Evidence Report/Technology Assessment
Number 111

Wound-Healing Technologies: Low-Level Laser and Vacuum-Assisted Closure

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-02-0026

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AHRQ Publication No. 05-E005-2
December 2004

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Suggested Citation:
Samson DJ, Lefevre F, Aronson N. Wound-Healing Technologies: Low-Level Laser and Vacuum-Assisted Closure. Evidence Report/Technology Assessment No. 111. (Prepared by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center, under Contract No. 290-02-0026.) AHRQ Publication No. 05-E005-2. Rockville, MD: Agency for Healthcare Research and Quality. December 2004.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. This report on low-level laser and vacuum-assisted closure for wound healing was requested by the American Association of Health Plans. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to **epc@ahrq.gov.**

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Acknowledgments

The research team would like to acknowledge the efforts of Kathleen M. Ziegler, Pharm.D., for clinical and technical input, editing, and layout; Claudia J. Bonnell, B.S.N., M.L.S., for information services; Maxine A. Gere, M.S., for general editorial assistance; Carol Gold-Boyd for administrative support; Tracey Perez, R.N., J.D., for program support; and Stacie Schilling Jones and Carmen Kelly, Pharm.D., of the Agency for Healthcare Research and Quality for advice as our Task Order Officers.

Structured Abstract

Context: Chronic wounds are a major source of morbidity, disability, and mortality, having a significant impact on public health and healthcare resource expenditure.

Objectives: To systematically review evidence on low-level laser therapy or vacuum-assisted closure on wound-healing outcomes.

Data Sources: MEDLINE® (through June 8, 2004), EMBASE (through June 14, 2004), and the Cochrane Controlled Trials Register (through 2003) were searched. Primary published evidence was supplemented with recent meeting abstracts and clinical trial protocols.

Study Selection: Included studies were randomized, controlled trials (RCTs) of one of the following comparison types: alternative intervention; incremental benefit; or placebo. Low-level laser trials had to include only chronic wounds, while vacuum-assisted closure trials could include various wound types. Trials were full-text journal articles reporting on at least one outcome of interest. Primary outcomes of interest were incidence of complete wound closure, time to complete closure, and adverse events.

Data Extraction: Titles and abstracts were screened by a single reviewer. A second reviewer reviewed citations marked ineligible for full-text retrieval. Rater agreement was required to exclude citations. Following retrieval, one reviewer determined whether an article should be included, excluded, or discussed with another reviewer. One reviewer performed primary data abstraction; evidence tables were fact-checked by a second reviewer.

Data Synthesis: For low-level laser therapy, 11 studies (n=413) met study selection criteria. For vacuum-assisted closure, 6 studies (n=135) met study selection criteria. Outcomes of interest were summarized in tables and synthesized across studies.

Conclusions: Evidence was limited by poor trial quality. Concerns centered on: randomization adequacy; group comparability at baseline and follow-up; use of complete healing as the primary endpoint; adjustment for confounders; and intention-to-treat analysis. Sample sizes were generally small, making it difficult to find statistically significant differences between groups.

The best available trial did not show a higher probability of complete healing at 6 weeks with the addition of low-level laser compared to sham laser treatment added to standard care. Study weaknesses were unlikely to have concealed existing effects. Future studies may determine whether different dosing parameters or other laser types may lead to different results.

Vacuum-assisted closure trials did not find a significant advantage for the intervention on the primary endpoint, complete healing, and did not consistently find significant differences on secondary endpoints and may have been insufficiently powered to detect differences. Ongoing RCT protocols may provide better evidence on outcomes of interest.

Given the sparse evidence for these two interventions, at the present time, it is not possible to find variables in these trials that may be associated with better results.

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Appendixes

Appendixes are provided electronically at http://www.ahrq.gov/clinic/tp/woundtp.htm

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Evidence Report/Technology Assessment

Number 111

Wound-Healing Technologies: Low-Level Laser and Vacuum-Assisted Closure

Summary

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Introduction

Chronic wounds are a major source of morbidity, lead to considerable disability, and are associated with increased mortality; therefore, they have a significant impact on public health and the expenditure of healthcare resources.[1]

The incidence of chronic wounds in the United States is approximately 5 to 7 million per year,[1] and the annual costs for management of these wounds is greater than $20 billion.[2,3] In addition, chronic wounds can lead to complications, such as infections, contractures, depression or limb amputation.[4] These complications are associated with a need for assisted living and with higher mortality.[5,6]

The objective of this report is to systematically review the evidence on the outcomes of two technologies for wound healing: low-level laser therapy and vacuum-assisted closure. This report addresses the following specific questions:

1. In the treatment of chronic nonhealing wounds, what are the outcomes of low-level laser therapy for specific indications and patient types
   - as a substitute for conventional therapy? or
   - as an adjunct to conventional therapy, compared with conventional therapy alone?
2. In the treatment of acute or chronic wounds, what are the outcomes of vacuum-assisted closure for specific indications and patient types
   - as a substitute for conventional dressings? and
   - as an adjunct to conventional therapy, compared with conventional therapy alone?

This report also provides an overview of clinical and methodologic issues relevant to evaluating the evidence on interventions for wound healing. Many variables affect the course of wound healing; so well-controlled, randomized trials are necessary to reach conclusions on treatment efficacy.

Skin wounds are a heterogeneous and complex group of disorders with a wide variety of causes.[7] Approximately 70 percent are classified as pressure ulcers, diabetic ulcers, or vascular ulcers.[8,9] Vascular ulcers are further classified as due to arterial or venous insufficiency. Other less-frequent causes include inflammatory conditions, malignancies, burns, and radiation injuries.[8] Often the causes of wounds are multifactorial, such as in the diabetic patient who has both arterial insufficiency and peripheral neuropathy.[8] Each wound type has distinct physiologic characteristics and exists in a unique host environment with varied clinical and psychosocial factors.[8]

Wounds are often classified as acute or chronic. Acute wounds are generally less than 8 weeks in duration and have not yet completed the natural healing cycle. Chronic wounds are defined as wounds that have failed to proceed through an orderly and timely process that produces anatomic and functional integrity.[10] Chronic wounds either require a prolonged time to heal,

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do not heal completely, or recur frequently. A large number of factors can impede wound healing and may predispose a patient to the development of chronic wound(s).[11,12] These include both systemic factors (poor nutrition, metabolic derangements, and drugs) and local factors (tissue hypoxia, infection, and dry wound bed).[13]

Conventional treatment for established wounds incorporates common principles that apply to the management of all wounds, including debridement of necrotic tissue, maintenance of a moist wound bed, and control of infection. These common elements are combined with treatment modalities targeted to each type of wound and the clinical characteristics of the patient.[14,15,16] Optimal treatment also entails consideration of the appropriate intensity of treatment.[17] Unfortunately, there are no widely accepted, standardized protocols that define optimal standard treatment or the appropriate intensity of treatment delivery.

Because treatment varies widely in clinical practice, it is difficult to determine whether a patient has actually received an adequate course of treatment, and whether a nonhealing wound should truly be called "refractory." In randomized, controlled trials, a relatively large proportion of refractory wounds heal with standard treatment (control arm). The large number of factors that contribute to wound healing, and the high degree of variability in wound characteristics, patient characteristics, and treatment delivery result in many potential confounding factors when attempting to measure treatment effect.

As a result of these multiple confounding factors, it is difficult to interpret outcomes from single-arm trials that lack a control group, since improvement may be due to factors other than the specific intervention being tested. A concurrent control group is necessary to permit measurement of a treatment effect above that related to optimization of standard treatment or due to the natural history of wound healing. Randomized assignment to treatment group is essential in maximizing the likelihood that confounding factors are equally distributed across treatment groups. Ascertainment of outcomes should be ideally performed by an independent, blinded individual.

The U.S. Food and Drug Administration (FDA) has prepared a draft guidance document that offers information on optimal design of trials to assess wound-healing interventions, including patient selection and assessment, treatment considerations, and definition of outcomes and outcomes assessment.[16] The principals set forth by the FDA have been adapted in the development of the protocol for this systematic review. In particular, outcome measurement should focus on outcomes that are quantitative and clinically meaningful.[4,11] The most important outcomes to be considered are (1) the percent of patients with complete healing and (2) time to complete healing. In some cases, particularly for vacuum-assisted closure, the treatment may not be expected to result in complete healing. Rather the treatment may be intended to advance the wound to a stage where healing is possible, either by continued conventional treatment or by surgical closure.

Methods

The objective of this evidence report is to systematically review and synthesize the available evidence on the effectiveness of low-level laser treatment and vacuum-assisted closure for wound healing. Outcomes of interest were

- Primary outcomes
  - incidence of complete wound closure
  - time to complete closure
  - adverse events
- Secondary outcomes
  - facilitating surgical closure
  - need for debridement
  - infections
  - pain
  - activities of daily living
  - quality of life
  - improved cosmesis

Other secondary outcomes abstracted were change in wound size and transcutaneous oxygen tension (t_cpO_2); however, these were considered to be of less clinical importance.

Electronic database searches were completed of MEDLINE® (via PubMed®), EMBASE, and the Cochrane Controlled Trials Register. The MEDLINE® search covered references entered onto the database from January 1, 1966 through June 8, 2004. The Cochrane Controlled Trials Register search was completed in 2003, through issue number 4. The EMBASE search covered references entered through June 14, 2004.

The search was limited to studies on human subjects with English-language abstracts. When abstracts were missing, the full-text article was retrieved for review if the title suggested it might possibly meet the study selection criteria. Papers published in foreign languages were reviewed if the English-language abstract appeared to meet inclusion criteria. Results of the search and study selection were reviewed by the Technical Expert Panel (TEP) for this project, in order to identify additional studies.

In addition, two companies that produce lasers used in wound healing (Microlight Corporation of America and Photothera), as well as the major producer of vacuum-assisted closure devices (V.A.C.®, Kinetics Concepts Inc. [KCI]), were contacted and were invited to submit evidence-based information for the review. The specific request was for "lists of published, randomized, controlled trials (RCTs), published abstracts of RCTs within the past 2 years, and published articles on study design, or protocols of any RCTs (published or in progress)."

This systematic review selected only randomized, controlled trials meeting the following criteria:

1. The trial must involve one of the following comparisons of interventions
   a. Either low-level laser treatment or vacuum-assisted closure, compared with other wound healing interventions (alternative intervention trials).
   b. Either low-level laser treatment or vacuum-assisted closure in addition to standard wound care, compared with standard wound care alone (incremental benefit trials).
   c. Either low-level laser treatment or vacuum-assisted closure, compared with a sham intervention (placebo trials).
2. For low-level laser treatment, patient selection criteria must target those with chronic wounds. For vacuum-assisted closure, patient selection may address those with chronic wounds or other types of wounds.
3. The trial must report on at least one of the outcomes of interest.
4. The trial must be published as a full journal article and not merely as a conference abstract.

Titles and abstracts were screened by a single reviewer who marked each citation as either eligible for review as full-text articles or ineligible for full-text review. A second reviewer reviewed all citations marked as ineligible by the first reviewer. An eligible rating was necessary from only one reviewer to place a citation in the pool of those to be retrieved for full-text review.

In reviewing full-text articles to determine eligibility for data abstraction, a single reviewer determined whether each paper should be (1) included in systematic review, (2) excluded from systematic review, or (3) discussed with additional reviewer. One reviewer performed primary data abstraction of all data elements into the evidence tables, and a second reviewer checked the evidence tables for accuracy.

A procedure was established in case of disagreements that could not be resolved between the two reviewers. In such cases, the EPC Program Director was consulted and then, if necessary, the relevant members of the TEP.

This systematic review applies the general approach to grading evidence developed by the U.S. Preventive Services Task Force.[18] Two independent reviewers rated study quality, and disagreements in ratings were resolved by consensus.

Results

Low-level laser. Eleven studies[19-29] met the study selection criteria for Part I of this review, nine of which were rated poor in quality,[19-23, 26-29] while one was rated good quality[25] and one was rated fair.[24]

Seven studies (n=262) compared standard care plus placebo with the combination of standard care and sham laser therapy.[19,21,22,23,26,27,29] Most of these patients had lower extremity venous ulcers. Of the three studies that reported on complete healing,[19,26,27] one provides weak evidence of a higher rate of healing for patients treated by machine-scanned laser versus those receiving sham laser.[19]

Standard treatment alone versus standard treatment plus laser was compared in three studies, which reported on a total of 151 patients with pressure ulcers.[24,25,28] All three studies reported on complete healing. One of these was rated as good in quality, and this higher-quality study did not show a higher probability of complete healing at 6 weeks with the addition of laser treatment,[25] nor did it show benefit for any of the other reported outcomes. Use of medical treatment plus ultraviolet light with medical treatment plus low-level laser therapy was compared in one study of six patients with chronic venous ulcers.[20] That study did not show a higher probability of complete healing at 6 weeks with the addition of laser treatment.

Overall, the quality of this body of evidence is poor, and does not permit definitive conclusions. However, the available data suggest that the addition of laser therapy does not improve wound healing, as the vast majority of comparisons in these studies do not report any group differences in the relevant outcomes. It is unlikely that the lack of significant differences is the result of a type II error, since there are no trends or patterns of outcomes that favor the laser group.

Vacuum-assisted closure. This body of evidence is insufficient to support conclusions about the effectiveness of vacuum-assisted closure in the treatment of wounds. There are only six trials that met the inclusion criteria for this review[30-35] and the included trials were of small size and poor quality. With the exception of one study of 54 patients with incomplete followup,[34] all studies included fewer than 25 patients. The randomization method was clearly adequate in only one study.[34] No study made clear that groups were comparable on all three

key baseline characteristics (age, wound duration, wound size). None provided group information about wound duration. A single study adjusted for confounders in the data analysis[35] and another performed an intention-to-treat analysis.[32]

Some outcomes in the available trials show a significant benefit for the vacuum-assisted closure group, while others do not. Only one study[30] gave data on the probability of complete healing, showing no significant difference between groups. A study reporting time to satisfactory healing[33] also found no significant difference between groups. One study found no difference between vacuum-assisted closure and control in time to readiness for surgical closure.[34]

Three studies reported on change in wound area,[31,33,34] one of which found a difference between vacuum-assisted closure and control,[34] while two did not.[31,33] Among four studies addressing change in wound volume,[30,31,32,35] two found a significant advantage for vacuum-assisted closure[31,32] and two did not achieve statistical significance.[30,35] One study found significant changes in wound width and depth for vacuum-assisted closure[32] and another found it only for depth.[31] It is possible that the lack of significant results in some or all of these trials result from a type II error. In most cases, the numerical results favor the vacuum-assisted closure group. Power calculations are lacking for these trials, but their small size raises the possibility that they are underpowered.

Trial protocols provided by the manufacturer of the V.A.C.® device (Kinetic Concepts, Inc., KCI) outline much larger trials that are condition-specific and address many of the quality problems found in the published studies. If implemented and completed successfully as planned, these trials will provide substantial advances in the evidence base for vacuum-assisted closure therapy, and may allow more definitive conclusions on the efficacy of vacuum-assisted closure.

Discussion

This systematic review focused on two specific interventions for wound healing, but the issues raised in this discussion should be applied broadly. Because of the large size of populations with nonhealing and other types of wounds, the impact on healthcare expenditures is considerable. Future research should address how to improve the delivery of care, quality of care, and outcomes of treatment of wounds in various settings. There is potential to reduce the frequency of nonhealing wounds and thus the overall costs of care. New interventions have the potential to improve wound care, but outcomes must be demonstrated in well-controlled randomized trials. Strategies for reducing the occurrence of wounds in various susceptible populations also have a place in the research portfolio. Given significant costs of chronic wounds, future comparisons of the cost-effectiveness of various strategies for preventing wounds, managing wounds, and improving quality of care would be of value to clinical decisionmakers.

Availability of the Full Report

The full evidence report used to create this summary was prepared for the Agency for Healthcare Research and Quality by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center, under Contract No. 290-02-0026. It is expected to be available in December 2004. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling (800)-358-9295. Inquiries should include a request for Evidence Report/Technology Assessment No. 111, *Wound Healing Technologies: Low-Level Laser and Vacuum-Assisted Closure.* In addition, Internet users will be able to access the report and this summary online through AHRQ's Website at www.ahrq.gov.

Suggested Citation

Samson D, Lefevre F, Aronson N. Wound Healing Technologies: Low-Level Laser and Vacuum-Assisted Closure. Summary, Evidence Report/Technology Assessment No. 111. (Prepared by the Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center, under Contract No. 290-02-0026). AHRQ Publication No. 05-E005-1. Rockville, MD: Agency for Healthcare Research and Quality. December 2004.

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www.ahrq.gov
AHRQ Pub. No. 05-E005-1
December 2004

ISSN 1530-440X

Evidence Report

Chapter 1. Introduction

Scope and Objectives

Chronic wounds are a major source of morbidity, lead to considerable disability, and are associated with increased mortality; therefore, they have a significant impact on public health and the expenditure of healthcare resources (Petrie, Yao, and Eriksson, 2003).

The incidence of chronic wounds in the U.S. is approximately 5 to 7 million per year (Petrie, Yao, and Eriksson, 2003), and the annual costs for management of these wounds is greater than $20 billion (Frykberg, Armstrong, Giurini et al., 2000; Harding, Morris, and Patel, 2002). In addition, chronic wounds can lead to complications, such as infections, contractures, depression, or limb amputation (Jeffcoate and Harding, 2003). These complications are associated with a need for assisted living and with higher mortality (Deery and Sangeorzan, 2001; Reiber, Boyko, and Smith, 1995).

The objective of this report is to systematically review the evidence on the outcomes of two technologies for wound healing: low-level laser therapy and vacuum-assisted closure. This report addresses the following specific questions:

1. In the treatment of chronic nonhealing wounds, what are the outcomes of low-level laser therapy for specific indications and patient types:
    - as a substitute for conventional therapy? or
    - as an adjunct to conventional therapy, compared with conventional therapy alone?

2. In the treatment of acute or chronic wounds, what are the outcomes of vacuum-assisted closure for specific indications and patient types:
    - as a substitute for conventional dressings? and
    - as an adjunct to conventional therapy, compared with conventional therapy alone?

This Introduction chapter provides an overview of clinical and methodologic issues relevant to evaluating the evidence on interventions for wound healing. Many variables affect the course of wound healing; so well-controlled, randomized trials are necessary to reach conclusions on treatment efficacy.

Clinical Overview

Wound healing progresses through well-recognized, pathophysiological stages, and those wounds that do not progress to healing as expected are considered to be chronic. Conventional treatment of wounds incorporates common principles for all wounds, along with specific treatment strategies targeted to wound type and overall clinical characteristics of the patient.

