therapy) Age: 65 y (±11 y) Diabetes: Type 1: 14 Type 2: 36 Ulcer duration: 9 ±6.6 mo Range: 2 - 70 mo All patients continued their medications and antibiotic treatment was administered according to the sensitivity of the microorganism. HBO group: 15 patients HBO and Laser group: 35 patients Unilaser Scan 60, 2 sources of laser: HeNe at λ=632.8 nm and infrared laser at λ=904 nm, 4 J/cm². Treatment: HBO-2.5 h, laser 20 min, 2 – 3 X per week No of treatments: 25 ±13 Range: 7 – 70 Duration: 3 ±1.8 mo Range: 1 – 8 Complete recovery: 43 Failure: 7 There was no significant difference between groups. Authors state that topical hyperbaric oxygen alone or combined with a low level energy laser for the treatment of patients with chronic diabetic foot ulcers were valuable adjuvants to conventional therapy. Poor level of scientific evidence</td>
<td></td>
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<tr>
<td>Gupta et al. (15) Double-blind, placebo-controlled study 1998</td>
<td>n=9 (12 venous ulcers) Control group Age: 64.7 (± 9.4 y) Ulcer duration: 36.0 ±21.6 wks Intervention group Age: 61.0 (± 7.8 y) Ulcer duration: 105.8 ±36.0 wks Control group: placebo treatment received sham therapy from identical-appearing light sources, from the same delivery system. Intervention group: Two monochromatic optical sources: one (red-light) source-660 nm used over ulcer for 180s. second (infrared) source-880 nm used on periphery of ulcer for 30s. Trtmts were 3X/wk, for 10 wks. Configuration used gave optimum coverage over wound areas. Unhealed ulcers in control group: 84.7%. Decrease in ulcer area (compared to baseline): 14.7 mm². One patient dropped out of the study after 3 wks. Unhealed ulcers in intervention group: 24.4%. Decrease in ulcer area (compared to baseline): 193.0 mm². A randomization bias was found toward the placebo group, ulcers were of a significantly shorter duration. There were no adverse effects. Authors state that despite the bias LEPT was an effective modality for the treatment of venous leg ulcers. Fair level of scientific evidence, very small patient sample.</td>
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</table>

HBO=hyperbaric oxygen HeNe=helium neon λ = wavelength US=ultrasound UVC=ultraviolet-C SATA=spacial average-temporal average * Jovell and Navarro-Rubio, reference 16
Telfer et al. \(^{(30)}\) completed their pilot study in order to more precisely define technical characteristics of low energy photon therapy to be used in a future placebo-controlled, double-blind study. This study was later completed and is included in Table 2 \(^{(15)}\).

Gogia et al. \(^{(14)}\) state that it is the favourable results in animal studies that have prompted researchers to try LLLT on humans. They point out that this logic fails when the type of wound is considered; a surgically-induced lesion versus a pressure sore. The healing process for these two types of wounds is very different and cannot be compared. They suggest the need to establish the laser parameters to produce optimal benefit and that guidelines are needed to establish treatment frequency.

Nussbaum et al. \(^{(24)}\) affirm that evaluation of different approaches to wound healing is complicated by the heterogeneous nature of the population of patients who have chronic wounds.

In the article by Shuttleworth and Banfield \(^{(28)}\) the laser type is not specified and the dressings are not described. Hence comparison with other studies is difficult. The authors suggest that the marked improvement in the control group may be partly explained by the Hawthorne effect whereby inclusion of individuals in a study can promote the desired outcome. However, one would expect the newer laser treatment to be influenced by this variable rather than the control treatment.

In the Landau study the topical oxygen was applied to the wounds by pumping oxygen into a disposable polyethylene bag 100 cm long and 60 cm wide. The bag was sealed on the open end by an elastic bandage. The benefit of topical oxygen or topical oxygen combined with laser treatment cannot be confirmed, as there was no comparison with conventional therapy. As well, topical use of oxygen, outside a hyperbaric oxygen (HBO) chamber, does not affect oxygen tension past the depth of the superficial dermis \(^{(25)}\). While the Landau study refers to topical oxygen treatment as “HBO”, true HBO therapy places the patient in a pressurized, pure oxygen environment and follows a specific and well-established protocol (Searles, personal communication).

