Electrical Stimulation for the Treatment of Chronic Wounds
Table of Contents

1.0 Executive Summary ........................................................................................................1

2.0 Healing Process and Ulceration ....................................................................................5
  2.1 Phases of Wound Healing .........................................................................................5
  2.2 Wounds and Ulcerations .........................................................................................7
  2.3 Evaluation and Therapies for Wound Healing .......................................................10
     2.3.1 Evaluation ........................................................................................................10
     2.3.2 General Therapies ..........................................................................................10
  2.4 Guidelines and Evidence of Present Practice Patterns ........................................16
     2.4.1 Consensus ........................................................................................................16
     2.4.2 Lack of Consensus ..........................................................................................17
     2.4.3 Practice Patterns ............................................................................................19
  2.5 Tables ......................................................................................................................21
     Table 2.1. Summary of Guidelines for Wound Healing Therapy ...............................21
     Table 2.2. Summary of Technology Assessments for Wound Healing Therapies ....29
     Table 2.3. Summary of Reports of Practice Patterns for the Treatment of Chronic
               Wounds ...........................................................................................................30

3.0 Electrical Stimulation for Wound Healing ..................................................................33
  3.1 Basic Description ......................................................................................................33
  3.2 Types of Electrical Stimulation and Treatment Protocols ....................................34
     3.2.1 Direct Current Applications ............................................................................34
     3.2.2 Pulsed Current Applications .........................................................................36
     3.2.3 Alternating Current Applications ..................................................................38
     3.2.4 Pulsed Electromagnetic Applications .........................................................40
     3.2.5 Spinal Cord Stimulation Applications .........................................................41
  3.3 Safety .......................................................................................................................43
     3.3.1 Reports from Published Studies ......................................................................43
     3.3.2 Contraindications and Warnings from Product Literature ...........................43
     3.3.3 ECRI Health Device Alerts Database ............................................................44
  3.4 Manufacturers and Costs ..........................................................................................45
  3.5 Tables ......................................................................................................................49
     Table 3.1. Examples of Preclinical Studies Evaluating the Effects of Electrical
               Stimulation on Wound Healing ......................................................................49
     Table 3.2. Synopses of Direct Current (DC) Stimulation Therapies for Wound Healing ...
               .........................................................................................................................51
     Table 3.3. Synopses of Pulsed Current (PC) Stimulation Therapies for Wound Healing ...
               .........................................................................................................................52

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286196.WGE
Table 3.4. Synopses of Alternating Current (AC) Stimulation Therapies for Wound Healing ................. 54
Table 3.5. Synopses of Pulsed Electromagnetic Induction (PEMI) Stimulation Therapies for Wound Healing .............................................................. 56
Table 3.6. Manufacturers, Models, and Device Specifications of Electrical Stimulators ....................... 58

4.0 Quality of Electrical Stimulation Studies for Chronic Wound Healing ............ 76
4.1 Databases and Search Strategies for Electrical Stimulation Studies ....................... 77
4.2 Possible Confounding Factors in Wound Healing Studies ...................... 80
  4.2.1 Study Types ........................................................................ 80
  4.2.2 Confounding Sources ......................................................... 82
  4.2.3 Outcome Measures ............................................................ 84
    4.2.3.1 Objective Outcomes: Percentage of Patients Completely Healed .............. 86
    4.2.3.2 Objective Outcomes: Healing Rates ........................................ 87
    4.2.3.3 Subjective Outcomes ..................................................... 88
4.3 Quality of Individual Electrical Stimulation Studies of Wound Healing .......... 89
  4.3.1 Direct Current Controlled Studies ........................................... 90
  4.3.2 Pulsed Current Controlled Studies .......................................... 92
  4.3.3 Alternating Current and TENS Controlled Studies ............................. 96
  4.3.4 Pulsed Electromagnetic Induction Controlled Studies ......................... 96
  4.3.5 ES Study Quality: General Findings ........................................ 98
4.4 Tables .................................................................................. 99
  Table 4.1. Assessment of Quality of Direct Current Stimulation Studies of Wound Healing .......... 99
  Table 4.2. Assessment of Quality of Pulsed Current Stimulation Studies of Wound Healing ........ 101
  Table 4.3. Assessment of Quality of Alternating Current Stimulation Studies of Wound Healing .......... 104
  Table 4.4. Assessment of Quality of Pulsed Electromagnetic Induction Studies of Wound Healing .......... 107