Types of Skin Wounds/Ulcers

Skin wounds are a heterogeneous and complex group of disorders with a wide variety of causes (Table 1) (Pierce, 2001). Approximately 70 percent are classified as pressure ulcers, diabetic ulcers, or vascular ulcers (Stadelman, Digenis, and Tobin, 1998a; Valencia, Falabella,

Table 1. Classification of Skin Wounds

Types of skin wounds	
Pressure wounds o Decubitus ulcers o Neuropathic ulcers	*Inflammatory wounds* o Autoimmune disorders o Primary cutaneous disorders
Vascular insufficiency wounds o Venous insufficiency o Arterial insufficiency	*Malignant wounds* o Primary cutaneous malignancies o Secondary cutaneous malignancies
M*iscellaneous wounds* o Burns o Radiation injury o Frostbite	 o Vasculitic ulcers o Spider bites

Kirsner, et al., 2001). Vascular ulcers are further classified as due to arterial or venous insufficiency. Other less-frequent causes include inflammatory conditions, malignancies, burns, and radiation injuries (Valencia, Falabella, Kirsner, et al., 2001). Often the causes of wounds are multifactorial, such as in the diabetic patient who has both arterial insufficiency and peripheral neuropathy (Valencia, Falabella, Kirsner, et al., 2001). Each wound type has distinct physiologic characteristics, and exists in a unique host environment with varied clinical and psychosocial factors (Valencia, Falabella, Kirsner, et al., 2001).

Wounds are often classified as acute or chronic. Acute wounds are generally less than 8 weeks in duration and have not yet completed the natural healing cycle. Chronic wounds are defined as wounds that have failed to proceed through an orderly and timely process that produces anatomic and functional integrity (Lazarus, Cooper, Knighton, et al., 1994). Chronic wounds either require a prolonged time to heal, do not heal completely, or recur frequently.

Phases of Wound Healing

There are three phases of wound healing: (1) inflammatory, (2) proliferative, and (3) remodeling (Steed, 2003b; Harding, Morris, and Patel, 2002). These phases are distinct, but overlap in time during the healing process.

During the inflammatory phase, neutrophils and macrophages enter the wound site. Neutrophils act primarily to prevent and respond to infection; macrophages release inflammatory mediators such as cytokines and growth factors (Henry and Garner, 2003), which clear the wound of devitalized tissue and set the stage for cellular regeneration. The proliferative phase begins after two or three days and is marked by a predominance of fibroblasts and endothelial cells. Fibroblasts secrete growth factors and extracellular matrix components that lead to tissue regeneration (Henry and Garner, 2003). Endothelial cells form the new blood vessels that are also necessary for tissue regeneration. The final phase is the remodeling phase, in which intact skin replaces scar tissue. This phase is characterized by continued cycles of new cellular component formation and degradation of the scar by proteases (Eming, Smola, and Krieg, 2002; Henry and Garner, 2003).

Wounds that heal properly progress through these phases in an orderly fashion within about 8 weeks. Nonhealing wounds are often "stuck" in one of these stages, usually continued inflammation or proliferation (Douglass, 2003; Henry and Garner, 2003). A large number of factors can impede wound healing (Figure 1) and may predispose a patient to the development of chronic wound(s) (Williams and Barbul, 2003; Steed, 2003b). These include both systemic factors (e.g., poor nutrition, metabolic derangements, and drugs) and local factors (e.g., tissue hypoxia, infection, dry wound bed) (Stadelman, Digenis, and Tobin, 1998b).

While the above paradigm is widely accepted in conceptualizing wound care, there are alternative frameworks that have been proposed. Mustoe (2004) addresses limitations of current wound-healing science by addressing unifying aspects of chronic wounds, rather than their differences. He proposes that most, if not all, chronic wounds share common features of (1) the cellular and systemic effects of aging, (2) repeated ischemia-reperfusion injury, and (3) bacterial colonization with the accompanying inflammatory response. In this model, treatment approaches logically address all three aspects of chronic wounds.

Conventional Treatment of Chronic Skin Wounds

Optimal management of wounds starts with prompt recognition and accurate diagnosis in order to properly treat wounds at the earliest stage possible. Early recognition depends on identification of patients at risk, education for appropriate patients, and proper surveillance (U.S. Food and Drug Administration, 2000). An accurate diagnosis can be made from the appearance of the wound and the patient's risk factors in up to 75 percent of skin wounds (de Araujo, Valencia, Federman, et al., 2003). In some cases, specialized testing such as blood flow measurement is necessary (de Araujo, Valencia, Federman, et al., 2003; Valencia, Falabella, Kirsner, et al., 2001).

Conventional treatment for established wounds incorporates common principles that apply to the management of all wounds, including debridement of necrotic tissue, maintenance of a moist wound bed, and control of infection (Table 2). These common elements are combined with treatment modalities targeted to each wound type and the clinical characteristics of the patient (Lionelli and Lawrence, 2003; Steed, 1998a; U.S. Food and Drug Administration, 2000) (Table 2). Optimal treatment also entails consideration of the appropriate intensity of treatment (Ratliff, Bryant, Dutcher, et al., 2002). For example, depending on the context, dressing changes may be performed once a day or several times per day. Nutritional support can entail a wide variety of approaches that may differ considerably. Treatment regimens that are considered intensive often involve a multidisciplinary team of clinicians, nurses, therapists, and other ancillary staff. Unfortunately, there are no widely accepted, standardized protocols that define optimal standard treatment or the appropriate intensity of treatment delivery.

For wounds that do not heal with conservative therapy, surgical intervention may be considered. Surgical restoration of adequate blood flow is the goal for wounds caused by vascular insufficiency. Arterial revascularization procedures are often curative; however, venous surgery is of uncertain benefit for this purpose (de Araujo, Valencia, Federman, et al., 2003; Valencia, Falabella, Kirsner, et al., 2001).

Skin grafting can be performed for chronic, nonhealing skin wounds that are not amenable to surgical revascularization. Skin grafts are usually taken from a portion of intact skin of the same individual (autograft), but may also be taken from a cadaveric source (allograft). The specific indications for skin grafting are not well standardized (Valencia, Falabella, Kirsner, et al., 2001).

Figure 1. Factors contributing to wound healing and chronic wound formation
(Source: Douglass 2003. Adapted with permission from the *British Journal of Community Nursing*.)

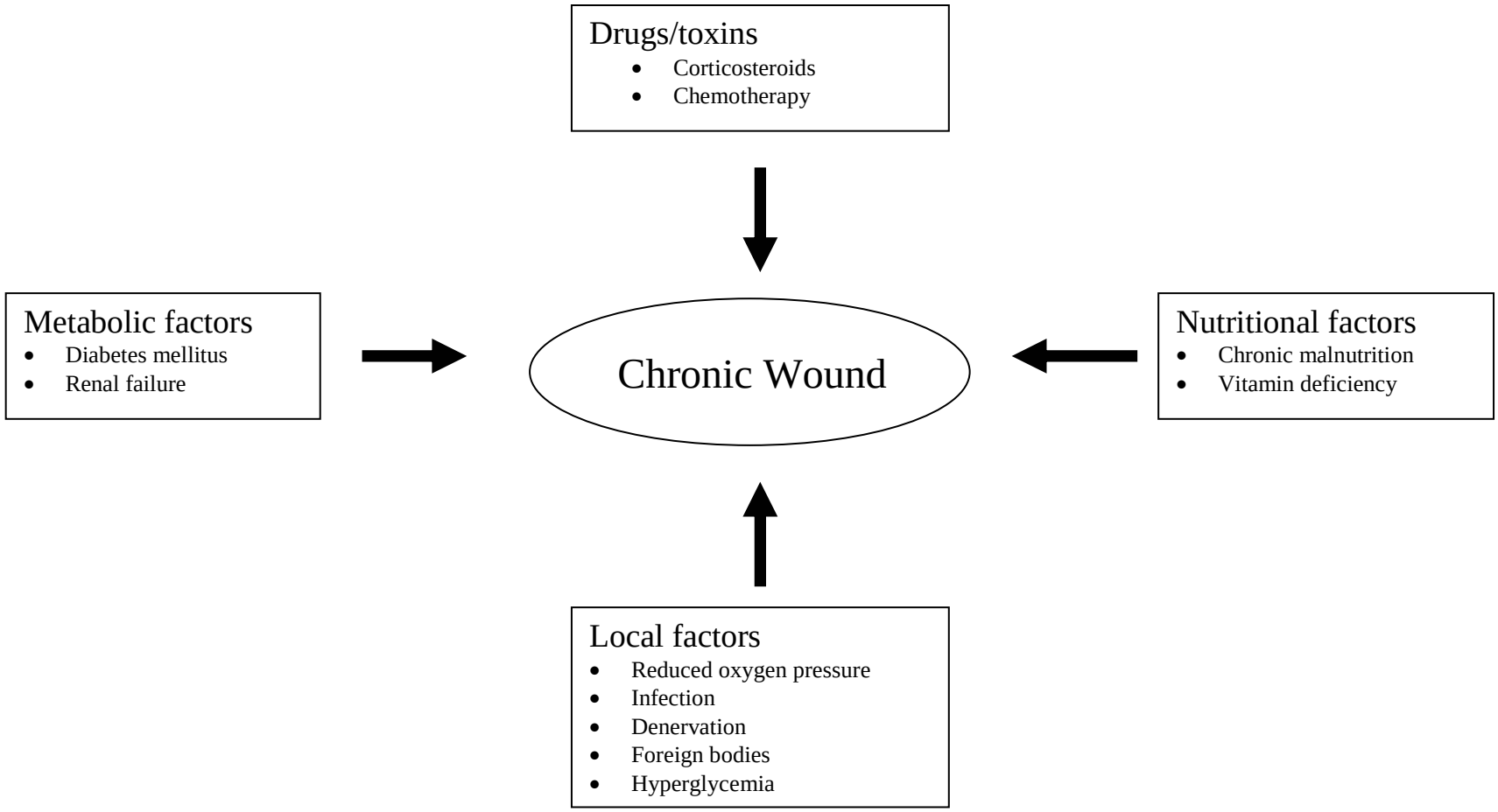

Table 2. Overview of Components of Standard Care for Skin Wounds

Common treatments	Wound-specific treatments			
	Pressure ulcers	**Diabetic ulcers**	**Vascular ulcers**	**Burns**
▪ Debridement of necrotic or infected tissue ▪ Maintenance of a moist wound environment ▪ Control of infection, and ▪ Nutritional support	▪ Weight off-loading ▪ Regular repositioning ▪ Protective dressing(s) ▪ Unna boot ▪ Bowel/bladder care for patients at risk for contamination	▪ Weight off-loading ▪ Moisture permeable dressing ▪ Blood glucose control ▪ Unna boot	▪ Moisture permeable dressing(s) *For venous ulcers:* ▪ Compression therapy ▪ Elevation of legs *For arterial ulcers:* ▪ Establishment of adequate circulation	▪ Hemodynamic resuscitation ▪ Management of comorbidities ▪ Infection control ▪ Pain control ▪ Nutritional support ▪ Rehabilitation

Also, skin grafting is not always successful, as the donor skin may not "take" at the graft site in up to 25 percent of cases (Valencia, Falabella, Kirsner, et al., 2001). In addition, the procedure is associated with a substantial amount of morbidity, such as pain and wound infections (Jones and Nelson, 2000). A recent Cochrane review of skin grafting for venous ulcers found the available efficacy studies to be of poor methodologic quality and concluded that there was limited evidence on whether skin grafting improves the rate of healing (Jones and Nelson, 2003). Finally, amputation may be the treatment of last resort for wounds that fail all other methods, if the benefit of healing the wound outweighs the adverse effects of amputation.

The setting in which wounds are treated varies widely, from home treatment to specialized wound treatment centers. This may influence the specific treatment modalities used and/or the intensity of treatment provided. In clinical practice, there is a high degree of variability in wound treatment, and there is evidence that standard wound care deviates substantially from optimal treatment (ECRI, 2000). Thus, patients who present with nonhealing wounds may not have received similar prior care. It is possible that many of these "nonhealing" wounds may actually heal with an adequate trial of optimal care. The variability in prior care is also a concern for clinical trials, since this variability contributes to the heterogeneity of the study sample.

Emerging Treatments for Skin Wounds

Vacuum-assisted closure and low-level laser therapy are two potential alternatives for treating skin wounds. Low-level laser-assisted wound healing uses a low-energy, low-power, low-level laser, also known as a "cold" laser. It is hypothesized that delivery of low-energy laser therapy in this way may stimulate the physiologic process of wound healing, thus facilitating and/or accelerating the healing process. This physiologic rationale is supported by in vitro studies, and some animal models (Basford, Hallman, Sheffield, et al., 1986; Kana, Hutchenreiter, Haina, et al., 1981; Robinson, Garden, Taute, et al., 1987).

Lasers used in wound-healing applications include the gallium-aluminum (GaAl), gallium-arsenide (GaAs), and helium-neon (HeNe) laser. The power of these lasers ranges from 0.001 watts (1 mW) to 0.05 watts (50 mW), producing minimal heating of tissue. These low-energy lasers do not damage tissue directly, as do high-energy lasers that are used to ablate or vaporize tissue. Critical aspects of laser treatment delivery include the wavelength, power density (mW/cm^2), and energy density ($Joules/cm^2$). Variability in these parameters may lead to variation in tissue response to treatment (Eells, Henry, Summerfelt, et al., 2003).

Vacuum-assisted closure uses negative pressure to assist wound healing. Negative pressure drains fluid from the wound, thus removing the substrate for growth of microorganisms. Negative pressure may also accelerate granulation tissue formation and promote angiogenesis (Lionelli and Lawrence, 2003). The mechanical stimulation of cells by tensile forces may also play a role, by increasing cellular proliferation and protein synthesis (Morykwas and Argenta, 1997).

The technique involves application of a sterile, open-pore foam dressing directly on the wound. The wound is then sealed with an occlusive drape in order to create a closed, controlled environment. A fenestrated vacuum tube is attached to the wound dressing, and connected to a collection device. Negative pressure is applied at 50–125 mm/Hg, resulting in a decrease in the local interstitial pressure, and effluent from the wound is drawn out into the collection device (Lionelli and Lawrence, 2003; Morykwas and Argenta, 1997). Initially, the vacuum pressure is applied continuously. As the amount of drainage decreases, the vacuum may subsequently be

applied on an intermittent basis (Morykwas and Argenta, 1997). The vacuum dressing is usually changed at approximately 48-hour intervals (Morykwas and Argenta, 1997).

Both the lasers used in wound healing and vacuum-assisted closure devices have been cleared for marketing by the U.S. Food and Drug Administration's (FDA's) 510(k) process, a regulatory mechanism that does not require submission of data from controlled efficacy trials.

There are a variety of other emerging treatments for skin wounds that are in various stages of development and FDA approval/clearance (Bennett, Griffiths, Schor, et al., 2003; Cross and Mustoe, 2003; Eming, Smola, and Krieg, 2002; Lionelli and Lawrence, 2003; Petrie, Yao, and Eriksson, 2003). These include: topical growth factors; bioengineered skin products; electrical stimulation; therapeutic ultrasound; novel dressings (e.g., hydrocolloids, alginates); hyperbaric oxygen; and gene therapy. However, discussion of these technologies is outside the scope of this evidence report.

Methodologic Issues in Wound-Healing Research

Confounding Factors in Healing and Treatment

As summarized in Figure 1, many factors influence wound healing (Harding, Morris, and Patel, 2002). Local factors include severity of wound (size/depth), viability of surrounding tissue, or the presence of infection or a foreign body. Systemic factors include age, functional status, nutritional status, and comorbid illnesses, such as diabetes and/or renal disease. The large number of factors that contribute to wound healing, and the high degree of variability in wound characteristics, patient characteristics, and treatment delivery result in many potential confounding factors when attempting to measure treatment effect.

Since treatment varies widely in clinical practice, it is difficult to determine whether a patient has actually received an adequate course of treatment, and whether a nonhealing wound should truly be called "refractory." In randomized, controlled trials, a relatively large proportion of "refractory" wounds heal with standard treatment (i.e., control arm). In two recent randomized, controlled trials of bioengineered skin substitute versus standard care (Falanga, Margolis, Alvarez, et al., 1998; Veves, Falanga, Armstrong, et al., 2001), 38 percent and 49 percent of "refractory" wounds, respectively, healed completely in the standard-care arm. Even in wounds present for at least 1 year (Falanga and Sabolinski, 1999), a substantial minority (19 percent) healed with standard treatment.

As a result of these multiple confounding factors, it is difficult to interpret outcomes from single-arm trials that lack a control group, since improvement may be due to factors other than the specific intervention being tested. A concurrent control group is necessary to permit measurement of a treatment effect above that related to optimization of standard treatment or due to the natural history of wound healing. Randomized assignment to treatment group is essential in maximizing the likelihood that confounding factors are equally distributed across treatment groups.

Design of Randomized, Controlled Trials for Wound-Healing Treatments

The FDA has prepared a draft guidance document that outlines difficulties in conducting trials to assess the effectiveness of interventions for wound healing. This document offers

guidance in optimal design of such trials (U.S. Food and Drug Administration, 2000). The principals set forth by the FDA are summarized here and have been adapted in the development of the protocol for this systematic review.

Patient selection. The study population should ideally consist of patients with one particular type of skin wound, because of the different pathophysiology of each wound type and potential differences in response to therapy. A standardized definition of an adequate course of optimal care should be used in order to enroll a clinically refractory population. Alternatively, a run-in treatment period in which all patients receive an adequate course of optimal care may be utilized in order to exclude patients who heal with optimal standard care. This ensures that patients who enter the study are truly refractory to standard care.

Specific enrollment criteria that exclude conditions known to impede healing, such as very deep wounds or immunosuppression, may be helpful in reducing variability in measured outcomes. This may aid in determining the specific effect of treatment, but may also lead to reduced generalizability.

Patient assessment. Thorough assessment prior to treatment is important in accurately characterizing the features of the wound and in measuring potential confounders of outcome. Accurate recording of wound size, depth, and duration are important, since these are major predictors of healing (de Araujo, Valencia, Federman, et al., 2003).

Wounds can be measured by a variety of objective means, including direct tracing, planimetry, and stereophotogrammetry (ECRI, 2000). Wound imaging by photographic methods may also aid in the objective measurement of wounds. Other objective measures such as transcutaneous oxygen tension (t_cpO_2), ankle/brachial index, and microfilament testing may also be helpful in assessing the baseline wound characteristics.

A thorough assessment and measurement of other potential confounding variables should be performed at baseline and at followup time points. These include patients' clinical and demographic characteristics, comorbid medical conditions, and prior treatment received.

Treatment issues. Double-blinding of treatment is the optimal study design to minimize bias in treatment delivery and outcome assessment. A sham placebo should be considered in the control arm to allow for double-blinding. However, double-blinding may be difficult for some devices, especially for a therapy such as vacuum-assisted closure. The difficulties of double-blinding need to be balanced against the benefit in minimizing bias in interpreting the trial outcomes.