The paper by Gupta et al. had the potential to provide a good level of scientific evidence about efficacy of laser therapy as it outlined a study that was randomized, double-blind and placebo-controlled. However, the patient numbers were very small.

None of these studies establish the efficacy of the technique.
Other evidence of effectiveness

Information collected by the Physical Therapy Department at the University of Delaware discusses both evidence of effectiveness and lack of effectiveness of laser therapy in accelerating wound healing. The Department reports that much of the evidence of effectiveness has been shown in animal studies. As well they stated that in spite of the large number of studies that dismissed lasers as a wound-healing tool, many patients and clinicians attested to its effectiveness (19, 31). The lack of evidence of effectiveness of LLLT for wound healing is at least in part associated with problems with research, including experimental design flaws, and use of heterogeneous and inappropriate subject populations. Treatment parameters are not consistently reported in the literature and that severely limits the ability to compare studies. In addition, studies have incomplete procedural descriptions, flawed methodology, limited blinding and, at times, non-existent controls. Before definitive conclusions about the efficacy of LLLT can be drawn, appropriate laser wavelengths, dosage schedules, and conditions to be treated must be tested and established with clinical research (28, 31, 33).

A postal survey of physical therapists in Flanders ranked LLLT in first place for treatment of wounds (5). Yet, only 30% of the respondents considered the use of LLLT to be well founded on research. Additionally, 70% thought that neither the efficacy of laser therapy nor the required treatment protocols were sufficiently backed by scientific research. Comments from more than 90% of the respondents said patients were prejudiced when receiving LLLT. Their hope for better results with a ‘high-tech and modern’ therapy, were preconceived opinions that were quoted and likely contributed to their wound-healing success (5).

A further study identified, but not included in Table 2, is that by Kleinman et al. (19) who report experience with 42 patients who had venous ulcers for more than 6 months. Complete wound closure occurred in 86% of patients, which was attributed to the biostimulating effect of laser therapy. However, the level of scientific evidence is poor. There is no control group, the period of the study was 28 years and no individual patient results were reported.

The scientific literature is sparse and available articles report only weak evidence of the ability of LLLT to accelerate wound healing. Moreover, any alternative therapy promoted as an adjunct to conventional therapy might be compared to other, possibly more effective, interventions - an example being electrical stimulation (1).
Wound classification

Use of LLLT needs to be considered in the context of other standard approaches to wound healing. Within this report ‘wound’ describes either a venous stasis ulcer or a pressure ulcer/sore. A large proportion of these types of wounds is located on the lower leg.

Wounds can be acute, as in the case of surgery, or chronic. In a healthy individual with no underlying factors, such as diabetes or venous disease, an acute wound should heal within 3 to 6 weeks. Chronic wounds are defined as those which have not proceeded though an orderly and timely process to produce anatomic and functional integrity, or proceeded through the repair process (Figure 1) without establishing a sustained anatomic and functional result (9, 18). As well, chronic wounds heal by different mechanisms depending on their cause. Pressure sores, for example, heal by a combination of angiogenesis, deposition of extracellular matrix and wound contraction. Venous stasis ulcers are typically relatively shallow and heal primarily by re-epithelialization (Figure 1) (6, 9).

Demands created by chronic wounds are a continuing medical and socioeconomic problem. Correction of the underlying pathophysiology is frequently not possible. The benefits of current technologies are limited and costs have been substantial. It is for these reasons that the clinical and scientific arenas have turned to alternative therapies in an effort to promote and speed the healing process (1, 9, 27).

The flowchart in Figure 1 outlines five discrete steps in the wound healing process. ‘Re-epithelialization’ has been highlighted to emphasize that some wounds halt here and become chronic, i.e. new epithelial cells do not grow and close over the wound (Searles, personal communication). It should be noted that some descriptions in studies combine stages of the wound healing process (6, 17, 18, 29, 31).