5.0 Electrical Stimulation Study Descriptions and Outcomes ....................... 109
  5.1 Direct Current Studies ................................................................ 110
    5.1.1 Uncontrolled Studies ....................................................... 110
    5.1.2 Controlled Studies .......................................................... 111
5.2  Pulsed Current Studies ................................................................. 114
    5.2.1  Uncontrolled Studies ...................................................... 114
    5.2.2  Controlled Studies .......................................................... 114
5.3  Alternating Current (and TENS) Studies .................................... 119
    5.3.1  Uncontrolled Studies ..................................................... 119
    5.3.2  Controlled Studies .......................................................... 120
5.4  Pulsed Electromagnetic Induction Studies .................................. 122
    5.4.1  Uncontrolled Studies ..................................................... 122
    5.4.2  Controlled Studies .......................................................... 122
5.5  Spinal Cord Stimulation Studies ............................................. 125
    5.5.1  Uncontrolled Studies ..................................................... 125
    5.5.2  Controlled Study ............................................................ 125
5.6  Ongoing Studies ........................................................................ 126
5.7  Tables .......................................................................................... 127
    Table 5.1. Outcomes Reported by Investigators in Direct Current
               Studies of Wound Healing .............................................. 127
    Table 5.2. Outcomes Reported by Investigators in Pulsed Current
               Studies of Wound Healing ............................................ 129
    Table 5.3. Outcomes Reported by Investigators in Alternating Current
               and TENS Studies of Wound Healing .................................. 131
    Table 5.4. Outcomes Reported by Investigators in Pulsed
               Electromagnetic Induction Studies of Wound Healing ......... 133
    Table 5.5. Outcomes Reported by Investigators in Spinal Cord
               Stimulation Studies of Wound Healing .............................. 134
    Table 5.6. Ongoing Studies of Electrical Stimulation for Wound Healing ........................................ 135

6.0  Quantitative Analysis and Meta-Analyses of Outcomes of Electrical
     Stimulation Studies ..................................................................... 136
6.1  Quantitative Analysis of Normalized Wound Healing Rates:
     Theta (θ) Values ......................................................................... 137
     6.1.1  Definition and Description of Theta .................................... 137
     6.1.2  Theta Outcomes for Individual Electrical Stimulation Studies ......................................................................... 141
     6.1.3  Summary of Normalized Healing Rates for Electrical Stimulation Studies .................................................. 143
6.2  Meta-Analyses of Outcomes of Electrical Stimulation for Wound Healing ................................................................. 146
     6.2.1  Overview of Meta-Analytic Methods .................................. 146
     6.2.2  Meta-Analysis of Normalized Wound Healing Rates .......... 148
            6.2.2.1  Overall Study Analysis ........................................... 148
6.2.2.2 Analysis of Study Heterogeneity ..........149
6.2.2.2.1 Influence of Study Design ..........149
6.2.2.2.2 Influence of Patient Characteristics, Wound Characteristics, or Treatment ..................150

6.2.3 Meta-Analysis of Complete Wound Healing ..........153
6.2.3.1 Overall Study Analysis ..................153
6.2.3.2 Analysis of Study Heterogeneity ..........153
6.2.3.2.1 Influence of Study Design ..........154
6.2.3.2.2 Influence of Patient Characteristics, Wound Characteristics, or Treatment ..................155

6.2.4 Publication Bias ..................................156
6.2.5 Conclusions of Meta-Analyses of Electrical Stimulation for Wound Healing ..................157

6.3 Figures and Tables ..................................159
Figure 6.1. Plots of Initial Wound Size versus Normalized Healing Rates (?) ..................159
Figure 6.2. Computer-Generated Negative Exponential Model Plots of Wound Healing ..................161
Table 6.1. Normalized Healing Rates for Direct Current Stimulation Studies of Wound Healing ..................162
Table 6.2. Normalized Healing Rates for Pulsed Current Stimulation Studies of Wound Healing ..................163
Table 6.3. Normalized Healing Rates for Alternating Current and TENS Stimulation Studies of Wound Healing ..................164
Table 6.4. Normalized Healing Rates for Pulsed Electromagnetic Induction Stimulation Studies of Wound Healing ..................165
Table 6.5. Summary of Normalized Healing Rates in Controlled Trials of Electrical Stimulation for Chronic Wound Healing ..................166
Table 6.6. Studies and Relevant Data for Meta-Analysis of Normalized Wound Healing Rates ..................167
Table 6.7. Meta-Analysis (Fixed Effects) of Normalized Wound Healing Rates: \( d \) Statistic with Confidence Limits ..................168
Table 6.8. Studies and Relevant Data for Meta-Analysis of Complete Wound Healing ..................170
Table 6.9. Meta-Analysis (Fixed Effects) of Complete Wound Healing: \( d \) Statistic with Confidence Limits ..................172
Figure 6.4. Effect Size Plot (d Values) for Complete Wound Healing ................................................................. 173
Figure 6.5. Funnel Plot for Detecting Publication Bias in Normalized Healing Rates ............................................. 174
Figure 6.6. Funnel Plot for Detecting Publication Bias in Complete Healing ........................................................ 175