Researchers should ensure that high-quality standard treatment is delivered to the control group. "High-quality" treatment means that all of the main modalities of standard care from wound treatment guidelines are included (Table 2). No definitive standard treatment guidelines exist, but there are guidelines that incorporate modalities of standard care (e.g., from the Wound Ostomy and Continence Nurses Society [www.wocn.org]).

It is also important to ensure that standard treatment modalities are identical between groups in order to avoid performance bias. The experimental treatment arm should not include additional elements of standard care that are not delivered to the control group. The experimental treatment arm should not incorporate a greater intensity of standard care than the control arm. The importance of equal intensity of care was demonstrated in a prior multicenter trial of platelet-derived growth factor for chronic wounds (Cross and Mustoe, 2003). In this

study, the rate of healing was significantly higher in centers that incorporated more frequent debridement (Cross and Mustoe, 2003).

An adequate followup period is required to demonstrate durability of response and adverse effects. It is recommended that patients remain enrolled in studies for at least 3 months following initiation of treatment (U.S. Food and Drug Administration, 2000). This is the minimum amount of time required to evaluate the number of healed wounds that recur. Some experts recommend an even longer minimum duration. For example, Steed (2003b) recommends that the minimum duration of a clinical trial include a run-in period of standard care, followed by 20 weeks of treatment, and an additional 12 weeks of followup.

Outcomes and outcome measurement. Outcome measurement should focus on outcomes that are quantitative and clinically meaningful (Jeffcoate and Harding, 2003; Steed, 2003b). The most important outcomes to be considered are: (1) the percent of patients with complete healing; and (2) time to complete healing.

Other outcomes that may also be clinically meaningful are: (1) facilitating surgical wound closure; (2) change in wound size; (3) improved cosmesis; (4) improved activities of daily living; (5) improved quality of life; (6) pain; (7) transcutaneous oxygen tension; (8) infections; and (9) need for debridement.

In some cases, particularly for vacuum-assisted closure, the treatment may not be expected to result in complete healing. Rather, the treatment may be intended to advance the wound to a stage where healing is possible, either by continued conventional treatment or by surgical closure. These goals represent intermediate treatment outcomes. If the overall treatment strategy is successful, the benefit of these intermediate outcomes will ultimately be reflected in improved rates of complete healing. The intermediate outcome states are more difficult to measure, but are likely partly represented by the secondary outcomes of wound size and facilitation of surgical closure.

Outcome assessment should also include measurement of adverse events that result from the treatment or from the natural history of the disorder. These include: (1) local adverse effects (pain, discharge, dermatitis); (2) immune reactions; (3) infections; (4) limb amputations; and (5) discontinuation from treatment, including assessment of whether discontinuation is a result of the treatment.

Ascertainment of outcomes should be ideally performed by an independent, blinded individual. This is especially important in situations where patients and/or treating physicians are not blinded to treatment.

Chapter 2. Methods

This report is the product of a systematic review of the evidence on the outcomes of two technologies for wound healing: low-level laser therapy and vacuum-assisted closure. The protocol for this review was designed prospectively as much as possible to define: study objectives; search strategy; patient populations of interest; study selection criteria; outcomes of interest; data elements to be abstracted and methods for abstraction; and methods for study quality assessment.

This chapter of the report describes the objectives, key questions, and search strategies used to find articles; the criteria and methods for selecting eligible articles; the methods for data abstraction; the methods for quality assessment; and finally, the peer review and technical assistance received during the project.

Objective and Key Questions

The objective of this evidence report is to systematically review and synthesize the available evidence on the effectiveness of low-level laser treatment and vacuum-assisted closure for wound healing. To achieve this objective, the following key questions will be addressed:

Low-Level Laser Treatment

In the treatment of chronic, nonhealing wounds, what are the outcomes of low-level laser therapy for specific indications and patient types:

a) as a substitute for standard therapy; or
b) as an adjunct to standard therapy, compared with standard therapy alone?

Vacuum-Assisted Closure

In the treatment of various wounds, what are the outcomes of vacuum-assisted closure for specific indications and patient types:

a) as a substitute for standard dressings; and
b) as an adjunct to standard therapy, compared with standard therapy alone?

Search Strategy

Electronic database searches were completed of MEDLINE® (via PubMed), EMBASE, and the Cochrane Controlled Trials Register. The MEDLINE® search covered references entered onto the database from January 1, 1966 through June 8, 2004. The Cochrane Controlled Trials Register search was completed in 2003, through issue number 4. The EMBASE search covered references entered through June 14, 2004. For detailed search terms, please refer to Appendix A.[1]

The search was limited to studies on human subjects with English-language abstracts. Papers published in foreign languages were reviewed if the English-language abstract appeared to meet

[1] Appendixes will be provided electronically at http://www.ahrq.gov/clinic/tp/woundtp.htm

inclusion criteria. Results of the search and study selection were reviewed by the Technical Expert Panel for this project, in order to identify additional studies.

In addition, two companies that produce lasers used in wound healing (Microlight Corporation of America and Photothera), as well as the major producer of vacuum-assisted closure devices (V.A.C.®, Kinetic Concepts Inc. [KCI]), were contacted and were invited to submit evidence-based information for the review. The specific request was for "lists of published, randomized, controlled trials (RCTs), published abstracts of RCTs within the past 2 years, and published articles on study design, or protocols of any RCTs (published or in progress)."

In some cases, device approval applications to the U.S. Food and Drug Administration (FDA) contain data from randomized, controlled efficacy trials. If available, such trials should be sought by the literature search. However, lasers used in wound healing and vacuum-assisted closure devices have been cleared for marketing by the FDA's 510(k) process, a regulatory mechanism that does not require submission of data from controlled efficacy trials.

Patients, Settings, Interventions, and Outcomes

Patient Populations

Low-level laser treatment. With respect to low-level laser treatment, chronic wounds may be classified in a variety of ways. The simplest way is to distinguish between cutaneous ulcers and burns. However, a more comprehensive classification system places chronic wounds into these categories:

- pressure ulcers
- metabolic disorders (e.g., diabetes mellitus)
- vascular insufficiency
- inflammatory disorders
- malignancies
- infections
- miscellaneous (e.g., burns)

Vacuum-assisted closure. The review for vacuum-assisted closure addressed:

- chronic wounds (as above)
- acute wounds
- traumatic wounds
- subacute wounds
- dehisced wounds
- partial thickness burns
- diabetic ulcers
- pressure ulcers
- flaps
- grafts

Study populations with both acute and chronic wounds will be examined carefully with respect to the duration of the wound and the types of interventions that have been performed prior to treatment with low-level laser therapy or vacuum-assisted closure. Some wounds may be described as refractory; that term should be defined as specifically as possible in terms of the types and duration of previous treatments. Similarly, the term "chronic" should be defined in as much detail as possible.

Practice Settings

Low-level laser treatment and vacuum-assisted closure may be used in the following settings:

- Surgical centers
- Hospitals
- Specialized wound care centers
- Nursing or rehabilitation facilities
- Physicians' offices
- Physical therapy offices
- Homes

Interventions/Technologies of Interest

Standard care. Standard wound care is multifactorial. Among its components are:

- Debridement
- Dressings
- Topical or systemic medications
- Compression
- Skin grafting
- Skin equivalents
- Improved nutrition
- Convalescence
- Physical therapy
- Treatment of underlying disorder

Low-level laser treatment. This review will focus on lasers that have been described as low-energy, low-power, low-level or "cold" lasers. The power of these lasers ranges from 0.001 watts (1 mW) to 0.05 watts (50 mW), producing minimal heating of tissue. Lasers used in wound healing applications include the gallium-aluminum (GaAl), gallium-arsenide (GaAs) and helium-neon (He-Ne) laser. Characteristics of laser treatment that would be of interest include laser type, intensity (measured in Joules per square centimeter of wound surface [Joules/cm^2]), duration of each session, frequency of sessions, and overall duration of treatment. Other prior and concurrent treatments will be examined in detail.

Vacuum-assisted closure. The vacuum-assisted closure technique involves application of a sterile, open-pore foam dressing directly on the wound, which is then sealed with an adhesive

drape, thus converting an open wound to a closed, controlled wound. An evacuation tube, embedded in the dressing, feeds into a collection canister. When subatmospheric pressure is applied, effluent from the wound is drawn out. Attention will be paid to the degree of negative pressure applied, frequency of dressing changes, and duration of use of the vacuum device. Other prior and concurrent treatments will be examined in detail.

Outcomes of Interest

In general, outcomes should be standard, valid, reliable and clinically meaningful. A 2000 draft guidance document produced by the FDA (U.S. Food and Drug Administration, 2000) stated that wound healing outcomes should focus on the probability or speed of achieving complete wound closure. Intermediate outcomes such as wound size are problematic because of uncertainty about the validity of measurement techniques and clinical meaningfulness.

- Primary outcomes:
  - incidence of complete wound closure
  - time to complete closure
  - adverse events

- Secondary outcomes
  - facilitating surgical closure
  - need for debridement
  - infections
  - pain
  - activities of daily living
  - quality of life
  - improved cosmesis

Other secondary outcomes abstracted were change in wound size and transcutaneous oxygen tension (t_cpO_2); however, these were considered to be of less clinical importance.

Study Selection Criteria

As noted in the Introduction chapter of this Report, randomized, controlled trials are necessary to adequately assess the effectiveness of wound-healing interventions. Wound care entails multiple treatment factors, and it can be very difficult to attribute an effect to a specific factor. In addition, confounding could occur due to differences in patient characteristics and the quality and type of treatment factors. Randomization is the best method to assemble treatment groups that are comparable on known and unknown patient confounders.

This systematic review will select only randomized, controlled trials meeting the following criteria:

1) The trial must involve one of the following comparisons of interventions
   a) Either low-level laser treatment or vacuum-assisted closure, compared with other wound healing interventions (alternative intervention trials).
   b) Either low-level laser treatment or vacuum-assisted closure in addition to standard wound care, compared with standard wound care alone (incremental benefit trials).
   c) Either low-level laser treatment or vacuum-assisted closure, compared with a sham intervention (placebo trials).

2) For low-level laser treatment, patient selection criteria must target those with chronic wounds. For vacuum-assisted closure, patient selection may address those with chronic wounds or other types of wounds (see "Patient Populations," above).

3) The trial must report on at least one of the outcomes listed above under "Outcomes of Interest."

4) The trial must be published as a full journal article and not merely as a conference abstract.

Any citation lacking an abstract was excluded if the article was published in a non-English-language journal. Otherwise, when abstracts were missing, the full-text article was retrieved for review if the title suggested it might possibly meet the study selection criteria.

For low-level laser, the searches found 482 references: 435 were excluded on the first screen, 47 were retrieved, 11 met selection criteria and were abstracted, and 36 were excluded on the second screen. For vacuum-assisted closure, the searches found 467 references: 416 were excluded on the first screen, 51 were retrieved, six met selection criteria and were abstracted, and 45 were excluded on the second screen.

Methods of the Review

Search results were stored in ProCite® databases. Titles and abstracts were screened by a single reviewer who marked each citation as either eligible for review as full-text articles or ineligible for full-text review. A second reviewer reviewed all citations marked as ineligible by the first reviewer. Agreement between raters was necessary to exclude a citation from full-text review. An "eligible" rating was necessary from only one reviewer to place a citation in the pool of those to be retrieved for full text review.

In reviewing full-text articles to determine eligibility for data abstraction, a single reviewer determined whether each paper should be either: (1) included in systematic review; (2) excluded from systematic review; or (3) discussed with additional reviewer.

Evidence tables were developed in Microsoft Excel® and Microsoft Word®. One reviewer performed primary data abstraction of all data elements into the evidence tables, and a second reviewer checked the evidence tables for accuracy.

A procedure was established in case of disagreements that could not be resolved between the two reviewers. In such cases, the EPC Program Director was consulted and then, if necessary, the relevant members of the Technical Expert Panel.

Assessment of Study Quality

This systematic review applies the general approach to grading evidence developed by the U.S. Preventive Services Task Force (Harris, Helfand, Woolf, et al., 2001). Two independent reviewers rated study quality and disagreements in ratings were resolved by consensus. Following are the study design criteria and rating definitions developed by Harris and colleagues.

Study Design Criteria

- Initial assembly of comparable groups: adequate randomization, including concealment and whether potential confounders (e.g., other concomitant care, patient characteristics) were distributed equally among groups
- Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- All important outcomes considered
- Analysis: adjustment for potential confounders, intention-to-treat analysis

Definition of Quality Ratings

In applying the Harris rating system to the studies selected for this systematic review, several rules were followed. To conclude that a study achieved initial assembly of comparable groups, it had to use an adequate randomization method and had to have equal distribution of confounders. Adequate randomization was defined as either central randomization or use of opaque envelopes (concealment). For the purposes of this review, equal distribution of confounders was defined as a minimal difference (less than 20%) in mean values between groups on age, wound duration and wound size. Low loss to followup and maintenance of comparable groups was defined as loss less than 20% of the initial sample and no differential loss to followup between groups.

To consider measurements reliable, valid and equal, the article had to provide a clear description of wound measurement methods that appeared reproducible. Examples include use of photographic or digital transfer of wound tracings and/or use of computer software to calculate wound size. Liquid or plaster used to measure wound volume was also acceptable. Use of a blinded outcome assessor was also necessary to fully satisfy this quality dimension. Clear, detailed descriptions of both control and treatment interventions were sought. Analysis of results was considered appropriate if the investigators adjusted for confounders and analyzed by intention-to-treat, which was defined as analyzing all randomized patients or no more than 5% loss of the initial sample. See Table 3 for the quality criteria and ratings system applied to the evidence tables in Chapter 3.

Good. Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (followup at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are

considered; and appropriate attention to confounders in analysis. In addition, for RCTs, intention-to-treat analysis is used.

Fair. Studies will be graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is done for RCTs.

Poor. Studies will be graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention-to-treat analysis is lacking.

Table 3. Quality Rating Criteria and Ratings

Dimension	Components
Initial Assembly of Comparable Groups	Adequate randomization (concealed or centralized)
	Equal distribution of confounders (at least age, wound size, wound duration)
Low Loss to Followup, Maintenance of Comparable Groups	No differential loss to F/U or Low Overall Loss to F/U (>20%)
Measurements Reliable, Valid, Equal	Clearly described, reproducible measurement
	Blinded outcome assessment
Interventions Comparable/Clearly Defined	
Appropriate Analysis of Results	Adjustment for Confounders
	Intention-to-treat analysis (all randomized analyzed to 5% or less loss)

Dimension Ratings	Quality Ratings
Yes = all components adequate, satisfied	Good = All dimensions satisfied
No = one or more component inadequate, not satisfied	Fair = all dimensions satisfied or partially satisfied
Partial = one or more components adequate, none inadequate, partially satisfied	Poor = one or more dimension not satisfied
? = unclear if any components satisfied	

Technical Expert Panel and Peer Review

The development of this evidence report was subject to extensive expert review, including ongoing guidance from a Technical Expert Panel (TEP) and document review by the TEP.

The draft report was also reviewed by a panel of external peer reviewers that included experts in anesthesiology, dermatology, nursing, otolaryngology and orthopedic surgery, physical therapy, plastic and reconstructive surgery, podiatry, therapeutic laser technology, and undersea and hyperbaric medicine. Reviews were also solicited from the American Academy of Wound Management, the Association for the Advancement of Wound Care, and Wound, Ostomy and Continence Nurses Society. Comments were elicited from external peer reviewers using a structured comment form, compiled, and submitted with a description of comment disposition to the Agency for Healthcare Research and Quality (AHRQ). Appendix B lists the members of the Technical Expert Panel and external peer reviewers.[2]

[2] Appendixes will be provided electronically at http://www.ahrq.gov/clinic/tp/woundtp.htm

Chapter 3. Results

Part I: Low-Level Laser Therapy

The first part of this chapter reviews evidence on the following questions:

In the treatment of chronic nonhealing wounds, what are the outcomes of low-level laser therapy for specific indications and patient types:

a) as a substitute for standard therapy; or

b) as an adjunct to standard therapy, compared with standard therapy alone?

Overview

The only previous systematic reviews available on the use of laser therapy for wound healing have been produced by a single group in the United Kingdom (Flemming and Cullum, 2003; Cullum, Nelson, Flemming et al. 2001; Flemming, Cullum and Nelson, 1999). These reviews found no supportive evidence for a benefit of low level laser therapy in healing of venous leg ulcers. All 4 studies abstracted by these reviews are included in the present review.

Among excluded studies, 3 were randomized controlled trials. Two were excluded because they did not select patients with chronic wounds (Lagan, Clements, McDonough, et al., 2001; Fernando, Hill, and Walker, 1993). The third study reported only on an outcome that was not of interest to this review, skin temperature (Schindl, Heinze, Schindl et al., 2002). Four comparative studies published in foreign languages were excluded. One German study was excluded because it did not select patients with chronic wounds (Zimmerman, 1990). Three Russian studies were examined by a Russian reader who determined that subjects were not assigned to groups randomly (Babadzhanov and Sultanov, 1998; Gostishchev, Vertianov, Novochenko, et al., 1987; Gostishchev, Vertianov, Shur, et al., 1985). No other nonrandom comparative studies published in English were found. All other excluded studies were case series or case reports.

Review of search results identified a total of 11 studies (n=413; (Bihari and Mester, 1989; Crous and Malherbe, 1988; Franek, Krol, and Kucharzewski, 2002; Iusim, Kimchy, Pillar, et al., 1992; Lagan, McKenna, Witherow, et al., 2002; Lucas, Coenen, and De Haan, 2000; Lucas, van Gemert, and de Haan, 2003; Lundeberg and Malm, 1991; Malm and Lundeberg, 1991; Nussbaum, Biemann, and Mustard, 1994; Santoianni, Monfrecola, Martellotta, et al., 1984) that met study selection criteria for low-level laser therapy (Evidence Table 1).

Details about studies meeting selection criteria are provided in Evidence Tables 2–5, each of which is divided into three subsets. The "A" subsets include seven studies with placebo controls, the "B" subsets contain three studies assessing the effects of low-level laser therapy plus standard treatment versus standard treatment alone, and the "C" subsets describe one study comparing the use of ultraviolet light and low-level laser therapy. Evidence Table 2 presents patient characteristics. Evidence Table 3 focuses on treatment details. Evidence Table 4 describes outcomes assessment. Evidence Table 5 provides results. Information shown in Evidence Tables 1–5 served as the basis for study quality ratings. Study quality ratings are included in Evidence Table 6 (See Table 3, Chapter 2, Methods, for study quality criteria and ratings).