Conventional therapy

The efficient management of wounds requires a multidisciplinary team made up of physicians, clinical nurse practitioners, dieticians, social workers, occupational and physical therapists (12, 18, 26). The main treatment goal is rapid wound closure followed by a functional and aesthetically satisfactory scar (29). Conventional wound therapy involves two basic principles; 1) identify and control the underlying causes, and 2) provide an environment for moist interactive wound healing (dressings) (1, 6, 18, 27). Characteristics of wound dressings are outlined in Appendix B.

There are improved healing rates in venous ulcers when compression therapy (see Appendix C) is used. Pressure ulcers will not heal if the patient does not pressure download the site. Compression therapy should be considered part of the standard of care in this patient population (Searles, personal communication).
Figure 1: Phases in the wound healing process

Hemostasis
- lasts several minutes
- disruption of blood vessels
- results in initiation of coagulation cascade
- cell migration into wound

Inflammatory phase
- lasts several days
- vasodilation
- increased capillary permeability
- complement activation
- triggers neutrophils and macrophage migration into wound
- macrophage play pivotal role in transition from inflammation to wound repair
- platelets release platelet-derived growth factor (a potent chemo-attractant for fibroblasts and smooth muscle cells)

Granulation
- Lasts up to 3 weeks in an acute wound
Simultaneous events that occur in this phase:
- fibroplasia
- matrix deposition
- angiogenesis

Re-epithelialization [Most chronic wounds halt at this stage of the healing process]
- basement membrane proteins reappear in a very ordered sequence from the margin of the wound inward in a zipper-like fashion closing the epidermal defect. Chronic wounds typically do not make it to this stage, i.e. granulation may occur but epithelial cells do not migrate over and close the wound.

Wound contraction and tissue remodeling
- occurs over 6 to 18 months
- growth factors and other peptides provide stimuli for wound contraction
- cellular components and extracellular matrix of the wound gradually and continually changing

Sources: (6, 17, 18, 29, 31)
Current wound management practices in Alberta

In Alberta the Calgary Regional Health Authority (CRHA) has developed a clinical pathway for wound healing. The pathway was designed by a multidisciplinary team and is meant as a guide for health care professionals who treat patients with acute or chronic wounds. The Capital Health Authority (CHA) developed a Regional Wound Care Guideline for use by health care professionals (26). Like the CRHA, the CHA used a multidisciplinary team to produce their Guideline.

Both health authorities treat wounds using conventional therapy. However, they do mention alternative therapies in their literature. The S.W.A.T. (skin & wound assessment and treatment) Team of the CRHA uses the text Chronic Wound Care (13) as a guide for instruction on the use of alternative therapies. This publication states that clinical safety and efficacy of LLLT has not been established. Further controlled clinical studies on large numbers of patients are needed to confirm the clinical efficacy of low intensity lasers on wound healing. Low intensity laser therapy should only be used as an adjunct treatment to conventional wound care (13).

The CHA mentions adjunctive therapies such as HBO, laser, ultrasound, and electrical stimulation. The CHA quotes the AHCPR’s clinical practice guideline stating that it is the responsibility of users to ensure they are using a modality with demonstrated efficacy through clinical research, and that the user has the appropriate training to apply that modality. Physiotherapists should attempt to advance the clinical management of wounds via further trials and research of these modalities (1, 26).

Suggested information needs for Alberta

It is not clear from previous published studies that LLLT is effective in accelerating the wound healing process. The current scientific evidence provides only very weak support for the use of this therapy and all studies suggest that further work is needed. At this time, available evidence does not justify use of LLLT. It is suggested that any further use in Alberta should be informed by the results of local empirical studies.

If local studies are to be established, the following stages should be addressed:

- Agreement on protocol. This should be well defined so that each centre participating in the study has an established protocol.

- Patient selection. Current scientific literature describes use of LLLT in heterogeneous populations of patients that do not allow comparisons between groups. Patient selection would require strict inclusion/exclusion criteria, well-defined outcomes (healed ulcers), and length of follow-up.
Study design. Evidence of efficacy should be obtained through one or more RCTs. A study of this sort would present a challenge but without it a definitive answer regarding the efficacy of LLLT in accelerating wound healing is unavailable and use of the technology in routine health care cannot be justified. A local study might incorporate methodology like that described by Gupta et al. (15) and Nussbaum et al. (24) and would include representative patient populations in Alberta.