7.0 Quality of Study Comparison: Electrical Stimulation versus Conventional and Alternative Therapies for Wound Healing ......................................................... 176
7.1 Quality Comparison for Venous Ulcers .......................................................... 177
  7.1.1 Comparison with Conventional Therapies .............................................. 177
  7.1.2 Comparison with Alternative Therapies ............................................... 179
7.2 Quality Comparison for Decubitus Ulcers .................................................... 181
  7.2.1 Comparison with Conventional Therapies ............................................ 181
  7.2.2 Comparison with Alternative Therapies .............................................. 184
7.3 Tables ........................................................................................................ 188
  Table 7.1. Randomized Controlled Studies of Conventional Therapies for Venous Ulcers Used in Qualitative Comparative Analysis .................................................. 188
  Table 7.2. Comparison of Quality of Conventional RCTs and Electrical Stimulation RCTs for the Treatment of Venous Ulcers ......................................................... 190
  Table 7.3. Randomized Controlled Studies of Alternative Therapies for Venous Ulcers Used in Qualitative Comparative Analysis .................................................. 193
  Table 7.4. Comparison of Quality of Alternative RCTs and Electrical Stimulation RCTs for the Treatment of Venous Ulcers ......................................................... 194
  Table 7.5. Randomized Controlled Studies of Conventional Therapies for Decubitus Ulcers Used in Qualitative Comparative Analysis .......................................... 197
  Table 7.6. Comparison of Quality of Conventional RCTs and Electrical Stimulation RCTs for the Treatment of Decubitus Ulcers ......................................................... 198
  Table 7.7. Randomized Controlled Studies of Alternative Therapies for Decubitus Ulcers Used in Qualitative Comparative Analysis .......................................... 201
  Table 7.8. Comparison of Quality of Alternative RCTs and Electrical Stimulation RCTs for the Treatment of Decubitus Ulcers ......................................................... 202
8.0 Comparison of Normalized Healing Rates: Electrical Stimulation versus Conventional and Alternative Therapies for Wound Healing ........205
8.1 Comparison of Normalized Healing Rates for Venous Ulcers ..........207
  8.1.1 Comparison with Conventional Therapies ..................207
  8.1.2 Comparison with Alternative Therapies ....................207
8.2 Comparison of Normalized Healing Rates for Decubitus Ulcers ....209
  8.2.1 Comparison with Conventional Therapies ..................209
  8.2.2 Comparison with Alternative Therapies ....................210
8.3 Tables ...............................................................................212
  Table 8.1. Normalized Healing Rates for RCTs of Conventional Therapies for Venous Ulcers ........212
  Table 8.2. Comparison of Individual Electrical Stimulation RCTs with Normalized Healing Rate Control Group-Matched (\(?_{\text{con}}\)) Conventional RCTs for Venous Ulcers .................................................................214
  Table 8.3. Normalized Healing Rates for RCTs of Alternative Therapies for Venous Ulcers ..........215
  Table 8.4. Comparison of Individual Electrical Stimulation RCTs with Normalized Healing Rate Control Group-Matched (\(?_{\text{con}}\)) Alternative RCTs for Venous Ulcers .................................................................216
  Table 8.5. Normalized Healing Rates for RCTs of Conventional Therapies for Decubitus Ulcers ..........217
  Table 8.6. Comparison of Individual Electrical Stimulation RCTs with Normalized Healing Rate Control Group-Matched (\(?_{\text{con}}\)) RCTs for Decubitus Ulcers ....218
  Table 8.7. Normalized Healing Rates for RCTs of Alternative Therapies for Decubitus Ulcers ..........219
  Table 8.8. Comparison of Individual Electrical Stimulation RCTs with Normalized Healing Rate Control Group-Matched (\(?_{\text{con}}\)) Alternative RCTs for Decubitus Ulcers .................................................................220

9.0 General Summary ....................................................................221
9.1 Basic Description of Electrical Stimulators ..............................221
9.2 Analyses of Electrical Stimulation Studies ................................223
  9.2.1 Quality of Electrical Stimulation Studies ...............223
  9.2.2 Quantitative Analysis of Electrical Stimulation Normalized Healing Rates ..................224
  9.2.3 Meta-Analyses of Electrical Stimulation Studies ........226
9.3 Comparison of Electrical Stimulation Studies with Other Therapies for Wound Healing ....................228
  9.3.1 Comparison of Qualities of Studies .......................228
  9.3.2 Comparison of Normalized Healing Rates ...............229
# Appendix I: List of Abbreviations

233

# Appendix II: Formulae Used in Meta-Analyses

235

## 11.1 Univariate Analysis

235

### 11.1.1 Formulae for Univariate Fixed Effects Models

235

#### 11.1.1.1 Hedges' $d$

235

#### 11.1.1.2 $Q$ Statistic

238

#### 11.1.1.3 Rosenthal's Method of Focused Contrasts

239

### 11.1.2 Formulae for Univariate Random Effects Models

239

## 11.2 Multivariate Analysis

241

### 11.2.1 Formulae for Multivariate Fixed Effects Models

241

### 11.2.2 Formulae for Multivariate Random Effects Models

241

## 11.3 Formulae for Publication Bias

243

# Appendix III: AHCPR Strength-of-Evidence Rating System

245

# Appendix IV: External Reviewer Comments

246

# Citations

247

## 14.1 Citations from ECRI Databases and Publications

293

## 14.2 Citations (Bibliographic Format)

295
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1.0 Executive Summary

Electrical stimulation (ES) has been studied as a possible therapy for accelerating wound healing. Preclinical studies have shown that externally applied electrical stimulation can increase ATP (adenosine triphosphate) concentrations in tissues, increase DNA synthesis, promote healing of soft tissue or ulcers, cause epithelial and fibroblasts to migrate into wound sites, accelerate the recovery of damaged neural tissue, reduce edema, and inhibit the growth of some pathogens.