Evidence Table 1. Summary of Low-Level Laser Therapy Studies

Study	n Random-ized	Patient Selec-tion	Control (Cx)	Treatment (Tx)	Comparable Characteristics	Alloca-tion	Tx Descrip-tion	Wound Measure-ment	Complete Healing	Adjust-ment	Intent-to-Treat
Franek, Krol, and Kucharzewski, 2002	65; Cx1: 22; Cx2: 22; Tx: 21	LE venous ulcers	Cx1: SC+sham Cx2: SC	SC+laser	Yes: age, size No: duration	random	Cx, Tx clear	Digital, plani-metry SW	NR	?	?
Lagan, McKenna, Witherow, et al., 2002	15; Cx: 7; Tx: 8	Chronic LE venous ulcers	SC+sham	SC+laser	?: age, size, duration	random	Cx, Tx clear	Digital, SW, blind	NR	?	Yes
Malm and Lundeberg, 1991	42; Cx: 21; Tx: 21	LE venous ulcers	SC+sham	SC+laser	Yes: age, size ?: duration	random	Cx, Tx clear	Tracings, blind	Tx=Cx	?	No
Lundeberg and Malm, 1991	46; Cx: 23; Tx: 23	LE venous ulcers	SC+sham	SC+laser	Yes: age, size ?: duration	random	Cx, Tx clear	Tracings, blind	Tx=Cx	?	No
Bihari and Mester, 1989	45; Cx: 15; Tx1: 15; Tx2: 15	Resist-ant LE ulcers	SC+sham	Tx1: SC+hand laser; Tx2; SC+machine laser	?: age, size, duration	random	Cx, Tx clear	Blind	Tx1=Cx Tx2>Cx	?	Yes
Santoianni, Monfrecola, Martellotta, et al., 1984	>28	Chronic LE venous ulcers	SC+laser misdirection	Tx1: SC+1 J laser; Tx2: SC+4 J laser	?: age, size, duration	random	Cx, Tx clear	Photos, tracings	NR	?	?
Iusim, Kimchy, Pillar, et al., 1992	21; Cx: 7, Tx1: 8; Tx2: 6	Resist-ant postop wounds	SC+sham	Tx1: SC+red laser; Tx2: SC+IR laser	Yes: age, size ?: duration	random	Cx, Tx clear	Photos	NR	?	Yes
Lucas, van Gemert, and de Haan, 2003	86; Cx: 47; Tx: 39	Pres-sure ulcers	SC	SC+Laser	Yes: age, size, duration	Central-ly ran-dom	Cx, Tx clear	Photos, tracing, blind	Tx=Cx	?	Yes
Nussbaum, Biemann, and Mustard, 1994	20; Cx: 9 Tx1: 6 Tx2: 5	Pres-sure ulcers	SC	Tx1: SC+Laser; Tx2: SC+US/UV	Yes: age, duration No: size	random	Cx, Tx clear	Digital, blind	Tx1=Cx Tx2=Cx Tx2>Tx1	?	No

Evidence Table 1. Summary of Low-Level Laser Therapy Studies (continued)

Study	n Random-ized	Patient Selec-tion	Control (Cx)	Treatment (Tx)	Comparable Characteristics	Alloca-tion	Tx Descrip-tion	Wound Measure-ment	Complete Healing	Adjust-ment	Intent-to-Treat
Lucas, Coenen, and De Haan, 2000	16 Cx: 8 Tx: 8	Pres-sure ulcers	SC	SC+Laser	Yes: age, duration, size	random	Cx, Tx clear	Photos, tracing, blind	Tx=Cx	?	Yes
Crous and Malherbe, 1988	6 Cx: 3 Tx: 3	Chronic LE venous ulcers	SC+UV	SC+Laser	?: age, duration, size	random	Cx, Tx clear	Photos, blind	NR	?	Yes

Abbreviations: See end of Report

Evidence Table 2. Low-Level Laser Therapy, Patient Characteristics

A. Placebo-Controlled Studies

Study	Comparison	Inclusion	Exclusion	n, Randomized	n, Withdrew	Age	Gender	Wound Duration	Wound Area	Wound Location
Franek, Krol, and Kucharzewski, 2002; Bytom, Poland	Cx1: compressive/ topical therapy + sham laser Cx2: compressive/ topical therapy Tx: compressive/ topical therapy + laser	symptomatic venous crural ulceration; chronic venous insufficiency; ABI > 0.8, Doppler US ruled out arterial component		65 Cx1: 22 Cx2: 22 Tx: 21		Cx1: mn 65, rng 41-88 Cx2: mn 66, rng 43-86 Tx: mn 65, rng 44-80	Cx1: 10 M, 12 F Cx2: 3 M, 19 F Tx: 4 M, 17 F	Cx1: mn 30 mo, rng 1 wk - 18 yr Cx2: mn 51 mo, rng 4 mo - 16 yr Tx: mn 41 mo, rng 2 wk - 24 yr	Cx1: mn 13.25 sq cm, rng 0.41-55.14 Cx2: mn 16.20, rng 1.9-87.62 Tx: mn 15.76, rng 0.51-59.64	(Cx1, Cx2, Tx): lateral ankle (4, 3, 5); medial ankle (5, 10, 4); lateral crural (4, 0, 7); medial crural (4, 1, 2); posterior crural (1, 3, 0); anterior crural (4, 5, 2); foot (0, 0, 1)
Lagan, McKenna, Witherow, et al., 2002; Ulster, UK	Cx: standard nursing care + sham laser Tx: standard nursing care + laser	15 pts with 16 chronic venous/ mixed venous/ arterial ulcers; recruited from specialized outpatient leg ulcer clinic; age 30-85; able to attend weekly assessment; no current/ previous laser;	grossly infected wounds; medications contraindicated for laser; noncompliant pts; active/ suspected carcinoma; photosensitive skin; contra-indications for laser; referral source re-quests particular treatment	15 Cx: 7 Tx: 8		Cx+Tx: mn 69.9, SD 13.8	Cx+Tx: 5 M, 10 F	Cx+Tx: mn 11.3 mo, SD 8.5		

Evidence Table 2. Low-Level Laser Therapy, Patient Characteristics (continued)

A. Placebo-Controlled Studies (cont'd)

Study	Comparison	Inclusion	Exclusion	n, Ran-domized	n, Withdrew	Age	Gender	Wound Duration	Wound Area	Wound Location
Malm and Lundeberg, 1991; Stockholm, Sweden	Cx: standard conservative treatment + sham laser Tx: standard conservative treatment + laser	venous leg ulcers	skin allergy to standard treatment, peripheral arterial disease, rheumatoid arthritis, diabetes mellitus, traumatic venous ulcer, ankle pressure < 75 mmHg	42 Cx: 21 Tx: 21	10 Cx: 6 Tx: 4 (2 allergy to paste bandage, 7 unable to attend laser treatment regularly, 1 excessive pain)	Cx: mn 61, rng 46-76 Tx: mn 60, rng 43-77	Cx: 9 M, 12 F Tx: 10 M, 11 F		Cx: mn 14 sq cm, rng 3-44 Tx: mn 12, rng 4-52	
Lundeberg and Malm, 1991; Stockholm, Sweden	Cx: standard treatment + sham laser Tx: standard treatment + laser	venous leg ulcers	skin allergy to standard treatment, peripheral arterial disease, rheumatoid arthritis, diabetes mellitus, traumatic venous ulcer	46 Cx: 23 Tx: 23	12 Cx: 4 Tx: 8 (4 allergy to paste bandage, 2 excessive pain, 6 unable to attend regularly)	Cx: mn 54, rng 41-69 Tx: mn 62, rng 49-73	Cx: 9 M, 14 F Tx: 8 M, 15 F		Cx: mn 11 sq cm, rng 4-36 Tx: 9, rng 3-32	

Evidence Table 2. Low-Level Laser Therapy, Patient Characteristics (continued)

A. Placebo-Controlled Studies (cont'd)

Study	Comparison	Inclusion	Exclusion	n, Randomized	n, Withdrew	Age	Gender	Wound Duration	Wound Area	Wound Location
Bihari and Mester, 1989; Budapest, Hungary	Cx: adjuvant therapy + sham laser Tx1: adjuvant therapy + hand-held laser Tx2: adjuvant therapy + machine-scanned laser	crural ulcers proven resistant to conventional therapy ('torpid' ulcers)		45 Cx: 15 Tx1: 15 Tx2: 15						
Santoianni, Monfrecola, Martellotta, et al., 1984; Naples, Italy	Cx: compresses + laser pointed away from wound Tx1: compresses + laser 1 J/sq cm Tx2: compresses + laser 4 J/sq cm	chronic venous leg ulcers; hospitalized		≥30				2-23 mo		

Evidence Table 2. Low-Level Laser Therapy, Patient Characteristics (continued)

A. Placebo-Controlled Studies (cont'd)

Study	Comparison	Inclusion	Exclusion	n, Randomized	n, Withdrew	Age	Gender	Wound Duration	Wound Area	Wound Location
Iusim, Kimchy, Pillar, et al., 1992; Haifa	Cx: regular treatment + placebo Tx1: regular treatment + red light laser Tx2: regular treatment + infrared light laser	Postoperative wounds resistant to conventional therapy: neuropathic foot ulcer, pressure sores, venous ulcers, diabetic foot, amputation/ other surgery with delayed wound healing		21 pts: Cx: 7, Tx1: 8 Tx2: 6; 31 wounds: Cx: 11, Tx1: 9, Tx2: 11		Cx: mn 74.5, rng 60-87 Tx1: mn 71.1, rng 57-85 Tx2: 74.5, rng 44-88	Cx: 4 M, 4 F Tx1: 3 M, 4 F Tx2: 4 M, 2 F	resistant to conventional therapy	Cx: mn 3.8 sq cm, rng 0.25-18 Tx1: mn 3.2, 0.1-10.5 Tx2: mn 4.7, rng 0.25-19	

Evidence Table 2. Low-Level Laser Therapy, Patient Characteristics (continued)

B. Studies of Incremental Effect over Standard Treatment

Study	Comparison	Inclusion	Exclusion	n, Randomized	n, Withdrew	Age	Gender	Wound Duration	Wound Area	Wound Location
Lucas, van Gemert, and de Haan, 2003; Amsterdam, Netherlands	Cx: consensus therapies Tx: consensus therapies + low level laser therapy	Consecutive pts, stage III (full-thickness, into subcutaneous/fat layer) decubitus ulcers, 3 nursing homes; 1 wound/pt; no age restriction	Wound area > 30 sq cm; wound completely occluded by eschar; wound duration > 1 yr; diabetic pts with serious metabolic disorders; terminally ill pts	86 Cx: 47 Tx: 39 (19/105 refused consent)	5 Cx: 3 (1 died, 1 hospitalized, 1 stage IV) Tx: 2 (1 died, 1 stage IV)	Cx: mn 83.5, SD 8.9, med 85, rng 49-100 Tx: mn 81.3, SD 9.6, med 82, rng 49-94	Cx: 18 M, 29 F Tx: 14 M, 25 F	Cx: mn 3.3 wk, SD 5.1, med 2, rng 0.5-30, msg 3 Tx: mn 2.9, SD 4, med 2, rng 0.5-22, msg 3	Cx: mn 350 sq mm, SD 378, < 100 - 17, 100-500 - 22, > 500 - 8 Tx: mn 317, SD 396, < 100 - 14, 100-500 - 20, > 500 – 5	(Cx, Tx): gluteal (8, 4), sacrum/ coccyx (14, 14), greater trochanter (1, 0), medial femoral condyle (0, 1), calcaneus (14, 13), lateral malleolus (5, 3), other (5, 4)
Nussbaum, Biemann, and Mustard, 1994; Toronto, Canada	Cx: standard treatment alone Tx1: standard treatment + laser Tx2: standard treatment + US/ UV-C	hospitalized, spinal cord injury, skin wound		20 pts Cx: 9 Tx1: 6 Tx2: 5; 22 wounds Cx: 9 Tx1: 7 Tx2: 6	4 Cx: 3 Tx1: 1 (2 transferred to acute care hospitals, 2 elected surgical closure)	Cx: mn 36, rng 15-46 Tx1: mn 42, rng 30-61 Tx2: mn 42.2, rng 26-59	Cx: 5 M, 1 F Tx1: 5 M, 1 F Tx2: 6 M, 0 F	> 6 wk: Cx: 4 Tx1: 6 Tx2: 6; < 1 wk: Cx: 2 Tx1: 0 Tx2: 0	Cx: mn 2.1 sq cm, rng 0.7 - 3.3 Tx1: 2.8, rng 0.9 - 5.4 Tx2: 1.9, rng 0.9 - 3.1 (NS)	(Cx, Tx1, Tx2): ankle (3, 1, 0); coccyx (2, 1, 2); trochanter (1, 1, 1); calf (0, 1, 0); chest (0, 1, 1); heel (0, 0, 1); ischium (0, 0, 1); thigh (0, 1, 0)

Evidence Table 2. Low-Level Laser Therapy, Patient Characteristics (continued)

B. Studies of Incremental Effect over Standard Treatment (cont'd)

Study	Comparison	Inclusion	Exclusion	n, Randomized	n, Withdrew	Age	Gender	Wound Duration	Wound Area	Wound Location
Lucas, Coenen, and De Haan, 2000; Amsterdam, Netherlands	Cx: consensus treatment Tx: consensus treatment + LLLT	consecutive pts, stage III pressure ulcers, 4 nursing homes	Wounds > 30 sq cm, wounds completely occluded by eschar, constant/ invariable ulceration > 1 yr, diabetics with serious metabolic disorders, terminal pts	16 Cx: 8 Tx: 8		Cx: med 88, rng 72-95 Tx: med 87.5, rng 73-92	Cx: 0 M, 8 F Tx: 2 M, 6 F	(wk) Cx: med 3, rng 1-10 Tx: med 3, rng 1-9	Cx: mn 82.5 sq mm, rng 30-527 Tx: mn 94, rng 9-513	(Cx, Tx): gluteal (3, 1); sacrum/coccyx (2, 1); calcaneus (2, 2); medical femoral condyle (1, 1); lateral malleolus (0, 2)

C. Laser Treatment versus Ultraviolet Light

Study	Comparison	Inclusion	Exclusion	n, Randomized	n, Withdrew	Age	Gender	Wound Duration	Wound Area	Wound Location
Crous and Malherbe, 1988	Cx: medical treatment + ultraviolet light Tx: medical treatment + laser	Distal lower extremity chronic venous ulcers; 5 of 6 hospitalized		6 Cx: 3 Tx: 3		Cx: rng 70-79 Tx: rng 65-77	Cx: 2 M, 1 F Tx: 1 M, 2 F	Cx: rng 0.4-30 yr Tx: rng 6-12 yr		

Evidence Table 3. Low-Level Laser Therapy, Treatments

A. Placebo-Controlled Studies

Study	Allocation	Comparison	Control	Treatment	Treatment Regimen
Franek, Krol, and Kucharzewski, 2002; Bytom, Poland	groups established at random, Cx1 and Tx groups in Dermatology Ward of same hospital, Cx2 group treated in different hospital	Cx1: compressive/ topical therapy + sham laser Cx2: compressive/ topical therapy Tx: compressive/ topical therapy + laser	compressive: single layer elastic dressings; topical: baths of potassium permanganate, 0.1% copper sulfate, compresses with colistins, fibrolaan, chloramphenicol and gentamicin under a dressing; changed every few days; sham: radiation absorbing system in laser	GaA1As 810 nm, 4 J/sq cm, 65 mW; duration of treatment adjusted to ulcer size keeping dose constant	5x/wk, mn 4.5-5.0 wk
Lagan, McKenna, Witherow, et al., 2002; Ulster, UK	prepared random allocation listing held by the physical therapist delivering the sham/laser treatment, only unblinded party, played no other role in the trial	Cx: standard nursing care + sham laser Tx: standard nursing care + laser	standard nursing care: cleansing with water, debridement, dressings and/or compression bandaging; sham laser: nonemitting array	Biotherapy 3ML system (Omega Laser Systems, UK) GaA1As 660-950 nm, 12 J/sq cm, 532 mW, noncontact technique, unit maintained 0.5 cm from surface	1x/wk, 4 wk
Malm and Lundeberg, 1991; Stockholm, Sweden	Randomized by permuted blocks	Cx: standard conservative treatment + sham laser Tx: standard conservative treatment + laser,	conservative wound care: cleaning with saline, paste bandage, elastic bandage at 15-25 mmHg; exercise program given on instruction sheet; sham laser: light removed	Irradia GaAs, 904 nm, 1.96 J/sq cm, 4 mW; laser held perpendicular to wound for 10 min	2x/wk, 12 wk
Lundeberg and Malm, 1991; Stockholm, Sweden	Assigned randomly, by permuted blocks	Cx: standard treatment + sham laser Tx: standard treatment + laser	Cleansing with saline, paste bandage followed by support bandage, exercise program	HeNe, 632.8 nm, 4 J/sq cm, 6 mW	2x/wk, 12 wk

Evidence Table 3. Low-Level Laser Therapy, Treatments (continued)

A. Placebo-Controlled Studies (cont'd)

Study	Allocation	Comparison	Control	Treatment	Treatment Regimen
Bihari and Mester, 1989; Budapest, Hungary	randomly divided into groups by age	Cx: adjuvant therapy + sham laser Tx1: adjuvant therapy + hand-held laser Tx2: adjuvant therapy + machine-scanned laser	adjuvant therapy: compressive bandages, antibiotics; sham: noncoherent nonpolarized filtered light	Hand-held Lasotronic HeNe; machine scanned Lasotronic HeNe/pulsed infrared, 904 nm, 4800 Hz, 4 J/sq cm	1x/wk, 9 mo
Santoianni, Monfrecola, Martellotta, et al., 1984; Naples, Italy	pts randomly assigned to laser group or control group; if single ulcer < 5 cm, whole ulcer irradiated, if single ulcer > 5 cm, 1 half irradiated, other half kept as control; if bilateral ulcers, < 30% difference in area, 1 irradiated, 1 used as control (within subjects?)	Cx: compresses + laser pointed away from wound Tx1: compresses + laser 1 J/sq cm Tx2: compresses + laser 4 J/sq cm	no surgery; antiseptic compresses changed 2x/d	Valfivre LCS 25 HeNe 632.8 nm, 1 or 4 J/sq cm, 25 mW, beam expander to cover entire wound	6 d/wk, > 1 mo
Iusim, Kimchy, Pillar, et al., 1992; Haifa, Israel	randomly allocated	Cx: regular treatment + placebo Tx1: regular treatment+red light laser Tx2: regular treatment+infrared light laser	patients continued to receive regular local and general treatment (Milton, Rivanol, Neomycin, H2O2, Synto, Dermalar)	Biobeam red light (660 nm, 7.5-18 mW); infrared light (940 nm, 2.7-25 mW), 7 min on continuous wave, 7 min on pulsed wave, focused on single point	7 min cont, 7 min pulsed, daily

Evidence Table 3. Low-Level Laser Therapy, Treatments (continued)