Characteristics of such a study might include:

- Randomized, double-blind, placebo-controlled trial (preferably multi-centre).
- Objective: to evaluate the efficacy of LLLT in the treatment of chronic venous leg ulcers in a home care population. This would require approval from ethics review boards and informed consent as outlined by Health Canada regulations.
- Hypothesis: LLLT, used as an adjunct to conventional therapy, will accelerate the wound healing process. This might be addressed by comparing the control group (conventional wound care plus (placebo) sham LLLT) with the intervention group (conventional therapy plus LLLT).

Follow-up:

- Measure the time taken until the defined outcome is reached, in both arms of study.
- Study group: those with chronic venous leg ulcers as determined by specific diagnostic criteria.

Patient numbers:

- Number of subjects per group would be determined with respect to expected percent change in the intervention group. If 40% of wounds heal with optimal therapy and laser therapy is expected to make a 25% improvement, then approximately 61 participants are needed per group. If the improvement is more modest, for example 15%, then the sample sizes will be much larger and in the order of 173 participants per group (Hessel, Searles, personal communications).

Treatment protocol:

- Laser type and a well-defined protocol to be determined.
- Inclusion: patients aged >50y with chronic venous leg ulcers; (ulcers of greater than 3 months duration, and unresponsive to conventional therapy).
- Exclusion: those with peripheral arterial disease, haematologic abnormalities, vasculitis, history of epilepsy, those receiving topical steroids around wound site, those receiving anticoagulant therapy, those receiving drugs known to cause photo-sensitivity reactions.
While such information would be needed to address the question of efficacy of LLLT, a further policy issue to be addressed is whether other alternative therapies for wound healing might require consideration. For example, the AHCPR clinical guideline number 15 (1) recommends a course of electrical stimulation for recalcitrant wounds. Given the status of that technology, use of a modality such as LLLT that has unproven efficacy becomes difficult to justify.

Finally, any findings need to be integrated into the broader strategies used for effective management of wounds.

In conclusion:

- The benefits of low level laser therapy for wound healing are not established. There is no good scientific evidence to support its use.
- Any local use of LLLT in this application should be supported by empirical data from good quality studies of its efficacy and effectiveness.
- Other, possibly more promising alternative therapies should be considered as adjunct therapies to conventional wound healing practices.
Appendix A: Methodology

Literature searches of the databases in the table below were made using the terms shown. The first search included the MEDLINE, HealthSTAR, EMBASE; Dissertation Abstracts and Current Contents databases using the Dialog Corporation, OneSearch® option. This search was restricted to terms in the title or descriptor field. The second search, on CINAHL, was accessed through OVID Technologies. The Cochrane Library was also searched, and several searches were run on the Internet using a variety of terms. With the exception of the Cochrane Library and Internet searches, the literature searches were restricted to the period 1993 – August, 1999.

<table>
<thead>
<tr>
<th>Databases</th>
<th>Keywords</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDLINE</td>
<td>low level laser? or low power laser? or low intensity laser? or low energy laser? or biostimulation or laser? therapeutic use AND wound healing or wounds or diabetic foot or skin diseases or leg ulcer? or foot ulcer or diabetic ulcer? or decubitus ulcer or wound care or skin necrosis or bedsores or pressure ulcer?</td>
</tr>
<tr>
<td>EMBASE</td>
<td></td>
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<tr>
<td>HealthSTAR</td>
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<tr>
<td>Dissertation Abstracts</td>
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<td>Online</td>
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<tr>
<td>Current Contents</td>
<td></td>
</tr>
<tr>
<td>CINAHL</td>
<td>laser or laser$ or biostimulation AND leg ulcer or pressure ulcer or skin care or surgical wound care or wound$ or injuries or skin ulcer or wound healing or decubitus or diabetic</td>
</tr>
<tr>
<td>Cochrane Library</td>
<td>laser* and (wound or ulcer or ulcer or sore*)</td>
</tr>
</tbody>
</table>

Date Limits: 1993 – 1999, no date limits on Cochrane Library or Internet searches

Publication types and number of studies found (Table 2):

- Randomized controlled clinical trials 2
- Controlled clinical trials 1
- Non-controlled clinical trials 2
- Multicentre studies 0
- Prospective comparative studies 1
- Retrospective studies 0
Single case reports and animal studies were excluded.