ES has been used or studied for many different therapeutic applications. It has been used for stimulating the healing of fractures in the lower leg, spine, and wrist and for relieving chronic intractable pain in the spine. Studies have also tested the effectiveness of ES to heal jaw fractures, reduce pain and swelling in soft tissue injuries, alleviate spinal cord lesions, eliminate intermittent claudication, improve healing from assorted hand injuries, reduce cerebral edema in cases of head trauma, reduce swelling in grades I and II ankle sprains, and accelerate healing after foot, dental, or oral surgery.

We identified several types of ES for wound healing:

- direct current (DC);
- pulsed current (PC), which includes pulsed direct current (PDC) and high-voltage pulsed current (HVPC) devices;
- alternating current (AC);
- pulsed electromagnetic induction (PEMI), which includes pulsed electromagnetic field (PEMF) and pulsed electromagnetic energy (PEE) devices; and
- spinal cord stimulation (SCS).

ECRI conducted extensive analyses of studies of ES for the treatment of chronic wounds (≥30 days duration) that included

- a qualitative analysis of all ES studies,
- a quantitative analysis of the normalized healing rates of ES studies,
- a meta-analysis of the normalized healing rates of ES studies,
• a meta-analysis of proportion of lesions completely healed in ES studies,

• a comparison of the quality of ES studies compared to conventional and alternative therapies for the treatment of venous and decubitus ulcers, and

• a control-matched comparison of ES therapies for venous ulcers and for decubitus ulcers compared to conventional and alternative therapies.

Based on these analyses, we make the following overall conclusions about ES for chronic wound healing:

**Qualitative Conclusions**—

• Although all ES studies have at least 1 weakness, not all are potentially confounded.

• ES controlled studies for venous ulcers are about equal to or slightly inferior in quality compared to other controlled studies for venous ulcers.

• ES controlled studies for decubitus ulcers are about equal to or slightly superior in quality compared to other controlled studies for decubitus ulcers.

**Quantitative Conclusions**—

• ES facilitates the healing rate of chronic ulcers.

• ES facilitates the complete healing of chronic ulcers.

• The relationship between outcomes and ES can be affected by wound size and type of stimulator.

• Decubitus ulcers are more likely to heal completely in response to ES than venous ulcers.

Based on these analyses, ECRI draws the following conclusions for different types of electrical stimulators for chronic wound healing:
Direct Current (DC)—

There is

- No evidence that DC stimulation improves the healing rate of chronic, decubitus, or diabetic ulcers.

Pulsed Current (PC)—

There is

- Evidence that PC stimulation improves the normalized healing rate of stage II through IV decubitus ulcers. This improvement in the healing rate of decubitus ulcers appears to be roughly comparable to that in many conventional and alternative therapies for stage II and III decubitus ulcers. (Randomized controlled trials would be needed to determine if these rates significantly differ.)
- No evidence that PC stimulation improves the healing rate of chronic venous or diabetic ulcers.
- Insufficient data for comparison of stage IV decubitus ulcers treated by ES therapy to other therapies.

Alternating Current (AC) or Transcutaneous Electrical Nerve Stimulation (TENS)—

There is

- Evidence that AC devices improve the normalized healing rate of decubitus ulcers.
- No evidence that AC or TENS improves the healing rate of chronic venous or diabetic ulcers.
- Insufficient data to compare AC therapy findings to those for any other therapy.

Pulsed Electromagnetic Induction (PEMI)—

There is

- Evidence that PEMF stimulation improves the normalized healing rate of venous ulcers. However, this improvement appears to be small and may not be clinically useful.
• Evidence that PEE stimulation improves the normalized healing rate for stage II decubitus ulcers. The improvement of stage II decubitus ulcer healing appears to be roughly comparable to conventional and alternative therapies for stage II and III decubitus ulcers. (Randomized controlled trials would be needed to determine if these rates significantly differ.)

• No evidence that PEMF stimulation improves the healing rate of chronic decubitus or diabetic ulcers.

• No evidence that PEE stimulation improves the healing rate of chronic venous or diabetic ulcers.

• Insufficient data to determine whether PEE stimulation improves the normalized healing rates for stage III or IV decubitus ulcers.

General Findings

• ES devices are safe when used appropriately.

• Most types of ES are more effective than minimal treatment (e.g., saline-soaked gauze).

• ES is not markedly superior to or inferior to conventional or alternative therapies (defined in Sections 7.1.1 and 7.2.2). There is insufficient evidence to determine if clinically significant differences exist.
2.0 Healing Process and Ulceration

2.1 Phases of Wound Healing

The normal wound healing process consists of 3 phases:

- inflammatory (substrate),
- proliferative, and
- remodeling.

INFLAMMATORY (SUBSTRATE) PHASE—After initial damage to blood vessels at the wound site, smooth muscle cells of injured vessels cause vasoconstriction (from circulating catecholamines and serotonin), which leads to hemostasis. Circulating platelets subsequently adhere to injured vessel walls, become activated, and release substances such as adenosine diphosphate (ADP); platelet-activating factor (PAF), which stimulates additional platelet aggregation and activation; and growth factors such as platelet-derived growth factor (PDGF) and alpha and beta transforming growth factors (TGF-α and TGF-β). Leukocytes (neutrophils, monocytes, and lymphocytes) enter the injured site. Neutrophils, stimulated by PAF, interleukin-1 (IL-1), and tumor necrosis factor (TNF), first adhere to the capillary endothelium then clear the wound of foreign debris and organisms by producing hydrogen peroxide and proteins that destroy bacteria. Monocytes, the most important leukocyte, are attracted by chemotactic agents in wounds, such as TGF-β, and are transformed into macrophages. The main function of macrophages is releasing biological agents called monokines (including IL-1, TNF, TNF-α, TGF-α, TGF-β, and colony stimulating factors) that regulate other inflammatory cells. T-lymphocytes secrete lymphokines (including interferon-β, TGF-β, fibroblast-activating factor, and IL-2 through IL-8). Fibroblasts, also critical to wound healing, are attracted by PDGF. Agents such as epidermal growth factor (EGF), insulin-like growth factor-1, and TGF-β in the presence of PDGF assist fibroblast replication.