B. Studies of Incremental Effect over Standard Treatment

Study	Allocation	Comparison	Control	Treatment	Treatment Regimen
Lucas, van Gemert, and de Haan, 2003; Amsterdam, Netherlands	randomly assigned by central computerized telephone service; minimization performed on wound size category and treatment center	Cx: consensus therapies Tx: consensus therapies+low level laser therapy	consensus therapies, daily over 6 wk, based on NPUAP recommendations: pt info/ instruction, wound cleansing, simple moist dressings, frequent position alteration	Combilaser C-501 GaAs, 904 nm, 1 J/sq cm, 12 x 8 mW, irradiated area 12 sq cm, 125 sec, no corticosteroids/ concurrent adjunctive interventions; probe at < 1 mm from center of wound surface	5x/wk, 6 wk
Nussbaum, Biemann, and Mustard, 1994; Toronto, Canada	Randomly assigned	Cx: standard treatment alone Tx1: standard treatment+laser Tx2: standard treatment+US/ UV-C	standard wound care: cleansing 2x/d with Hygeol, Jelonet moist dressings, avoidance of lying or sitting on existing ulcers; participation in rehabilitation program	plastic covered Intelect 800 cluster probe; 820 nm laser diode, 4 J/sq cm, 15 mW, treatment time 35 sec; probe in contact with wound; one exposure for small wounds; central and perimeter application for large wounds	3x/wk, to closure
Lucas, Coenen, and De Haan, 2000; Amsterdam, Netherlands	randomly assigned	Cx: consensus treatment Tx: consensus treatment+LLLT	consensus treatment: information/instruction, cleansing, simple moist dressings, frequent position alteration, no additional medication (corticosteroids), no concurrent physical therapy	Combilaser C-501 GaAs, 904 nm, 830 Hz, 1 J/sq cm, 8 mW, exposure time 2 min 5 sec	5x/wk, 6 wk

Evidence Table 3. Low-Level Laser Therapy, Treatments (continued)

C. Laser Treatment Versus Ultraviolet Light

Study	Allocation	Comparison	Control	Treatment	Treatment Regimen
Crous and Malherbe, 1988	Randomly referred	Cx: ultraviolet light Tx: laser	Medical treatment: dressings using saline, Granuflex and betadine, ultraviolet light, dose E4 for necrotic tissue, dose E1 for granulation tissue	Medical treatment, M3-UP scanning laser, 16 cm from ulcer, beam diameter 2 cm wider than ulcer, 1.4 mW, 10 min	3x/wk, 4 wk

Evidence Table 4. Low-Level Laser Therapy, Outcome Assessment

A. Placebo-Controlled Studies

Study	Primary Outcomes	Secondary Outcomes	Wound Measurement	Observer	F/U	Unit of Analysis	Intention-to-Treat?
Franek, Krol, and Kucharzewski, 2002; Bytom, Poland	Wound area, volume, suppurative area, granulation area		planimetry, traced transparency, digitizing tablet		4.5 - 5.0 wk	Pt	?
Lagan, McKenna, Witherow, et al., 2002; Ulster, UK	wound surface area	visual analogue scale pain	traced on sterile transparency by one investigator following debridement; digitizing tablet; photography	analysis of wound surface area measurements completed under blinded conditions	1, 2, 3, 4, 8, 12 wk	pt	?
Malm and Lundeberg, 1991; Stockholm, Sweden	time to complete healing	rate of healing	tracings	tracings identified by code number to exclude observer bias	12 wk	pt	no
Lundeberg and Malm (1991); Stockholm, Sweden	time to complete healing	rate of healing	tracings	tracings identified by code number to exclude observer bias	12 wk	pt	no
Bihari and Mester, 1989; Budapest, Hungary				independent trained technician unaware which therapy pts received	9 mo	pt	?
Santoianni, Monfrecola, Martellotta, et al., 1984; Naples	epithelialization		photographs, traced transparencies		30 d		no
Iusim, Kimchy, Pillar, et al., 1992; Haifa	complete healing, wound area		photographs		20 d	pt (wound)	?

Evidence Table 4. Low-Level Laser Therapy, Outcome Assessment (continued)

B. Studies of Incremental Effect over Standard Treatment

Study	Primary Outcomes	Secondary Outcomes	Wound Measurement	Observer	F/U	Unit of Analysis	Intention-to-Treat?
Lucas, van Gemert, and de Haan, 2003; Amsterdam, Netherlands	absolute, relative wound area reduction	Incidence stage IV, Norton Score	1:1 Polaroid; traced transparency	Independent evaluator outlined wound on transparency, area determined by another blinded evaluator	6 wk	pt	?, used last observation carried forward for Cx, not for Tx
Nussbaum, Biemann, and Mustard, 1994; Toronto, Canada	healing rate	time to complete healing	traced on transparency, digitizer tablet, stylus pen	tracings made by 1 investigator blinded to group assignment	< 20 wk, to com-plete healing	wound	?
Lucas, Coenen, and De Haan, 2000; Amsterdam, Netherlands	wound area	Complete healing	1:1 Polaroid, outlined perimeter, transposed to transparency	investigator blinded to clinical details measured wound area	6 wk	pt	?

C. Laser Treatment versus Ultraviolet Light

Study	Primary Outcomes	Secondary Outcomes	Wound Measurement	Observer	F/U	Unit of Analysis	Intention-to-Treat?
Crous and Malherbe, 1988	ulcer size (perimeter and area)		Photography	Physiotherapist not involved with the investigation		pt	

Evidence Table 5. Low-Level Laser Therapy, Results

A. Placebo-Controlled Studies

Study	Comparison	Complete Healing	Wound Area
Franek, Krol, and Kucharzewski, 2002; Bytom, Poland	Cx1: compressive/ topical therapy + sham laser Cx2: compressive/ topical therapy Tx: compressive/ topical therapy + laser		f/u average rate of change in relative area (%/wk): Cx1: 15 Cx2: 9 Tx: 16 (NS) average rate of change of relative suppurative area (%/wk): Cx1: 19 Cx2: 20 Tx: 9 (NS)
Lagan, McKenna, Witherow, et al., 2002; Ulster, UK	Cx: standard nursing care + sham laser Tx: standard nursing care + laser		(% change): 4 wk: Cx mn –23 Tx mn–26 8 wk Cx mn -7 Tx mn –45.1 SEM 20.6 SEM 16.6 12 wk Cx mn +11.6 Tx mn –61.3 SEM 41.2 SEM 15.6 (p=0.14)
Malm and Lundeberg, 1991; Stockholm, Sweden	Cx: standard conservative treatment + sham laser Tx: standard conservative treatment + laser,	12 wk Cx Tx Dropped 6/21 4/21 Healed 11/21 13/21 Not healed 4/21 4/21 Life-table analysis NS	(% change/wk): NS
Lundeberg and Malm, 1991; Stockholm, Sweden	Cx: standard treatment + sham laser Tx: standard treatment + laser	12 wk Cx Tx Dropped 4/23 8/23 Healed 3/23 4/23 Not healed 16/23 11/23 Life-table analysis NS	(% of original ulcer size): Cx: mn 49, SD 12 Tx: mn 48, SD 9 (NS)

Evidence Table 5. Low-Level Laser Therapy, Results (continued)

A. Placebo-Controlled Studies (cont'd)

Study	Comparison	Complete Healing	Wound Area
Bihari and Mester, 1989; Budapest, Hungary	Cx: adjuvant therapy + sham laser Tx1: adjuvant therapy + hand-held laser Tx2: adjuvant therapy + machine-scanned laser	Cx Tx1 Tx2 Dropped 2/15 Complete 5/15 10/15 12/15 Improved 3/15 4/15 2/15 No change 3/15 1/15 1/15 Worse 2/15 0/15 0/15 Complete healing: RR (95% CI) Tx1:Cx: 2.0 (0.9, 4.5) RR (95% CI) Tx2:Cx: 2.4 (1.1, 5.1)	
Santoianni, Monfrecola, Martellotta, et al., 1984; Naples, Italy	Cx: compresses + laser pointed away from wound Tx1: compresses + laser 1 J/sq cm Tx2: compresses + laser 4 J/sq cm		(area epithelialized, sq cm, ulcer < 5 cm): Cx: n=14, mn 3.3, SD 2.13 Tx1: n=9, mn 3.21, SD 3.15 (p<0.95) Tx2: n=5, mn 4.52, SD 3.49 (p<0.5) (area epithelialized, ulcer > 5 cm, by half, control vs. laser): Tx1: n=7, mn (SD) 2.99 (2.55) vs. 2.3 (1.94) (NS) Tx2: n=10, mn (SD) 3.03 (4.47) vs. 3.22 (4.25) (NS)
Iusim, Kimchy, Pillar, et al., 1992; Haifa, Israel	Cx: regular treatment + placebo Tx1: regular treatment + red light laser Tx2: regular treatment + infrared light laser	Cx: 3/11 Tx1: 3/9 Tx2: 4/11	(% change): Cx: mn -41 Tx1: mn -89 (p=0.0345) Tx2: mn -58 (p=0.46)

Evidence Table 5. Low-Level Laser Therapy, Results (continued)

B. Studies of Incremental Effect over Standard Treatment

Study	Comparison	Complete Healing	Wound Area
Lucas, van Gemert, and de Haan, 2003; Amsterdam, Netherlands	Cx: consensus therapies Tx: consensus therapies + low level laser therapy	Cx Tx N 43/47 36/39 Complete 15/43 18/36 Incomplete 26/43 12/36 Larger 2/43 6/36	(sq mm), Cx n=47/47, Tx n=36/39 absolute improvement: Cx Tx Mn 138 48 SD 270 394 (p=0.23) relative improvement (%): Cx Tx Mn 34 5 SD 204 194 (p=0.42) LN improvement: Cx Tx mn 2.3 2.6 SD 2.2 2.6 (p=0.59)
Nussbaum, Biemann, and Mustard, 1994; Toronto, Canada	Cx: standard treatment alone Tx1: standard treatment + laser Tx2: standard treatment + US/ UV-C	Cx Tx1 Tx2 Mn wks to complete healing 7.0 11.0 4.2	(% change/wk): Cx: - 32.4 Tx1: -23.7 Tx2: -53.5 (p=0.032, Tx2 better than Tx1, Tx1 not different from Cx; Tx2 not different from Cx)
Lucas, Coenen, and De Haan, 2000; Amsterdam, Netherlands	Cx: consensus treatment Tx: consensus treatment + LLLT	6 wk: Cx Tx Complete 4/8 3/8	(% change): Cx: med 95 Tx: med 83 (p=0.47)

C. Low-Level Laser Treatment, Results, Laser Treatment versus Ultraviolet Light

Study	Comparison	Complete Healing	Wound Area
Crous and Malherbe, 1988	Cx: medical treatment + ultraviolet light Tx: medical treatment + laser		(% change): Cx: mn -34, SD 21 Tx: mn -50, SD 7

Evidence Table 6. Study Quality Ratings, Low-Level Laser Therapy

Study	Yr	Initial Assembly of Comparable Groups	Low Loss to Followup, Maintenance of Comparable Groups	Measurements Reliable, Valid, Equal	Interventions Comparable/ Clearly Defined	Appropriate Analysis of Results	Overall Rating
Franek, Krol, and Kucharzewski	2002	No	Yes	No	Yes	No	Poor
Lagan, McKenna, Witherow, et al.	2002	?	Yes	Yes	Yes	Partial	Poor
Malm and Lundeberg	1991	?	No	Partial	Yes	No	Poor
Lundeberg and Malm	1991	?	No	Partial	No	No	Poor
Bihari and Mester	1989	?	Yes	Partial	Yes	Partial	Poor
Santoianni, Monfrecola, Martellotta, et al.	1984	?	?	No	Yes	No	Poor
Iusim, Kimchy, Pillar, et al.	1992	No	Yes	No	No	Partial	Poor
Lucas, van Gemert, and de Haan	2003	Yes	Yes	Yes	Yes	Yes	Good
Nussbaum, Biemann, and Mustard	1994	?	No	Yes	Yes	No	Poor
Lucas, Coenen, and De Haan	2000	Partial	Yes	Yes	Yes	Yes	Fair
Crous and Malherbe	1988	?	Yes	Partial	Yes	Partial	Poor

Placebo-controlled studies. Of the 11 studies meeting study selection criteria, seven studies enrolling 262 patients compared standard treatment plus sham low-level laser versus standard treatment plus active low-level laser (Bihari and Mester, 1989; Franek, Krol, and Kucharzewski, 2002; Iusim, Kimchy, Pillar, et al., 1992; Lagan, McKenna, Witherow, et al., 2002; Lundeberg and Malm, 1991; Malm and Lundeberg, 1991; Santoianni, Monfrecola, Martellotta, et al., 1984). Six of seven studies included patients with primarily lower extremity venous ulcers, while the seventh (Santoianni, Monfrecola, Martellotta, et al., 1984) selected a heterogeneous group of patients with diabetes or peripheral vascular disease.

Study quality. Overall study quality ratings were poor for all seven placebo-controlled studies (Evidence Table 6). None of these seven studies demonstrated that groups were comparable on all three critical baseline characteristics: age, wound size and wound duration (Evidence Table 2). Randomization methods were poorly described. High loss to followup was common. It was rare for studies to use both reliable and valid measurement techniques and blinded outcome assessors. Less than half of the studies reported on the main outcome, complete healing, and none made it clear that analysis was by intention-to-treat and controlled for confounders.

It is unclear whether any study assembled groups that were comparable on a sufficient range of key baseline patient characteristics. The study by Franek, Krol, and Kucharzewski (2002) assembled a control group receiving compressive and topical therapy plus sham low-level laser treatment that had a shorter mean wound duration (30 months) than the group receiving standard care plus active low-level laser therapy (41 months). The other six placebo-controlled studies did not provide comparisons between groups on wound duration at baseline. The studies by Franek, Krol, and Kucharzewski (2002), Malm and Lundeberg (1991), Lundeberg and Malm (1991), and Iusim, Kimchy, Pillar, et al. (1992) enrolled patient groups of comparable mean age, as well as comparable wound size.

In order for this review to describe the randomization method as adequate, the article had to state either that central randomization was performed or opaque (concealed) envelopes were employed. None of the seven placebo-controlled studies satisfied this quality component. Loss to followup exceeded 20 percent of the initial sample size in two studies: Malm and Lundeberg (1991) and Lundeberg and Malm (1991). Description of treatment and control procedures was clear in all cases.

Wound measurement was assumed to be reliable and valid if the article described use of photographic or digital transfer of wound tracings and/or use of computer software to calculate wound size. The studies by Franek, Krol, and Kucharzewski (2002) and Lagan, McKenna, Witherow, et al. (2002) satisfied this quality component. Data abstraction also sought information on whether a blinded observer performed outcome assessment. Blinded outcome assessors were used by Lagan, McKenna, Witherow, et al. (2002), Malm and Lundeberg (1991), Lundeberg and Malm (1991), and Bihari and Mester (1989). In only one study (Lagan, McKenna, Witherow, et al., 2002) was it clear that investigators used both blinded assessment and measurement that was reliable and valid.

None of these articles stated whether statistical analyses used adjustment procedures to deal with baseline confounding variables. Intention-to-treat analysis was performed by Lagan, McKenna, Witherow, et al. (2002), Bihari and Mester (1989), and Iusim, Kimchy, Pillar, et al. (1992). The primary endpoint, complete healing, was reported in three studies: Malm and Lundeberg (1991), Lundeberg and Malm (1991), and Bihari and Mester (1989). Analysis of

results was considered appropriate if both adjustment for confounders and intention-to-treat analysis was carried out. None of these studies satisfied both components.

Complete healing. Three of seven studies reported data on the primary outcome specified for this systematic review, complete healing. Using the GaAs laser, Malm and Lundeberg (1991, n=42) performed a life-table analysis of time to complete healing by 12 weeks and found no significant difference between groups. Lundeberg and Malm (1991, n=46) used the HeNe laser and similarly found no differences between groups on life-table analysis at 12 weeks. Selecting three groups of 15 subjects each, Bihari and Mester (1989) compared a sham low-level laser group with one group treated with a hand-held HeNe laser and another group treated with a machine-scanned HeNe/pulsed infrared laser. Results favored the hand-held laser group over sham, but the difference was not statistically significant: the relative risk and 95 percent confidence interval (RR, 95 percent CI) of complete healing at 9 months was 2.0 (0.9–4.5). Results were significant in the machine-scanned laser group (RR=2.4, 95 percent CI: 1.1–5.1); however, two control patients were excluded from the analysis. If they had achieved complete healing, the results would not be statistically significant. None of the available studies provides clear evidence that use of laser treatment leads to a higher probability of complete healing, compared with sham treatment.

Change in wound area. Six of seven studies reported on this outcome. At 12 weeks' followup, Franek, Krol, and Kucharzewski (2002) found no significant differences between groups on either the mean rate of change in relative area or in the mean rate of change of relative suppurative area. Lagan, McKenna, Witherow, et al. (2002) found no difference between groups on percent change in wound area at 12 weeks. Malm and Lundeberg (1991) reported no difference between groups in rate of wound area change over 12 weeks. Lundeberg and Malm (1991) found that the average percent change at 12 weeks did not differ between groups. Santoianni, Monfrecola, Martellotta, et al. (1984) observed no differences between groups in the area epithelialized. Iusim, Kimchy, Pillar, et al. (1992) compared sham low-level laser with one group treated by red light laser and another treated with infrared light laser. By percent change in area at 20 days, the red light laser performed significantly better than sham, which did not differ from the infrared laser group. Only one of six studies reported a significant advantage favoring low-level laser treatment over sham.

Other outcomes. Franek, Krol, and Kucharzewski (2002) reported that the rate of change in relative defect volume was better in the standard treatment alone arm versus the low-level laser arm. Lagan, McKenna, Witherow, et al. (2002) found that visual analog scale pain did not differ between groups.

Studies without a placebo control. Three studies enrolling 151 patients compared patients receiving standard treatment alone with those undergoing standard treatment plus low-level laser (Lucas, van Gemert, and de Haan, 2003; Lucas, Coenen, and De Haan, 2000; Nussbaum, Biemann, and Mustard, 1994). All three selected patients with pressure ulcers.

Study quality. Both the Lucas, van Gemert, and de Haan (2003) and the Lucas, Coenen, and De Haan (2000) studies showed that groups were comparable on age, wound size and wound duration. The groups in the study by Nussbaum, Biemann, and Mustard (1994) were comparable

on age and wound duration, but not on wound size. The Lucas, van Gemert, and de Haan (2003) study stated that central randomization was used, while the other two studies provided insufficient details about the randomization technique. Loss to followup exceeded 20 percent of the initial sample in the Nussbaum, Biemann, and Mustard (1994) study. Wound measurement was reliable and valid in all three studies and blind outcome assessors were used in all. Both control and treatment interventions were clearly described in all three studies. The Lucas, van Gemert, and de Haan (2003) and the Lucas, Coenen, and De Haan (2000) studies analyzed results by intention-to-treat, while Nussbaum, Biemann, and Mustard (1994) did not; neither did it mention use of adjustment for confounders.