Regulatory status should be considered before implementing or using any therapeutic medical device. Standards published by the Canadian Standards Association (CSA) or Underwriters' Laboratories (UL), are in place to ensure electrical devices, including medical equipment, are safe against fire and shock. However, it is not the mandate for these agencies to test efficacy or effectiveness in any physiological way, rather that is the responsibility of the Health Protection Branch in Canada and the Food and Drug Administration (FDA) in the U.S. Each was contacted with respect to low level laser regulatory status.

Jovell and Navarro-Rubio (16) published a classification scheme that comments on quality of evidence. Assignment to categories is dependent on conditions of scientific rigour. This scheme forms the basis of the classification of studies in Table 2 into the following categories:

**Good:** Meta-analysis of randomized controlled trials (RCTs) or from large sample RCTs;

**Good to Fair:** Small sample RCTs and non-randomized controlled prospective trials;

**Fair:** Non-randomized controlled retrospective trials, cohort studies and case-control studies;

**Poor:** Non-controlled clinical series and various other approaches.

In this health technology assessment:

**Efficacy** refers to the performance of a technology under ‘ideal’ conditions or conditions of best practice; and

**Effectiveness** refers to the performance of a technology under ‘routine’ conditions. For example when it has become widely distributed in a health care system.
Appendix B

Following is additional information regarding the staging of pressure sores and classifying venous stasis ulcers.

**Staging criteria for pressure sores**

The following staging criteria are consistent with those of the National Pressure Ulcer Advisory Panel (NPUAP, 1989) Consensus Development conference (1).

- **Stage I** Nonblanchable erythema of intact skin; the heralding lesion of skin ulceration. In dark-skinned individuals discoloration of the skin, warmth, edema, or hardness may also be indicators.

- **Stage II**: Partial thickness skin loss involving epidermis and/or dermis. The ulcer is superficial and presents clinically as an abrasion, blister, or shallow crater.

- **Stage III**: Full thickness skin loss involving damage or necrosis of subcutaneous tissue that may extend down to, but not through, underlying fascia. The ulcer presents clinically as a deep crater with or without undermining of adjacent tissue.

- **Stage IV**: Full thickness skin loss with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures (for example, tendon or joint capsule). Undermining and sinus tracts may also be associated with Stage IV pressure ulcers.

According to the Practice Guideline the staging definitions recognize the following limitations:

- Assessment of Stage I pressure ulcers may be difficult to perform in patients with darkly pigmented skin.

- When eschar (a scab) is present, accurate staging of the pressure ulcer is not possible until the eschar has sloughed or the wound has been debrided.

**Venous stasis ulcers**

Although venous stasis ulcers may be staged using the pressure sore criteria the following classification system is generally used (26).

Partial-thickness – skin loss involving the epidermis, dermis or both, a shallow crater, blister, abrasion or skin tear.

Full-thickness – skin loss involving damage to or necrosis of the dermis and epidermis, it may also affect subcutaneous tissue, muscle, tendon and bone.

Red/Yellow/Black (RYB) is another classification tool that assesses the wound bed.

Red – clean and uniformly pink to red; often heal by secondary intention. Dressings need to be changed less often, but should be moist at all times.
Yellow – varies from ivory to canary yellow or even green in colour, depending on whether there is infection. The goal of care is to manage exudate and to remove slough through enzymatic, autolytic or surgical debridement.

Black – ranging in colour from dark brown, gray to black. The goal for most individuals is to remove the necrotic tissue by enzymatic, autolytic or surgical debridement. Where there is no drainage or boggy surrounding tissue, hard, dry eschar or black scab may be left intact on the lower legs, feet or heels of individuals whose healing potential is compromised by inadequate circulation. It provides a protective base for the wound.