PROLIFERATIVE PHASE—During this phase, which begins 2 days post-trauma and lasts for 3 weeks, the wound fills in with new tissue. Primary activities during this period are

- epidermal regeneration,
- neoangiogenesis,
- collagen synthesis,
• wound contraction.

Most activity is carried out by fibroblasts, epithelial cells, endothelial cells, and macrophages.

During **epidermal regeneration**, epidermal cells migrate over the wound at a rate of 2 to 3 cell diameters per hour, assisted by fibronectin and vitronectin. Proliferation begins at the wound edge and is affected by numerous factors (fibroblastic growth factor (FGF), Ca, EGF, keratinocyte growth factor, PDGF, IL-1, TGF-α, and TGF-β). **Neoangiogenesis**, new capillary formation, begins from venules at the wound edge and is stimulated by angiogenic factors including TNF-α and FGF. **Collagen synthesis** begins in cellular rough endoplasmic reticulum of fibroblasts with production of procollagen that is transported by the Golgi apparatus to extracellular space, where it is degraded by proteolytic enzymes, yielding collagen monomers. These are cross-linked and assembled into collagen. Oxygen is essential to collagen synthesis. Fibroblasts also produce the ground substance (proteoglycans), which act as adhesive agents. **Wound contraction** begins within 1 to 2 weeks of injury, resulting from fibroblast movement and myofibroblast interaction. Fibronectin and other factors regulate the process.

**REMODELING PHASE**—Approximately 3 weeks after injury, the wound begins a continual process of collagen synthesis and breakdown that leads to remodeling of the site. There are several different types of collagen compounds. Type I is synthesized by more mature fibroblasts and is associated with fiber-rich scar tissue. Type III appears within 24 to 48 hours after injury in children. Type IV is associated with the rebuilding of the basement membrane and attaching the newly formed epidermal layer to the dermis. Type VII contains anchoring fibrils. Changes also occur in the ground substance to increase wound tensile strength.
2.2 Wounds and Ulcerations

Many factors can interrupt or alter wound healing, including:

- aging;
- obesity;
- inadequate perfusion (e.g., atherosclerosis);
- anemia—due to blood loss (volumetric);
- edema—interstitial edema increases the distance between capillary beds and the wound site, which makes $O_2$ diffusion more difficult;
- repeated trauma to site;
- foreign bodies in site;
- infection—local or systemic;
- nutritional deficiencies—including proteins and vitamin C which affect collagen synthesis; vitamins A and B, which lower host defense mechanisms and immunity; and trace elements (e.g., Zn, Fe, Cu);
- smoking;
- radiation;
- medications (e.g., exogenous steroids); and
- topical agents (e.g., Betadine, Dakin's solution, and $H_2O_2$).

Some diseases that can predispose patients to develop chronic wounds include:

- diabetes mellitus—leading to artherosclerosis, neuropathies, immune compromise;
- chronic venous stasis ulceration;
• inherited disorders of wound healing—such as (a) Ehlers-Danlos syndrome, an inability to produce normal collagen; (b) epidermolysis bullosa, wherein there is inadequate adhesion of epidermis, dermis, and basement membrane of skin; and (c) Marfan’s syndrome (associated with abnormalities in collagen maturation and cross-linking);

• neoplasms;

• connective tissue disorders—such as osteoarthritis, rheumatoid arthritis, scleroderma;

• blood abnormalities—such as sickle cell anemia, thalassemia, multiple myeloma, macroglobulinemia, cryoglobulinemia;

• lymphedema; and

• other disorders such as inflammatory bowel disease and ulcerative necrobiosis lipoidica.

VENOUS ULCERS—Venous insufficiency can develop as a result of thrombosis, obstruction, dilation (varicosity), or hemorrhage. These disruptions in venous return can lead to inadequate oxygenation and nutrition of subcutaneous tissue, causing breakdown and necrosis. Ambulatory venous hypertension is the most common pathway leading to venous ulceration. The valves of leg veins are usually incompetent, leading to venous reflux, retrograde flow of blood, and subsequent tissue breakdown. The resulting ulceration may have a covering of fibrous debris with a firm bed of granulation tissue.

Venous ulcers are shallow with flat borders, often wet with exudate, and frequently painless. These lesions develop slowly over years and can lead to loss of ankle function and bony ankylosis.

Venous ulcerations are common. Approximately 1% of the population will develop such poorly healing ulcers during their lifetime. Between 1990 and 1992, there were 1.3 million outpatient visits in the United States for the treatment of venous ulcers.