The Lucas, van Gemert, and de Haan (2003) study was the only study that met all five quality dimensions and received an overall good rating. The earlier study by Lucas, Coenen, and De Haan (2000) met all but one of the quality dimensions, and received an overall fair rating. The main detail lacking from this study was an adequate description of the randomization procedure. The Nussbaum, Biemann, and Mustard (1994) study was given an overall poor quality rating. Randomization was poorly described, wound size differed between groups, loss to followup was high and appropriate analysis of results was not carried out.

Complete healing. All three studies reported on complete healing, but none provide support that use of laser therapy results in a higher probability of complete healing as compared to standard treatment alone. Lucas, van Gemert, and de Haan (2003) did not show a higher probability of complete healing at 6 weeks with laser. In the study by Nussbaum, Biemann, and Mustard (1994), patients receiving low-level laser treatment had a higher mean number of weeks to complete healing than standard treatment alone, by a followup as high as 20 weeks, but no statistical test result was provided. Lucas, Coenen, and De Haan (2000) observed that four of eight control patients and three of eight low-level laser patients achieved complete healing by 6 weeks.

Change in wound area. In Lucas, van Gemert, and de Haan (2003), no significant differences between groups were observed for absolute improvement, relative improvement or natural log-transformed improvement. Nussbaum, Biemann, and Mustard (1994) found that the rate of wound size change for laser was not better than that of control. Lucas, Coenen, and De Haan (2000) found no significant difference between groups in percent change of wound area.

Other outcomes. Lucas, Coenen, and De Haan (2000) assessed the Norton wound scale and found no differences between groups. These authors also found no difference between groups in the incidence of stage IV pressure ulcers.

Studies comparing ultraviolet light and low-level laser therapy. One study of only six patients with chronic leg venous ulcers compared use of medical treatment plus ultraviolet light with medical treatment plus laser therapy (Crous and Malherbe, 1988). The overall study quality rating was poor. It is unclear whether the two groups of three subjects were comparable on age, wound duration or wound size. The randomization procedure was inadequately described. Interventions were clearly described. Wound measurement was performed with photographs and a blinded observer. Adjustment for confounders was not mentioned. Results were given for all randomized patients. Complete healing was not reported.

The article reported on percent change in wound area and wound perimeter. The mean change in area in the ultraviolet light group was 34 percent, compared with 50 percent for low-

level laser. Mean change in perimeter was 18 percent for ultraviolet light and 27 percent for low-level laser. No statistical test results were reported, but t-tests performed for this systematic review did not find statistically significant differences between groups.

Conclusions

Eleven studies (Bihari and Mester, 1989; Crous and Malherbe, 1988; Franek, Krol, and Kucharzewski, 2002; Iusim, Kimchy, Pillar, et al., 1992; Lagan, McKenna, Witherow, et al., 2002; Lucas, Coenen, and De Haan, 2000; Lucas, van Gemert, and de Haan, 2003; Lundeberg and Malm, 1991; Malm and Lundeberg, 1991; Nussbaum, Biemann, and Mustard, 1994; Santoianni, Monfrecola, Martellotta, et al., 1984) met the study selection criteria for Part I of this review, nine of which were rated poor in quality (Bihari and Mester, 1989; Crous and Malherbe, 1988; Franek, Krol, and Kucharzewski, 2002; Iusim, Kimchy, Pillar, et al., 1992; Lagan, McKenna, Witherow, et al., 2002; Lundeberg and Malm, 1991; Malm and Lundeberg, 1991; Nussbaum, Biemann, and Mustard, 1994; Santoianni, Monfrecola, Martellotta, et al., 1984), while one was rated good quality (Lucas, van Gemert, and de Haan, 2003) and one was rated fair (Lucas, Coenen, and De Haan, 2000).

Seven studies (n=262) compared standard care plus placebo with the combination of standard care and sham laser therapy (Bihari and Mester, 1989; Franek, Krol, and Kucharzewski, 2002; Lagan, McKenna, Witherow, et al., 2002; Iusim, Kimchy, Pillar, et al., 1992; Lundeberg and Malm, 1991; Malm and Lundeberg, 1991; Santoianni, Monfrecola, Martellotta, et al., 1984). Most of these patients had lower extremity venous ulcers. Of the three studies that reported on complete healing (Bihari and Mester, 1989; Lundeberg and Malm, 1991; Malm and Lundeberg, 1991), one provides weak evidence of a higher rate of healing for patients treated by machine-scanned laser versus those receiving sham laser (Bihari and Mester, 1989).

Standard treatment alone versus standard treatment plus laser was compared in three studies, which reported on a total of 151 patients with pressure ulcers (Lucas, Coenen, and De Haan, 2000; Lucas, van Gemert, and de Haan, 2003; Nussbaum, Biemann, and Mustard, 1994). All three studies reported on complete healing. One of these was rated as good in quality, and this higher quality study did not show a higher probability of complete healing at 6 weeks with the addition of laser treatment (Lucas, van Gemert, and de Haan, 2003), nor did it show benefit for any of the other reported outcomes. Use of medical treatment plus ultraviolet light with medical treatment plus low-level laser therapy was compared in one study of six patients with chronic venous ulcers (Crous and Malherbe, 1988). That study did not show a higher probability of complete healing at 6 weeks with the addition of laser treatment.

Overall, the quality of this body of evidence is poor, and does not permit definitive conclusions. However, the available data suggests that the addition of laser therapy does not improve wound healing, as the vast majority of comparisons in these studies do not report any group differences in the relevant outcomes. It is unlikely that the lack of significant differences is the result of a type II error, since there are no trends or patterns of outcomes that favor the laser group.

Part II: Vacuum-Assisted Closure

The second part of this chapter reviews evidence on the following questions:

In the treatment of various wounds, what are the outcomes of vacuum-assisted closure for specific indications and patient types:

a) as a substitute for standard dressings; and

b) as an adjunct to standard therapy, compared with standard therapy alone?

Overview

A single previous systematic review is available on the use of vacuum-assisted closure for treating chronic wounds (Evans and Land, 2003). The authors concluded that the 2 small trials (Joseph, Hamori, Bergman, et al., 2000; McCallon, Knight, Valiulus, et al., 2000) that met their selection criteria offer weak evidence that vacuum-assisted closure is more efficacious than moist dressings. They noted that small sample sizes and methodological limitations require that the results of these 2 studies be interpreted with extreme caution. While Evans and Land restricted themselves to chronic wounds, the present review is broader in focus. Both studies reviewed in that report are also included here.

Two randomized trials on the use of vacuum-assisted closure are excluded from the current review (Buttenschoen, Fleischmann, Haupt, et al., 2001; Genecov, Schneider, Morykwas, et al., 1998) because they provided data only on outcomes that were not of interest to this review. The former reported on immune response markers and the latter gave data on skin biopsies. Two comparative studies published in Chinese were reviewed by a Chinese reader and found to be nonrandomized (Huang, Yao, and Huang, 2003; Yao, Huang, and Ma, 2002). No other nonrandomized comparative studies published in English were found. All other excluded studies were case series or case reports.

Six studies using vacuum-assisted closure met study selection criteria, with a collective total of 135 patients (Eginton, Brown, Seabrook, et al., 2003; Ford, Reinhard, Yeh, et al., 2002; Moues, Vos, van den Bemd, et al., 2004; Joseph, Hamori, Bergman, et al., 2000; McCallon, Knight, Valiulus, et al., 2000; Wanner, Schwarzl, Strub, et al., 2003). Details about these studies are given in Evidence Tables 7–12; information in these tables served as the basis for study quality ratings, which may be viewed in Evidence Table 13. Evidence Table 7 summarizes the included studies. Evidence Table 8 presents patient inclusion and exclusion criteria. Evidence Table 9 shows patient characteristics. Evidence Table 10 gives details of treatment. Evidence Table 11 includes information on how outcomes were assessed. Evidence Table 12 depicts results.

Evidence Table 7. Summary of Vacuum-Assisted Closure Studies

Study	n Ran-domized	Patient Selec-tion	Control (Cx)	Treatment (Tx)	Comparable Characteristics	Alloca-tion	Treat-ment Descrip-tion	Wound Measure-ment	Complete Healing	Adjust-ment	Intention-to-Treat
Moues, Vos, van den Bemd, et al., 2004	54; Cx: 25 Tx: 29	Full-thick-ness wounds	SC/dressings	V.A.C.®	Yes: age; ? size, duration	Random, envelopes	Cx, Tx clear	Photo-copies, SW	NR	?	No
Wanner, Schwarzl, Strub, et al., 2003	22; Cx: 11; Tx: 11	Pres-sure ulcers	SC/dressings	V.A.C.®	Yes: age, size ?: duration	Random	Cx, Tx clear	Saline volume	NR	Yes	No
Joseph, Hamori, Bergman, et al., 2000	24; Cx: 12; Tx: 12	Non-healing wounds	SC/dressings	V.A.C.®	Yes: age No: size ?: duration	Random	Cx, Tx clear	Plaster mold, blind	NR	?	Yes
Ford, Reinhard, Yeh, et al., 2002	28	Pres-sure ulcers	gel products	V.A.C.®	No: age ?: size, duration	Random	Cx, Tx clear	Alginate mold, blind	Tx=Cx	?	No
Eginton, Brown, Seabrook, et al., 2003	10	Diabetic foot wounds	SC/dressings	V.A.C.®	?: age, size, duration	Random	Cx, Tx clear	Digital photos, plani-metry SW, blind	NR	?	No
McCallon, Knight, Valiulus, et al., 2000	10; Cx: 5; Tx: 5	Non-healing diabetic foot wounds	SC/dressings	V.A.C.®	Yes: age ?: size, duration	Coin flip, then alternate	Cx, Tx clear	Tracings, photos, biometric SW	Tx=Cx	?	No

Evidence Table 8. Vacuum-Assisted Closure, Patient Selection Criteria

Study	Inclusion	Exclusion
Moues, Vos, van den Bemd, et al., 2004; Rotterdam	Full-thickness wound that could not be closed immediately because of infection, contamination, or chronic character; type: trauma (2), infection (17), dehiscence (5), pressure ulcer (20), miscellaneous (10)	Malignant disease, deep fistulas, sepsis, active bleeding, uncontrolled diabetes, psychiatric patients, and unstable skin around the wound
Wanner, Schwarzl, Strub, et al., 2003; Nottwil, Switzerland	all consecutive pts with a pressure sore in the pelvic region, deeper than grade 2 (at least into SC fat); paraplegics or tetraplegics	pressure ulcer not in pelvic region (7); < grade 3 (3); lack of data (1); severe diarrhea (1)
Joseph, Hamori, Bergman, et al., 2000; Boston	chronic, nonhealing wounds (open wound, any site no closure ≥ 4 wk), recalcitrant to multiple prior treatments; setting: hospital (5), nursing home (9), home (10); wound type (Cx, Tx): dehisced (3, 0); pressure (13, 12); pressure-recurrent (1, 2); radiated (0, 1); traumatic (1, 1); venous insufficiency (0,2)	Infection; albumin < 3 g/dL; chronic disease requiring ongoing therapy for stabilization, uncontrolled diabetes, thyroid disease, hypertension; steroids, immunosuppressants, anticoagulants; pregnant/lactating; biopsy-proven osteomyelitis; uncooperative/unsuitable participant in dressing changes; malignant/neoplastic diseases in wound margin; fistulas to the wound
Ford, Reinhard, Yeh, et al., 2002; Boston	Stage III-IV pressure ulcers, 21-80 yo; > 4 wk; albumin > 2.0 g/dl; post-debridement ulcer volume 10–150 mL	fistulas to organs/body cavities; malignancy in wound; pregnant/lactating; Hashimoto thyroiditis; Graves disease; iodine allergy; systemic sepsis; electrical burn; radiation exposure; chemical exposure; cancer; connective tissue disease; chronic renal/pulmonary disease; uncontrolled diabetes; steroids/immunosuppressants; pacemaker; ferromagnetic clamps; recently placed orthopedic hardware
Eginton, Brown, Seabrook, et al., 2003; Milwaukee	diabetic foot wounds of size not expected to heal in 1 mo	growth factors, hyperbaric oxygen < 30 d, untreated cellulitis, malignancy in wound, necrotic tissue, osteomyelitis, no insurance for VAC or f/u
McCallon, Knight, Valiulus, et al., 2000; Shreveport	nonhealing (> 1 mo) diabetic foot ulceration; 18–75 yo;	venous disease; active infections not resolved by initial debridement; coagulopathy

Evidence Table 9. Vacuum-Assisted Closure, Patient Characteristics

Study	Comparison	n, Randomized	n, Withdrew	Wound Duration	Age	Gender	Wound Size	Comorbidities
Moues, Vos, van den Bemd, et al., 2004; Rotterdam Full-thickness wound that could not be closed immediately	Cx: standard moist dressing Tx: V.A.C.®	54 Cx: 25 Tx: 29		< 4 wk: 8 Cx, 12 Tx > 4 wk: 17 Cx, 17 Tx	Cx: mn 47.9, SD 17.0 Tx: mn 47.7, SD 19.6	Cx: 14 M, 11 F Tx: 21 M, 8 F		
Wanner, Schwarzl, Strub, et al., 2003; Nottwil, Switzerland; Pelvic pressure ulcers into SC fat	Cx: traditional care Tx: V.A.C.®	22 Cx: 11 Tx: 11			Cx: mn 53, rng 34-77 Tx: mn 49, rng 25-73	Cx: 8 m, 3 F Tx: 7 M, 4 F	(volume) Cx: mn 42 ml, SD 16, rng 5-68 Tx: mn 50, SD 33, rng 3-132	(Cx, Tx): diabetes (0, 0); vascular disorders (2, 0); zinc depletion (5, 5); hypoalbuminemia (1, 3); hypoproteinemia (3, 5); anemia (5, 8); nicotine (2, 3); steroids (0, 0)
Joseph, Hamori, Bergman, et al., 2000; Boston Nonhealing wounds (> 4 wk, 78% pressure ulcers)	Cx: standard wound care Tx: V.A.C.®	24 pts Cx: 12 Tx: 12 36 wounds Cx: 18 Tx: 18		> 4 wk	Cx: mn 49; Tx: mn 56 (p=0.17)	Cx: 5 M, 7 F Tx: 8 M, 4 F (p=0.18)	(volume) UA=pt Cx: mn 24 cu cm Tx: mn 38 (p=0.08);	

Evidence Table 9. Vacuum-Assisted Closure, Patient Characteristics (continued)

Study	Comparison	n, Randomized	n, Withdrew	Wound Duration	Age	Gender	Wound Size	Comorbidities
Ford, Reinhard, Yeh, et al., 2002; Boston Full-thickness pressure ulcers	Cx: Healthpoint System (gel products) Tx: V.A.C.®	28 pts 41 wounds	6 (3 lost to followup, 1 noncompliant, 2 died)	≥ 4 wk	Cx: mn 54.4 Tx: mn 41.7			
Eginton, Brown, Seabrook, et al., 2003; Milwaukee Diabetic foot wounds	Crossover Cx: moist dressings 2 wk Tx: V.A.C.® 2 wk	10 pts 11 wounds	4 (1 did not return for f/u, 1 coverage denied, 1 hyperbaric oxygen, 1 failed V.A.C.®)				(length): Cx+Tx: mn 7.7 cm, SD 1.6 (width): mn 3.5, SD 0.6 (depth): mn 3.1, SD 0.9	
McCallon, Knight, Valiulus, et al., 2000; Shreveport Nonhealing diabetic foot wounds	Cx: saline-moistened gauze dressings Tx: V.A.C.®	10 Cx: 5 Tx: 5		≥ 1 mo	Cx: mn 50.2, SD 8.7 Tx: mn 55.4, SD 12.8		(area): Cx: 20 sq cm Tx: 23	

Evidence Table 10. Vacuum-Assisted Closure, Treatments

Study	Allocation	Comparison	Control	Treatment	Treatment Regimen
Moues, Vos, van den Bemd, et al., 2004; Rotterdam Full-thickness wounds that could not be closed immediately	Randomly assigned by patient picking a closed envelope	Cx: standard moist dressings Tx: V.A.C.®	Debridement before and during therapy when clinically needed; standard moist gauze, using: 0.9% saline, 0.2% nitrofuralam, 1% acetic acid, 2% sodium hypochlorite, changed 2x/day	Debridement before an during therapy when clinically needed; V.A.C.®; 125 mmHg continuous suction, wounds inspected and dressings changed every 48 hr	Until ready for surgical therapy
Wanner, Schwarzl, Strub, et al., 2003; Nottwil, Switzerland; Pelvic pressure ulcers into SC fat	Randomized	Cx: traditional care Tx: V.A.C.®	traditional care - 1 day after debridement, wet-to-dry/dry-to-wet dressings, Ringer's solution, changed 3x/d until granulation tissue, then 1-3x/d; closure with flap after 50% decrease in wound volume	V.A.C.®, <125 mmHg below ambient pressure; polyvinyl foam/transparent polyurethane dressing changed after 2-7 d (when canister full); closure with flap after 50% decrease in wound volume	
Joseph, Hamori, Bergman, et al., 2000; Boston; Nonhealing wounds (> 4 wk, 78% pressure ulcers)	prospectively randomized: folders in 2 colors randomly organized in locked cabinet; after consent, folder picked for each wound	Cx: standard wound care Tx: V.A.C.®	standard wound care: wet-to-moist (saline) gauze dressings changed 3x/d, not allowed to dry the wound bed, occlusive covering; nutritional assessment, supplements, multivitamin, debridement; pressure-relieving surface; frequent assessment, pressure reduction	V.A.C.®, < 125 mmHg below ambient pressure; custom-cut foam dressings with film drape changed each 48 hr; nutritional assessment, supplements, multivitamin, debridement; pressure-relieving surface; frequent assessment, pressure reduction	6 wk
Ford, Reinhard, Yeh, et al., 2002; Boston; Full-thickness pressure ulcers	random assignment; table of random letters (V, H) generated before trial began; 3 pts with 3 wounds each crossed over for 2nd 6-wk course of opposing treatment	Cx: Healthpoint System (gel products) Tx: V.A.C.®	debridement, Healthpoint System - gel products (Iodosorb, Iodoflex, Panafil); pts with substantial exudate received Iodosorb or Iodoflex, clean/granulating wounds received Panafil; dressings changed 1-2x/d	debridement, V.A.C.®, dressings changed 3x/wk	6 wk

Evidence Table 10. Vacuum-Assisted Closure, Treatments (continued)