If all three colours are present then treatment is aimed at the colour that is present over 50% of the wound.

The majority of pressure ulcers can be prevented provided that a tool such as the Braden Pressure Ulcer Risk Assessment is used for monitoring and intervening with at-risk patients. Existing wounds should be continually monitored using a guide such as the Bates Jensen Pressure Sore Status Tool (Orsted, Searles, personal communications).

Additional information about wound characteristics
The AHCPR Clinical Practice Guideline #15, (1) makes recommendations for the prediction, prevention and early treatment of pressure ulcers in adults. As well, it provides grading or staging information. A pressure ulcer is defined as any lesion or sore caused by unrelieved pressure that results in damage of underlying tissue. Pressure ulcers typically occur over bony prominences and are graded or staged by the amount of tissue damage that has occurred. The same staging criteria can be used for venous stasis ulcers, which are lower extremity ulcerations related to disruption in blood flow between the superficial and deep venous system causing chronic venous insufficiency (26).

Additional information about wound dressings
The ‘ideal’ wound dressing for treating pressure sores would (4, 6, 18):

- allow excess exudate to be removed from the wound surface
- provide a moist micro-environment
- be sterile/contaminant free
- not leave dressing material in the wound
- reduce ulcer pain
- be easy to change
- not cause an allergic reaction
- act as a semi-permeable membrane
- cause no trauma when removed, be impermeable to micro-organisms
- provide thermal insulation.
Semi-permeable and impermeable dressings should only be used on non-infected wounds.

A moist, pressure dressing maintains hemostasis of wound, prevents bleeding or hematoma formation. As well, a pressure bandage keeps dead space collapsed, again preventing a hematoma or seroma. The moist environment prevents eschar (scab) formation. Eschars impede keratinocyte migration; they are required to repopulate the wound surface. A wound may have to be debrided of necrotic tissue that supports growth of pathological organisms. Next, the wound is packed with wound dressing material to ensure that the wound heals bottom up. Antibiotics are used either topically and/or systemically for treatment of infection (1, 18, 26).
Appendix C

Alternative therapies

Alternative therapies, other than LLLT, purported to promote or accelerate wound healing include electrical stimulation, hyperbaric oxygen therapy, whirlpool, ultrasound, and compression therapy.

Electrical stimulation, to date, is the most promising alternative therapy used to accelerate wound healing. The AHCPR’s CPG for treatment of pressure sores recommends a course of treatment with electrotherapy for Stage III and IV pressure ulcers that have proved unresponsive to conventional therapy (1, 12, 13). The CPG was recently revisited by Ovington (25). This updated review focused on dressings and adjunctive therapies. Based on findings in the current literature it not only supported the 1994 CPG but stated that the strength-of-evidence had increased for use of electrical stimulation.

The study also supported the CPG stating that therapeutic use of hyperbaric oxygen and ultrasound has not been sufficiently established to permit recommendation of these therapies for the treatment of pressure ulcers (25).

In an overview of physical therapies used for wound management, whirlpool is mentioned as a way to reduce the risk of infection as it removes dirt, debris, foreign contaminants and loose necrotic tissue from the wound bed. However, the effect of whirlpool on healing has not been studied (12, 13).

Ultrasound can be used both diagnostically to monitor the rate of healing and therapeutically to stimulate the rate of wound healing (12). However, there is no scientific evidence of effectiveness of ultrasound on the rate of wound healing (25).

There is much scientific literature that supports compression therapy for venous ulcers (8, 12, 13, 26, 27). It involves the deliberate application of pressure and is most commonly employed to control edema and reduce swelling in the treatment of venous disorders of the lower limb. Compression bandages have been divided into four groups according to their ability to produce predetermined levels of compression; light, moderate, high and extra high (8). The National Clinical Guidelines recommended for use in Scotland mentions 24 RCTs of compression treatment for venous ulcers. Each demonstrated that compression improves healing and should be used routinely (27).
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