ARTERIAL (ISCHEMIC) ULCERS—Arterial ulcers result from inadequate perfusion to a site. Diseases associated with arterial ulcers include arteriosclerosis obliterans, thromboangiitis obliterans (Buerger's disease), necrotizing vasculitides (e.g., polyarteritis nodosa, rheumatoid arthritis, systemic lupus erythematosus), sickle cell anemia, and diabetes mellitus. Ischemic ulcers usually present as punched-out lesions with a well-demarcated border (without epithelium) over toes, interdigital spaces, the lateral malleolus, or dorsum of the foot. The ulcer base is very deep (possibly with exposed tendons),
black, necrotic, and has no granulation tissue. Such lesions are very painful. Surrounding tissue also shows signs of arterial insufficiency (e.g., loss of nail growth, absence of hair, atrophic skin).

DECUBITUS (PRESSURE SORE) ULCERS—Pressure ulcers occur when soft tissue is compressed over a period of time. These localized areas of tissue necrosis tend to develop when soft tissue is compressed between a bony prominence (e.g., femoral trochanter) and an external surface (e.g., mattress). They may also be caused or aggravated by friction or shearing forces. Pressure ulcers are also known as decubitus ulcers, bedsores, and pressure sores.

Staging (or grading) of pressure ulcers has been inconsistent and chaotic. In 1989, the National Pressure Ulcer Advisory Panel (NPUAP) issued a consensus statement classification of decubitus ulcers:12

Stage I: Nonblanchable erythema of intact lightly pigmented skin or a darker tone or violet hue to darkly pigmented skin; heralding lesion or skin ulceration.

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

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

Stage IV: Full-thickness skin loss with extensive destruction, tissue necrosis or damage to muscle, bone, or supporting structures (e.g., tendon, joint capsule).

Decubitus ulcers are common. NPUAP reports a 1% to 5% annual incidence (number of new cases per year) and a 3% to 14% annual prevalence (new and old cases per year) among hospitalized patients.13 Prevalence rates may reach 15% to 25% in skilled nursing facilities. Twenty-six percent of patients with nonhealing decubitus ulcers develop osteomyelitis.14 Patient risk factors for developing decubitus ulcers include immobility, inactivity, malnutrition, fecal and urinary incontinence, decreased level of consciousness, advanced age, chronic systemic illness, and (nonambulatory) fractures.15
2.3 Evaluation and Therapies for Wound Healing

2.3.1 Evaluation

Patients with chronic wounds should initially undergo complete vascular and neurological evaluations. Their nutritional status should also be established.\textsuperscript{16} Wounds should be staged and photographed at each visit. Wound parameter measurements performed each visit should include:\textsuperscript{17,18}

- accurate measurement of wound volume (critical)[see section 4],
- accurate measurement of surface area (critical),
- length,
- width,
- depth,
- degree of undermining,
- location,
- stage, and
- presence of sinus tracts, granulation tissue, necrotic tissue, and epithelialization.

Wounds can be measured by planimetry, direct tracing, or stereophotogrammetry. Noninvasive vascular testing should be performed to determine possible arterial insufficiency. These procedures include segmental pressure measurements, pulse-volume recordings, and transcutaneous oxygen levels (\(T_c\)PO\(_2\)) at the level of the chest and upper wall.\textsuperscript{19} An absolute \(T_c\)PO\(_2\) of 30 mm Hg or PO\(_2\) index \(\geq\)0.2 are positive prognostic factors for healing; PO\(_2\) values <0.2 suggest that the wound will not heal unless additional oxygen is provided to the site.

2.3.2 General Therapies

Conservative therapy for venous ulcers is based on compression and includes (1) below-the-knee graded elastic stockings (providing 30 to 40 mm Hg at the ankle), (2) Unna boots, and (3) pneumatic compression devices.
Pressure relieving devices for decubitus ulcers include (1) static devices that immobilize sites and rely on materials that cushion and mold to body surfaces (e.g., foam overlays; devices filled with gel, water, or air; heel and elbow pads) and (2) dynamic pressure-relieving devices that use electricity to alter currents of air which redistribute pressure against the body, removing pressure from affected sites.\textsuperscript{20} (Frequent and routine repositioning of bedridden patients may prevent the formation of these ulcers.)

Weingarten\textsuperscript{21} classified direct wound care therapies into 2 basic categories: passive and active. Passive therapies are those that alter the wound environment through application of various topical agents such as antiseptics or debriding agents. Such therapies enhance, but do not alter, natural wound healing processes. Passive therapies include antibacterial and antiseptic agents, debriding agents, and various dressings. Active therapies are defined as agents applied to a wound site to directly stimulate the wound healing process. These include hyperbaric oxygen (HBO) therapy, electrical stimulation (ES), ultrasonography (US), ultraviolet light (UV), and growth factors such as platelet-derived growth factor-BB (PDGF-BB), platelet-derived wound healing factors (PDWHF), and epidermal growth factor (EGF).

ECRI conducted an extensive evaluation of guidelines for ulcer therapy. [See section 2.4 and Table 2.1.]

\textbf{DEBRIDEMENT}—Debridement includes\textsuperscript{22,23}

- wet-to-dry dressings,
- surgical (sharp) debridement,
- dextranomers,
- enzymatic debriding agents, and
- autolytic debridement.