Study	Allocation	Comparison	Control	Treatment	Treatment Regimen
Eginton, Brown, Seabrook, et al., 2003; Milwaukee Diabetic foot wounds	randomly assigned, random number generator: even numbers treated with V.A.C.® 1st, odd numbers treated with moist dressings 1st	Crossover Cx: moist dressings 2 wk Tx: V.A.C.® 2 wk	initial debridement, moist dressings, hydrocolloid gel, gauze, changed daily, 2 wk	initial debridement, V.A.C.®, - 125 mmHg continuous negative pressure, custom-cut foam dressings with transparent occlusive film changed > 3x/wk, 2 wk	2 wk
McCallon, Knight, Valiulus, et al., 2000; Shreveport Nonhealing diabetic foot wounds	randomized by coin flip, then alternating groups	Cx: saline-moistened gauze dressings Tx: V.A.C.®	debridement, physical therapy, saline-moistened gauze dressings, changed 2x/d; bedrest or strict nonweight bearing	V.A.C.®, 125 mmHg continuous suction 1st 48 hr, then intermittent suction; dressing changed each 48 hr; bedrest or strict nonweight bearing	

Evidence Table 11. Vacuum-Assisted Closure, Outcome Assessment

Study	Comparison	Primary Outcomes	Secondary Outcomes	Wound Measurement	Observer	F/U	Unit of Analysis	Intention-to-Treat
Moues, Vos, van den Bemd, et al., 2004; Rotterdam	Cx: standard moist dressings Tx: V.A.C.®	Median time to reach "ready for surgical therapy"	Wound surface area, bacterial load	Tracings onto polyethylene film, photocopying onto paper, computer software calculated area	Not blinded			
Wanner, Schwarzl, Strub, et al., 2003; Nottwil, Switzerland; Pelvic pressure ulcer into sc fat	Cx: traditional care Tx: V.A.C.®	time to 50% decrease in wound volume		ulcer covered with transparent sheet of elastic polymer, injected with saline until full, fluid volume measured		21-56 d	patient	?
Joseph, Hamori, Bergman, et al., 2000; Boston; Nonhealing wounds (> 4 wk, 78% pressure ulcers)	Cx: standard wound care Tx: V.A.C.®	Time to target decline in wound volume	wound length, width, depth; wound biopsies	Photography, dimensions, volume by alginate impression molds	independent blinded observer, not involved in daily patient care	6 wk	wound	?
Ford, Reinhard, Yeh, et al., 2002; Boston	Cx: Healthpoint System (gel products) Tx: V.A.C.®	complete healing	wound length, width, depth, volume, bone biopsy	photography, dimensions, volume by plaster mold	blinded assessment	3-10 mo	wound	?
Eginton, Brown, Seabrook, et al., 2003; Milwaukee Diabetic foot wounds	Crossover Cx: moist dressings 2 wk Tx: V.A.C.® 2 wk	Rate of wound healing, dimensions, area, volume		digital photography, computerized planimetry software	blinded evaluation, wound length, width, depth, volume	4 wk		

Evidence Table 11. Vacuum-Assisted Closure, Outcome Assessment (continued)

Study	Comparison	Primary Outcomes	Secondary Outcomes	Wound Measurement	Observer	F/U	Unit of Analysis	Intent-to-Treat
McCallon, Knight, Valiulus, et al., 2000; Shreveport	Cx: saline-moistened gauze dressings Tx: V.A.C.®	time to closure/ satisfactory healing (delayed primary intention - surgical closure, or secondary intention - granulation, epithelialization)	rate, wound area	tracings on acetate film, photography, area calculated by computer biometric software				

Evidence Table 12. Vacuum-Assisted Closure, Results

Study	Comparison	F/U	Complete Healing	Wound Area	Wound Volume	Wound Dimensions
Moues, Vos, van den Bemd, et al., 2004; Rotterdam Full-thickness wound	Cx: standard moist dressings (25) Tx: V.A.C.® (29)		(time until "ready for surgical therapy"): Cx: md 7.0, SEM 0.81 Tx: md 6.0, SEM 0.52 (p=0.19)	(% change/d): Cx (n=13) mn 1.7, SEM 0.5 Tx: (n=15) mn 3.8, SEM 0.5 (p<0.05)		
Wanner, Schwarzl, Strub, et al., 2003; Nottwil, Switzerland; Pelvic pressure ulcers into SC fat	Cx: traditional care (11) Tx: V.A.C.® (11)	21-56 days			(time to 50% drop in vol): Cx: mn 28 d, SD 7 Tx: mn 27 d, SD 10; (unadjusted p=0.9, adjusted p=0.2)	
Joseph, Hamori, Bergman, et al., 2000; Boston; Nonhealing wounds (> 4 wk, 78% pressure ulcers)	Cx: standard wound care (12) Tx: V.A.C.® (12)	6 wk			(time to > 95% fall in vol): Cox Proportional Hazards Model significant predictors: VAC (p=0.046), initial tendon/bone exposure (p=0.05) (% change): Cx: mn 30; Tx: mn 78 (p=0.038)	(% change, length): Cx: -38; Tx: -46 (p=0.38) (% change, width): Cx: -35 Tx: -63 (p=0.02) (% change, depth): Cx: -20 Tx: -66 (p<0.001)

Evidence Table 12. Vacuum-Assisted Closure, Results (continued)

Study	Comparison	F/U	Complete Healing	Wound Area	Wound Volume	Wound Dimensions
Ford, Reinhard, Yeh, et al., 2002; Boston Full-thickness pressure ulcers	Cx: Healthpoint System (gel products) Tx: V.A.C.® Cx+Tx (22)	3-10 mo	Cx: 2/15; Tx: 2/20 (8-10 wk) Tx:Cx RR = 0.75, 95%CI: 0.12, 4.73		(% change): Cx: -42.1 Tx: -51.8 (p=0.46)	(change, length): Cx: mn -18.7 cm Tx: -36.9 (p=0.10) (change, width): Cx: -19.0 Tx: -40.0 (p=0.11) (change, depth): Cx: -31.0 Tx: -33.6 (p=0.90)
Eginton, Brown, Seabrook, et al., 2003; Milwaukee Diabetic foot wounds`	Crossover, Cx: moist dressings 2 wk; Tx: V.A.C.® 2 wk Cx+Tx (6)	4 wk		(% change): Cx: mn +5.9, SD 17.4 Tx: mn - 16.4, SD 6.2 (NS);	(% change): Cx: mn -0.1, SD 14.7 Tx: mn -59, SD 9.7 (p<0.005)	(% change, length): Cx: mn +6.7, SD 11.5 Tx: mn -4.3, SD 4.7 (NS) (% change, width): Cx: mn +2.4, SD 7.5 Tx: mn – 12.9, SD 5.2 (NS) (% change, depth): Cx: mn –7.7, SD 5.2 Tx: mn –49, SD 11.1 (p<0.05)

Evidence Table 12. Vacuum-Assisted Closure, Results (continued)

Study	Comparison	F/U	Complete Healing	Wound Area	Wound Volume	Wound Dimensions
McCallon, Knight, Valiulus, et al., 2000; Shreveport Nonhealing diabetic foot wounds	Cx: saline-moistened gauze dressings (5) Tx: V.A.C.® (5)		(time to satisfactory healing): Cx: mn 42.8 d, SD 32.5 Tx: mn 22.8, SD 17.4 (NS); (delayed 1^{o} closure): Cx: 2/5; Tx: 4/5; (2^{o} intention): Cx: 3/5; Tx: 1/5	(% change): Cx: mn +9.5, SD 16.9 Tx: mn -28.4, SD 24.3 (NS)		

Evidence Table 13. Vacuum-Assisted Closure, Study Quality Ratings

Study	Yr	Initial Assembly of Comparable Groups	Low Loss to Followup, Maintenance of Comparable Groups	Measurements Reliable, Valid, Equal	Interventions Comparable/ Clearly Defined	Appropriate Analysis of Results	Overall Rating
Moues, Vos, van den Bemd, et al.	2004	Partial	?	No	Yes	No	Poor
Wanner, Schwarzl, Strub, et al.	2003	?	?	Partial	Yes	No	Poor
Joseph, Hamori, Bergman, et al.	2000	?	?	Yes	Yes	Partial	Poor
Ford, Reinhard, Yeh, et al.	2002	?	No	Yes	Yes	No	Poor
Eginton, Brown, Seabrook, et al.	2003	?	No	Yes	Yes	No	Poor
McCallon, Knight, Valiulus, et al.	2000	?	?	No	Yes	No	Poor

All studies used the V.A.C.® (Kinetic Concepts, Inc., KCI) device. Three studies included patients who primarily had pressure ulcers (Wanner, Schwarzl, Strub, et al., 2003; Ford, Reinhard, Yeh, et al., 2002; Joseph, Hamori, Bergman, et al., 2000). Joseph, Hamori, Bergman, et al. (2000) selected patients with chronic (i.e., ≥4 weeks' duration) nonhealing wounds of various etiologies, of which 78 percent were pressure ulcers. Pressure ulcers in the Ford, Reinhard, Yeh, et al. (2002) study were of 4 weeks duration or longer. Wanner, Schwarzl, Strub, et al. (2003) did not specify the duration of the pressure ulcers. Eginton, Brown, Seabrook, et al. (2003) included diabetic foot wounds not expected to heal within 1 month and McCallon, Knight, Valiulus, et al. (2000) selected diabetic foot wounds of more than 1 month duration.

The comparison of interventions was conventional/standard wound care (mainly, moist dressings changed at least once daily) versus vacuum-assisted closure in five studies (Moues, Vos, van den Bemd, et al., 2004; Wanner, Schwarzl, Strub, et al., 2003; Joseph, Hamori, Bergman, et al., 2000; Eginton, Brown, Seabrook, et al., 2003; McCallon, Knight, Valiulus, et al., 2000). One study (Ford, Reinhard, Yeh, et al., 2002) compared vacuum-assisted closure with the Healthpoint® system, consisting of gel/pad products (Iodosorb®, Iodoflex™, Panafil®).

Study quality. All six studies were rated poor in quality (Evidence Table 13). Only one study made it clear that an adequate randomization method was used (i.e., sealed envelopes in Moues, Vos, van den Bemd, et al., 2004). One study (McCallon, Knight, Valiulus, et al., 2000) used an allocation method that was probably inadequate to be considered true randomization: coin flip to assign the first patient, then alternating group assignment.

No study indicated that groups were comparable on all three key baseline characteristics (age, wound duration, and wound size, see Evidence Table 9). Age was comparable between groups in these four studies: Moues, Vos, van den Bemd, et al. (2004); Wanner, Schwarzl, Strub, et al. (2003); Joseph, Hamori, Bergman, et al. (2000); and McCallon, Knight, Valiulus, et al. (2000). Vacuum-assisted closure patients were younger than control patients in the study by Ford, Reinhard, Yeh, et al. (2002). Wanner, Schwarzl, Strub, et al. (2003) assembled groups that were comparable in wound size. Wounds were smaller in the vacuum-assisted closure group than the control group in the study by Joseph, Hamori, Bergman, et al. (2000). None of the seven studies provided information on the comparability of groups with respect to wound duration. All studies gave clear descriptions of interventions. All studies also described reliable and valid measurement methods and three used blinded observers (Joseph, Hamori, Bergman, et al., 2000; Ford, Reinhard, Yeh, et al., 2002; Eginton, Brown, Seabrook, et al., 2003). One study (Ford, Reinhard, Yeh, et al., 2002) reported on the primary endpoint, complete healing, while McCallon, Knight, Valiulus, et al. (2000) provided data on time to satisfactory healing. Only Wanner, Schwarzl, Strub, et al. (2003) performed adjustment for confounders in the data analysis. Joseph, Hamori, Bergman, et al. (2000) provided the only intention-to-treat analysis.

Complete healing. The proportion of patients who achieved complete healing was reported in only one study (Ford, Reinhard, Yeh, et al., 2002). In the control group receiving gel products for full-thickness pressure ulcers, two of 15 wounds had complete healing within 8–10 weeks, compared with two of 20 in the vacuum-assisted closure group. The relative risk of complete healing was 0.75 with a 95 percent confidence interval from 0.12 to 4.73. Although the numerical rate of complete healing was lower in the vacuum-assisted closure group, the 95 percent confidence interval is quite wide and overlaps with 1.0, indicating a lack of statistical difference between groups.

McCallon, Knight, Valiulus, et al. (2000) defined a related outcome, "satisfactory healing," as achieving definitive closure either by reaching a stage suitable for surgical intervention such as skin grafting (delayed primary intention) or by complete healing without surgical intervention (secondary intention). The mean time to satisfactory healing was 42.8 days in the control group and 22.8 days in the vacuum-assisted closure group, a difference that was not statistically significant in this study of 10 patients with diabetic foot wounds. Most of the vacuum-assisted closure wounds (4 of 5) were healed by delayed primary intention, while most of the control wounds (3 of 5) healed by secondary intention.

Facilitation of surgical closure. One study (Moues, Vos, van den Bemd, et al., 2004) reported on the time to readiness for surgical closure, among patients with full-thickness wounds of various etiologies. Log-rank test analysis of Kaplan-Meier time to readiness did not show any statistically significant differences between groups. The median time to readiness for surgical closure was 6 days for vacuum-assisted closure patients and 7 days for conventionally treated patients ($p=0.19$).

Change in wound area. Two studies of diabetic foot wounds reported nonsignificant results favoring vacuum-assisted closure over moist dressings in percent change in wound area, and one study of full-thickness wounds reported a similar finding. Eginton, Brown, Seabrook, et al. (2003) used a crossover design in six patients who first had 2 weeks of either moist dressings or vacuum-assisted closure, then switched to the other for 2 weeks. The mean change in area was an increase of 5.9 percent for the control intervention and a decrease of 16.4 percent for vacuum-assisted closure. In the study by McCallon, Knight, Valiulus, et al. (2000, n=10), the mean change in wound area in the control group was a gain of 9.5 percent, compared with a mean decrease of 28.4 percent in the vacuum-assisted closure group. In a subset of only 52 percent of the original group of patients with full-thickness wounds, Moues, Vos, van den Bemd, et al. (2004) found a significantly higher daily percent change in wound area among vacuum-assisted closure patients (3.8), compared with conventionally treated patients (1.7, $p<0.05$).

Change in wound volume. Four studies have reported on changes in wound volume: all three studies of pressure ulcers and one study on diabetic foot wounds. Wanner, Schwarzl, Strub, et al. (2003) included 22 patients with pelvic pressure ulcers. The endpoint was time to 50 percent decrease in wound volume. The mean time for traditional care was 28 days, compared with 27 days for vacuum-assisted closure. The unadjusted p value was 0.9, while adjustment for initial wound volume yielded a p value of 0.2. In the study by Ford, Reinhard, Yeh, et al. (2002) of 19 patients with full-thickness pressure ulcers, after 3–10 months, the mean percent change in wound volume was –42.1 percent in the group receiving gel products and –51.8 percent in the vacuum-assisted closure group ($p=0.46$). The group of 24 patients with nonhealing wounds (78 percent pressure ulcers) studied by Joseph, Hamori, Bergman, et al. (2000) were evaluated in two ways. First, the mean percent reduction in volume at 6 weeks was compared: 30 percent for standard wound care and 78 percent for vacuum-assisted closure ($p=0.038$). Second, a Cox proportional hazards model analysis found that use of vacuum-assisted closure and initial exposure of tendon or bone were significant predictors of time to greater than 95 percent reduction in volume. In the crossover study of six patients with diabetic foot wounds (Eginton, Brown, Seabrook, et al., 2003), the mean percent reduction in wound volume was 0.1 percent in the moist dressing phase and 59 percent in the vacuum-assisted closure phase ($p<0.005$).

Change in wound dimensions. Three studies report changes in length, width and depth of wounds, and two of the three studies report significant differences in favor of the vacuum-assisted closure group for one or more of these outcomes. In the Ford, Reinhard, Yeh, et al. (2002) study of pressure ulcers, the mean changes (cm) for the gel product group and vacuum-assisted closure group, respectively, were: –18.7 and –36.9 (length, p=0.10); –19.0 and –40.0 (width, p=0.11); and –31.0 and –33.6 (depth, p=0.90). Mean percent change in the Joseph, Hamori, Bergman, et al. (2000) study of nonhealing wounds, for standard care and vacuum-assisted closure, respectively, were: –38 and –46 (length, p=0.38); –35 and –63 (width, p=0.02); –20 and –66 (depth, p<0.001). In the crossover study by Eginton, Brown, Seabrook, et al. (2003) of diabetic foot wounds, the following comparisons of mean percent change values for moist dressings and vacuum-assisted closure, respectively, were observed: +6.7 and –4.3 (length, p>0.05); +2.4 and –12.9 (width, p>0.05); and –7.7 and –49 (depth, p<0.05).

Complications. Two studies reported data on complications during wound treatment. Ford, Reinhard, Yeh, et al. (2002) reported two deaths (group assignments not specified) and one vacuum-assisted closure patient with diabetes, hypertension, vascular insufficiency and sepsis who required distal lower extremity amputation. More cases of pre-existing osteomyelitis improved in the vacuum-assisted closure group (37.5 percent) than in the group receiving gel products (0 percent), but the difference was not statistically significant (p=0.25). In the Joseph, Hamori, Bergman, et al. (2000) study, eight of 18 wounds treated with standard care developed complications, compared with three of 18 vacuum-assisted closure wounds (p=0.0028). Complications included: fistulas; wound infection; osteomyelitis; and calcaneal fractures.

Biopsy results. The study comparing gel products and vacuum-assisted closure in 22 patients with full thickness pressure ulcers (Ford, Reinhard, Yeh, et al., 2002) reported quantitative biopsy results. The mean number of polymorphonuclear (PMN) leukocytes per high-powered field increased in the gel product group, but decreased in the vacuum-assisted closure group (p=0.13). Lymphocytes also increased in the gel product group and decreased in the vacuum-assisted closure group (p=0.41). The mean number of capillaries declined in both groups, but to a slightly lesser extent in the vacuum-assisted closure group (p=0.75).

Randomized trials in progress. KCI, the manufacturer of the V.A.C.® device, has shared protocol documents for 10 randomized trials in progress (Evidence Table 14). These protocols cover a wide variety of wound types, including burns, pressure ulcers, diabetic ulcers, traumatic and surgical wounds, venous stasis wounds, and diabetic wounds. Large sample sizes are planned, determined by power analyses. Sophisticated randomization techniques will be used in many trials. A wide range of outcomes will be assessed, often by a blinded observer. Plans to adjust for confounders in the analysis, if necessary, are common. Concerns remain about the criteria for allowable withdrawals, including: noncompliance; worsened condition; complications; and treatment difficulties/failures. If such withdrawals are excluded from analysis, it would constitute violation of the intention-to-treat principle.