\textbf{Wet-to-dry dressings} can be effective. They initially adhere to devitalized tissue, then once dressings are dry (usually 4 to 6 hours), they can be removed along with devitalized tissue and exudate. A disadvantage is that they are nonselective and can remove both viable (e.g., granulation tissue, new epithelial tissue) and nonviable tissues. \textbf{Dextranomers} are absorbent beads placed into wound beds. They absorb exudate, bacteria, and other debris. Disadvantages include costs and difficulties in applying them to wounds in some anatomical locations. \textbf{Enzymatic debridement} with topical agents (e.g., Collagenase®, Elase®) can remove devitalized tissue. Such therapy may be appropriate in patients with noninfected wounds and who are confined to long-term care facilities, who receive care at home, or who are not surgical candidates.
**Autolytic debridement** utilizes synthetic dressings that cover a wound and allow devitalized tissue to self-digest from enzymes normally present in wound fluids.

The Agency for Health Care Policy and Research (AHCPR)\(^a\) 1995 recommendations for debridement of decubitus ulcers are as follows:\(^{24}\)

- Remove devitalized tissue in pressure ulcers when appropriate for the patient's condition and consistent with patient goals. (Strength of Evidence = C.\(^b\))

- Select the method of debridement most appropriate to the patient's condition and goals. Sharp, mechanical, enzymatic, and/or autolytic debridement techniques may be used when there is no urgent clinical need for drainage or removal of devitalized tissue. If there is an urgent need for debridement, as with advancing cellulitis or sepsis, sharp debridement should be used. (Strength of Evidence = C.)

- Use clean, dry dressings for 8 to 24 hours after sharp debridement associated with bleeding; then reinstitute moist dressings. Clean dressings may be used in conjunction with mechanical or enzymatic debridement techniques. (Strength of Evidence = C.)

- Heel ulcers with dry eschar need not be debrided if they do not have edema, erythema, fluctuance, or drainage. Assess these wounds daily to monitor for pressure ulcer complications that would require debridement. (Strength of Evidence = C.)

- Prevent or manage pain associated with debridement as needed. (Strength of Evidence = C.)

**WOUND CLEANSING**—AHCPR (1995) recommendations for cleansing of decubitus ulcers are as follows:\(^{25}\)

- Cleanse wounds initially and at each dressing change. (Strength of Evidence = C.)

- Use minimal mechanical force when cleansing ulcers with gauze, cloth, or sponges. (Strength of Evidence = C.)

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\(^a\) The Strength-of-Evidence ratings for AHCPR guidelines are shown in Appendix III.

\(^b\) According to the AHCPR rating scale, a 'C' rating means that the conclusion is based on (a) results of 1 controlled trial, (b) results of at least 2 case series or descriptive clinical studies, or (c) expert opinion.
• Do not clean ulcer wounds with skin cleansers or antiseptic agents (e.g., povidone iodine, iodophor, sodium hypochlorite solution {Dakin’s solution}, hydrogen peroxide, acetic acid). (Strength of Evidence = B.)*

• Use normal saline for cleansing most pressure ulcers. (Strength of Evidence = C.)

• Use enough irrigation pressure to enhance wound cleansing without causing trauma to the wound bed. Safe and effective ulcer irrigation pressures range from 4 to 15 pounds per square inch (psi). (Strength of Evidence = B.)

• Consider whirlpool treatment for cleansing pressure ulcers that contain thick exudate, slough, or necrotic tissue. Discontinue whirlpool when the ulcer is clean. (Strength of Evidence = C.)

DRESSINGS—Synthetic dressings types include:

• hydrocolloid,

• polyurethane, and

• biodressings and gels.

**Hydrocolloid** dressings are adhesive, gel-producing, water-impermeable membranes that can be left on sites for ≤1 week. These dressings typically have an adhesive wound contact surface, an impermeable outer face, a carboxymethylcellulose exude absorbing component, and varying amounts of pectin and/or gelatin. Examples include Duoderm, Comfeel ulcer dressing, J & J ulcer dressing, and Restore. **Polyurethane** dressings have transparent adhesive materials necessitating frequent redressing. Examples include Mitraflex, Op-Site, Bio-occlusive, Tegaderm, Synthaderm, and Primaderm. **Biodressings and gels** are dressings composed of hydrogels of water and polyethylene oxide reinforced with polyethylene film. These hydrogels are nonadherent and are more appropriate for abrasion-like wounds. Examples include Vigilon, Spenco Second Skin, Biobrane, Metro Gel, and Spand-Gel.

These synthetic (occlusive) dressings are intended for noninfected wounds in which there is no cellulitis, extensive erythema, purulence, fever, or abnormally high number of organisms in cultures. These dressings are easy to use and have many advantages; they (1) absorb exudate, (2) require few dressing changes,
(3) protect the wound from external contaminants, (4) enhance wound repair, and (5) minimize wound disruption. There are disadvantages; they (1) may cause excessive tissue maceration, (2) may be inefficient for wounds with excessive exudate, (3) require healthy tissue margins, (4) may be messy to apply and use, and (5) may not be well retained in areas subject to excessive motion. They are contraindicated in ischemic ulcers; if bone or tendon is exposed; or in patients with wounds that are infected or that have draining sinus tracts, excessive necrosis, excessive exudate, or osteomyelitis.