Evidence Table 14. Vacuum-Assisted Closure, KCl Randomized Trials in Progress

Study	Patients	Target n	Randomization	Allowable Withdrawals	Treatments	Outcomes	F/U	Planned Adjust-ment for Confound-ers?	Planned Intent-to-Treat?
Molnar-Wake Forest	bilateral 2nd/3rd degree hand burns, 12-24 hrs post injury		by hand, random fashion like toss of coin		usual institutional regimen, V.A.C.®, 48 hr	photography, ROM, pinch/grip strength, need for surgery, general appearance	30 d, 60 d		
Protocol VAC2001-01	stage III/IV pressure ulcer	258, power analysis	by patient, standard tables of random numbers, opaque envelopes	investigator/ KCI discretion of noncompliance/ worsening, complications, treatment difficulties or failure, reasons documented	WOCN guideline (1992) moist therapy; V.A.C.®; 84 d	blinded, photography, bilayer tracing, complete closure (and time), facilitation of surgical closure, AEs, area, volume, pain	84 d	yes	interim
Protocol VAC2001-02	venous stasis ulcers, > 30 d duration, ABI 0.7-1.2	258, power analysis	by patient, standard tables of random numbers, opaque envelopes	investigator/ KCI discretion of noncompliance/ worsening, complications, treatment difficulties or failure, reasons documented	WOCN guideline (1996, 1993) moist therapy; V.A.C.®; 112 d	blinded, photography, bilayer tracing, complete closure (and time), area, AEs, pain, QOL, cost	112 d	yes	interim
Protocol VAC2001-04	draining hematoma, orthopedic surgical procedure following trauma	258, power analysis	by patient, central computerized randomization	investigator/ KCI discretion of noncompliance/ worsening, complications, treatment difficulties; reasons documented	pressure dressings; V.A.C.®; 10 d	incidence of draining hematomas, infections, wound dehiscence, AEs, QOL, cost	12 mo	yes	yes

Evidence Table 14. Vacuum-Assisted Closure, Randomized Trials in Progress (continued)

Study	Patients	Target n	Randomization	Allowable Withdrawals	Treatments	Outcomes	F/U	Planned Adjust-ment for Confound-ers?	Planned Intent-to-Treat?
Protocol VAC2001-05	surgically treated calcaneus, tibial plateau, pilon fractures	348, power analysis	by patient, central computerized randomization	investigator/ KCI discretion of noncompliance/ worsening, complications, treatment difficulties; reasons documented; data up to withdrawal included in analysis	standard care; V.A.C.®; to discharge	drainage, wound healing, surgical revision, infection, wound dehiscence, AEs, QOL, cost	12 mo	yes	yes
Protocol VAC2001-06	open fractures	258, power analysis	by patient, central computerized randomization	investigator discretion of noncompliance/ worsening, complications, treatment difficulties; reasons documented; data up to withdrawal included in analysis	standard care, V.A.C.®; until ready for surgical closure	postoperative AEs/complic-ations, time to closure	12 mo	yes	yes
Protocol VAC2001-07	amputation wounds of the diabetic foot	146, power analysis	by patient, central computerized randomization, opaque envelopes	investigator/ KCI discretion of noncompliance/ worsening, complications, treatment difficulties or failure; reasons documented	guideline-based care; V.A.C.®; 112 d	complete closure (and time), facilitation of surgical closure, area, foot salvage, complications, QOL, cost	38 wks	yes	

Evidence Table 14. Vacuum-Assisted Closure, Randomized Trials in Progress (continued)

Study	Patients	Target n	Randomization	Allowable Withdrawals	Treatments	Outcomes	F/U	Planned Adjust-ment for Confound-ers?	Planned Intent-to-Treat?
Protocol VAC2001-08	diabetic foot ulcers	248, power analysis	by patient, central computerized randomization, opaque envelopes	investigator/KCI discretion of noncompliance/ worsening, complications, treatment difficulties or failure; reasons documented	guideline-based care; V.A.C.®; 112 d	blinded, complete closure (and time), facilitation of surgical closure, area, foot salvage, complications, QOL, cost	38 wks	yes	
Protocol VAC2002-09	open chest wounds	116, power analysis	by patient, central computerized randomization	investigator/KCI discretion of noncompliance/ worsening, com-plications, treatment difficulties or failure; reasons documented	guideline-based moist therapy; V.A.C.®; 84 d	blinded, facilitation of surgical closure, complications, pain, cost	3 mo	yes	
Protocol VAC2002-10	open abdominal wounds	116, power analysis	by patient, central computerized randomization	investigator/KCI discretion of noncompliance/ worsening, com-plications, treatment difficulties or failure; reasons documented	guideline-based moist therapy; V.A.C.®; 84 d	blinded, facilitation of surgical closure, complications, pain, cost	3 mo	yes	

KCI also furnished abstracts presented at the 2nd World Union of Wound Healing Societies, which met in Paris, France, July 8–12, 2004. While these abstracts provide too little detail for meaningful analysis in this systematic review, they are summarized in Evidence Table 15 to document the progress of ongoing randomized trials.

Conclusions

This body of evidence is insufficient to support conclusions about the effectiveness of vacuum-assisted closure in the treatment of wounds. There are only six trials that met the inclusion criteria for this review and the included trials were of small size and poor quality. With the exception of one study of 54 patients with incomplete followup, all studies included fewer than 25 patients. The randomization method was clearly adequate in only one study. No study made it clear that groups were comparable on all three key baseline characteristics (age, wound duration, wound size). None provided group information about wound duration. A single study adjusted for confounders in the data analysis and another performed an intention-to-treat analysis.

Some outcomes in the available trials show a significant benefit for the vacuum-assisted closure group, while others do not. Only one study gave data on the probability of complete healing, showing no significant difference between groups. A study reporting time to satisfactory healing also found no significant difference between groups. One study found no difference between vacuum-assisted closure and control in time to readiness for surgical closure. Three studies reported on change in wound area; one of which found a difference between vacuum-assisted closure and control, while two did not. Among four studies addressing change in wound volume, two found a significant advantage for vacuum-assisted closure and two did not achieve statistical significance. One study found significant changes in wound width and depth for vacuum-assisted closure and another found it only for depth. It is possible that the lack of significant results in some or all of these trials result from a type II error. In most cases, the numerical results favor the vacuum-assisted closure group. Power calculations are lacking for these trials, but their small size raises the possibility that they are underpowered.

The randomized, controlled trial protocols provided by KCI outline much larger trials that are condition-specific and address many of the quality problems found in the published studies. If implemented and completed successfully as planned, these trials will provide substantial advances in the evidence base for vacuum-assisted closure therapy, and may allow more definitive conclusions on the efficacy of vacuum-assisted closure.

Evidence Table 15. Abstracts Presented at the 2nd World Union of Wound Healing Societies, Paris, France; July 8–12, 2004

Abstract #	Author	Patient Selection	n	Cx	Tx	Tx=Cx	Tx>Cx Significant	Tx>Cx Significant?	Tx>Cx NS	Comment
A001	Moues	full-thickness wounds	54	conven-tional moist gauze therapy	VAC®		area	Surgical closure		published, included
A016	Foo	diabetic foot	25	moist gauze dressing	V.A.C.®		area, granulation tissue formation			interim (target n= 40)
D008	Molnar	bilateral thermal hand burns	23	silver sulfa-diazine	V.A.C.®	volume (14 d), range of motion	volume (3 d, 5 d), edema			interim; KCI Wake Forest protocol
E008	Stannard	draining hematoma post-surgical stablization of skeletal trauma	79	pressure dressing	V.A.C.®			drainage time, surgical evacuation		interim; Protocol VAC2001-04
E009	Stannard	open reduc-tion, internal fixation of high-risk fractures	90	standard postop dressings	V.A.C.®			drainage time to Grade 3/to wound sealing		interim; Protocol VAC2001-05
E010	Stannard	open fractures	28	wet-to-moist dressings	V.A.C.®				deep infections, osteomyelitis, dehiscence	interim; Protocol VAC2001-06

Evidence Table 15. Abstracts Presented at the 2nd World Union of Wound Healing Societies, Paris, France; July 8-12, 2004 (continued)

Abstract #	Author	Patient Selection	n	Cx	Tx	Tx=Cx	Tx>Cx Significant	Tx>Cx Significant?	Tx>Cx NS	Comment
E011	Payne	diabetic foot amputation wounds	43	moist dressings	V.A.C.®	wound closure		foot salvage		interim; Protocol VAC2001-07
H013	Armstrong	complex diabetic foot ulcers	46	moist dressings	V.A.C.®		wound closure	area, volume		interim; Protocol VAC2001-08
P029	Vuerstaek	recalcitrant leg ulcers	60	control	V.A.C.®		cleaning time, heal-ing time			
P036	Lantis	venous stasis leg ulcers		split-thick-ness skin graft	graft + V.A.C.®				graft take, 4-7 d, 90d	premature stop
X001	Niezgoda	pressure ulcers	98	moist wound healing	V.A.C.®				area, volume	interim; Protocol VAC2001-01
DD004	Bayer	median sternotomy wound	8	moist dressings	V.A.C.®					wound closure too early; Protocol VAC2001-09
DD010	Orgill	open abdominal wounds	30	moist wound therapy	V.A.C.®		depth (4/5 followup periods)		wound closure	interim; Protocol VAC2001-10
E012	Obdeijn	acute and chronic wounds	35	hydro-colloids and alginates	V.A.C.®					no data in abstract

Chapter 4. Discussion

Chronic wounds are a source of major disability, morbidity, and increased risk of mortality, and thus have a significant impact on the public health and the expenditure of health care resources. There are many factors that can impede wound healing and may predispose a patient to the development of chronic wounds. Local factors include severity of wound (area/depth), viability of surrounding tissue, presence of infection or foreign body. Systemic factors include age, functional status, nutritional status, and comorbid illnesses such as diabetes and/or renal disease. Moreover, in clinical practice, there is a high degree of variability in wound treatment, and evidence that standard wound care deviates substantially from optimal guidelines. Thus, patients who present with nonhealing ulcers may actually heal with an adequate trial of optimal care.

Drawing on a draft U.S. Food and Drug Administration guidance document and other sources, this systematic review identified key features of trials that are necessary to provide good quality evidence on the effects of an intervention on wound healing. First, randomized controlled trials are required to control for the many confounding factors that affect the course of wound healing. Trials should be double-blinded or use independent blinded assessment of outcome if double-blinding is not feasible. The patient population should represent a single type of wound, since each type of wound has distinct physiologic characteristics, which may differ in their response to a particular therapy. Well-defined entry criteria or a run-in period of optimal treatment can establish whether a study population is refractory to best conventional care. The intensity and quality of care provided to study and control groups should differ only with respect to the use or absence of the intervention under study. The outcomes of greatest clinical significance are the percent of patients with complete healing and time to complete healing. Secondary outcomes such as wound size and facilitation of surgical closure are of interest, but are not sufficient.

The evidence for this systematic review consisted of 11 (n=419) randomized, controlled trials of low-level laser therapy and six (n=135) randomized, controlled trials of vacuum assisted closure. Overall, these trials were of poor quality. All six of the vacuum-assisted closure studies were rated as poor quality. Nine of 11 laser studies were rated poor quality; one was rated good and another fair. Quality concerns center on: adequacy of randomization methods, the comparability of groups at baseline and followup, use of complete healing as the primary endpoint, adjustment for confounders, and intent-to-treat analysis. Sample sizes were generally small, making it difficult to find statistically significant differences between groups. As to results, the best available trial did not show a higher probability of complete healing at 6 weeks with the addition of low-level laser treatment care compared to sham laser treatment added to standard care. Weaknesses in the available low-level laser studies were not likely to have concealed existing effects. Future studies may determine whether different dosing parameters or use of lasers other than the helium-neon and gallium-arsenide types may lead to different results. Trials using the vacuum-assisted closure device did not find a significant advantage for the intervention on the primary endpoint, complete healing, and did not consistently find significant differences on secondary endpoints. The small vacuum-assisted closure studies may have been insufficiently powered to detect differences. Given the sparse evidence for these two wound healing interventions, it is not possible to find variables in these trials that may be associated with better results.

KCI, the manufacturer of the V.A.C.® device, has shared protocol documents for 10 randomized trials in progress. These protocols cover a wide variety of wound types, including burns, pressure ulcers, diabetic ulcers, traumatic and surgical wounds, venous stasis wounds, and diabetic wounds. Large sample sizes are planned, determined by power analyses. Sophisticated randomization techniques will be used in many trials. A wide range of outcomes will be assessed, often by a blinded observer. Plans to adjust for confounders in the analysis, if necessary, are common. Concerns remain about the overly broad criteria for allowable withdrawals, including: noncompliance; worsened condition; complications; and treatment difficulties/failures. Excluding patients for these reasons may give an unrealistic sense of the effectiveness of vacuum-assisted closure therapy. However, if intention-to treat analyses are reported, these trials have the potential to substantially advance the evidence base for vacuum-assisted closure therapy.

It is notable that surprisingly large numbers of control patients achieved complete healing in these trials, implying that optimal conventional treatment is often not delivered. Of the 4 trials that reported on complete healing as an outcome, 24 of the total of 81 patients (30 percent) in the control arm had complete healing. Similar improvement in the control groups has been observed in randomized trials of other wound healing interventions. For example, in two recent trials of bioengineered skin substitute versus standard care, 38 percent and 49 percent of "refractory" ulcers, healed completely in the standard care arm. Even in wounds present for at least 1 year, a substantial minority (19 percent) healed with standard treatment.

This systematic review focused on two specific interventions for wound healing, but the issues raised in the discussion should be applied broadly. Due to the large size of populations with nonhealing and other types of wounds, the impact on healthcare expenditures is considerable. Future research should address how to improve the delivery of care, quality of care and outcomes of treatment of wounds in various settings. There is potential to reduce the frequency of nonhealing wounds and thus the overall costs of care. New interventions have the potential to improve wound care, but outcomes must be demonstrated in well-controlled randomized trials. Strategies for reducing the occurrence of wounds in various susceptible populations also have a place in the research portfolio. Given significant costs of chronic wounds, future comparisons of the cost-effectiveness of various strategies for preventing wounds, managing wounds and improving quality of care would be of value to clinical decisionmakers.

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List of Acronyms/Abbreviations

AE	adverse events
AHRQ	Agency for Healthcare Research and Quality
CI	confidence interval
cx	control
d	day
F	female
f/u	followup
FDA	U.S. Food and Drug Administration
GaAl	gallium-aluminum
GaAs	gallium-arsenide
HeNe	helium-neon
hr	hour
LLL	low-level laser
M	male
mn	mean
mo	month
NR	not reported
NS	not significant
PMN	polymorphonuclear
QOL	quality of life
rng	range
ROM	range of motion
SC	standard care
SC	subcutaneous
SD	standard deviation
SW	software
t_cpO_2	transcutaneous oxygen tension
TEP:	Technical Expert Panel
tx	treatment
U.S.	United States
US	ultrasound
UV	ultraviolet
VAC	vacuum-assisted closure
wk	week
WOCN	Wound, Ostomy and Continence Nurses Society
yr	year

Appendix A. Exact Search Strings

Electronic database searches using the following terms were completed of MEDLINE® (via PubMed), EMBASE, and the Cochrane Controlled Trials Register. The MEDLINE® search covered references entered onto the database from January 1, 1966 through June 8, 2004. The Cochrane Controlled Trials Register search was completed in 2003, through issue number 4. The EMBASE search covered references entered through June 14, 2004.

The search was limited to studies on human subjects with English-language abstracts. Papers published in foreign languages were reviewed if the English-language abstract appeared to meet inclusion criteria. Results of the search and study selection were reviewed by the Technical Expert Panel (TEP) for this project, in order to identify additional studies.

In addition, two companies that produce lasers used in wound healing were contacted (Microlight Corporation of America and Photothera), as well as the major producer of vacuum-assisted closure devices (V.A.C.®, Kinetics Concepts Inc. [KCI]) and invited them to submit evidence-based information for the review. The specific request was for "lists of published, randomized, controlled trials (RCTs), published abstracts of RCTs within the past 2 years, and published articles on study design, or protocols of any RCTs (published or in progress)."

Low-Level Laser Therapy

For low-level laser therapy, the search is somewhat narrower than for vacuum-assisted closure because the question is limited to chronic, nonhealing wounds.

A Medical Subject Headings ® (MeSH®) term, "laser therapy, low-level," was introduced in 2002. The following entry terms map to it:

- Laser Therapies, Low-Level
- Laser Therapy, Low Level
- Low-Level Laser Therapies
- Laser Irradiation, Low-Power
- Irradiation, Low-Power Laser
- Laser Irradiation, Low Power
- Laser Therapy, Low-Power
- Laser Therapies, Low-Power
- Laser Therapy, Low Power
- Low-Power Laser Therapies
- LLLT
- Laser Biostimulation
- Biostimulation, Laser Low-Level
- Laser Therapy Low Level
- Laser Therapy Low-Power
- Laser Irradiation Low Power
- Laser Irradiation Low-Power
- Laser Therapy Low Power
- Laser Therapy

The following text phrases will also be searched:

- “low level laser”
- “low power laser”
- “low intensity laser”
- “low energy laser”
- “low level energy laser”
- “low output laser”
- “nonablative laser”
- “cold laser”

These terms related to wounds will be searched:

- “skin ulcer[MeSH]”
  - “decubitus ulcer”
  - “foot ulcer”
  - “leg ulcer”
  - “varicose ulcer”
  - “diabetic foot”
- “wound*”
- “ulcer*”

The intersection of the laser therapy terms and wound terms served as the initial pool of references. These were cross-referenced with the terms for randomized trials compiled by the Cochrane Collaboration (Clark and Oxman, 2003).

Vacuum-Assisted Closure

Searches on the terms below relate to vacuum-assisted closure:

- “topical negative pressure”
- “sub-atmospheric pressure therapy” (also “subatmospheric”)
- “sub-atmospheric pressure dressing” (also “subatmospheric”)
- “vacuum sealing”
- “vacuum assisted closure”
- “negative pressure dressing”
- “negative pressure therapy”
- “foam suction dressing”
- “vacuum compression”
- “vacuum pack”
- “sealed surface wound suction”
- “sealing aspirative therapy”

These terms related to wounds will be searched:

- “wound*”
- “ulcer*”
- “decubit*”
- “incision*”
- “dressing”
- “free flap”
- “skin graft*”
- “skin transplantation”
- “degloving injuries”
- “degloving injury”

Excluded terms:

- “mechanical ventilation”
- “ear pressure”
- “venous pressure”
- “hypertension”
- “abortion”
- “core needle”
- “colonic anastomos*”

The intersection of the vacuum-assisted closure terms and wound terms served as the initial pool of references. These were cross-referenced with the terms for randomized trials compiled by the Cochrane Collaboration (Clark and Oxman, 2003).

Appendix B. Technical Expert Panel (TEP) and Reviewers

Technical Expert Panel (TEP)

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