AHCPR (1995) recommendations for dressings of decubitus ulcers are as follows:  

- Use a dressing that will keep the ulcer bed continuously moist. Wet-to-dry dressings should be used only for debridement and are not considered continuously moist saline dressings. (Strength of Evidence = B.)

- Use clinical judgment to select a type of moist wound dressing suitable for the ulcer. Studies of different types of moist wound dressings showed no difference in pressure ulcer healing outcomes. (Strength of Evidence = B.)

- Choose a dressing that keeps the surrounding intact (periulcer) skin dry while keeping the ulcer bed moist. (Strength of Evidence = C.)

- Choose a dressing that controls exudate but does not desiccate the ulcer bed. (Strength of Evidence = C.)

- Consider caregiver time when selecting a dressing. (Strength of Evidence = B.)

- Eliminate wound dead space by loosely filling all cavities with dressing material. Avoid overpacking the wound. (Strength of Evidence = C.)

- Monitor dressings applied near the anus, since they are difficult to keep intact. (Strength of Evidence = C.)

**ELECTRICAL STIMULATION (ES)**—ES therapy is the application of an externally applied electrical current to wound sites to accelerate healing. ES is extensively assessed in the balance of this report.
The AHCPR (1995) recommendation for ES therapy for decubitus ulcers is as follows:\textsuperscript{29}

- Consider a course of treatment with electrotherapy for stage III and IV pressure ulcers that have proven unresponsive to conventional therapy. ES may also be useful for recalcitrant stage II ulcers. (Strength of Evidence = B.)

**HYPERBARIC OXYGEN (HBO) THERAPY**—HBO therapy is a treatment designed to administer oxygen to tissues at a much higher content than is available at sea level.\textsuperscript{30} Usually patients undergo therapy in a sealed tank, but some techniques have utilized topical applications. Although many case reports and case series evaluating HBO therapy for wound healing have been published,\textsuperscript{31,32,33,34,35,36,37,38,39,40,41,42,43,44,45} there are fewer controlled trials.\textsuperscript{46,47,48,49}

The AHCPR (1995) recommendation for HBO therapy for decubitus ulcers is as follows:\textsuperscript{50}

- The therapeutic efficacy of hyperbaric oxygen has not been sufficiently established to permit recommendation for the treatment of pressure ulcers. (Strength of Evidence = C.)

**GROWTH FACTORS**—A number of studies have evaluated different topical growth factors for the treatment of ulcers including recombinant PDGF-BB,\textsuperscript{51,52,53,54,55,56} autologous PDWHF,\textsuperscript{57,58,59,60} TGF-\(\beta\),\textsuperscript{61} basic fibroblast growth factor (bFGF),\textsuperscript{62,63} and EGF.\textsuperscript{64,65}

The AHCPR (1995) recommendation for growth factor and/or cytokine therapy for decubitus ulcers is as follows:\textsuperscript{66}

- The therapeutic efficacy of miscellaneous topical agents (e.g., sugar, vitamins, elements, hormones), growth factors, and skin equivalents has not yet been sufficiently established to warrant recommendation of these agents at this time. (Strength of Evidence = C.)

**ULTRASOUND (US), ULTRAVIOLET (UV), AND LASERS**—A few studies have evaluated the efficacy of US,\textsuperscript{67,68,69,70,71} UV,\textsuperscript{72} or helium-neon lasers\textsuperscript{73} for the treatment of ulcers.

The AHCPR (1995) guideline states that\textsuperscript{74}

- the therapeutic efficacy of ultraviolet, low-energy laser irradiation, and ultrasound have not been sufficiently established to permit recommendation of these therapies for the treatment of pressure ulcers. (Strength of Evidence = C.)
2.4 Guidelines and Evidence of Present Practice Patterns

Our research identified 12 guidelines, 4 technology assessments, and 4 studies with evidence of present practice patterns for the treatment of chronic ulcers. Guideline publications include formal practice guidelines or consensus statements (e.g., Wound Ostomy and Continence Nurses Society (WOCN), AHCPR) and review articles intended to identify optimal treatments for chronic ulcers. Chosen technology assessments evaluated technologies relevant to the treatment of chronic ulcers. Studies with evidence of present practice patterns were surveys. Summaries of these guidelines are presented in Table 2.1; summaries of technology assessments for specific wound healing therapies are presented in Table 2.2.

2.4.1 Consensus

There is a consensus about several aspects of treating chronic wounds.

Maintenance therapy is usually sufficient to arrest stage I (nonblanchable erythema of skin) decubitus ulcers. Treatments include

- regular repositioning of the patient;
- avoiding positioning the patient directly on the trochanter;
- reducing friction and shear forces by using protective dressings;
- protecting wounds from excessive moisture, particularly in incontinent patients;
- reducing pressure on sites, particularly on heels;
- avoiding the use of donut-type ring cushions; and
- maintaining adequate nutrition, especially protein and vitamin C.

Open ulcers (decubitus stage II to IV, venous, and arterial) require a moist healing environment relatively free from impediments to healing (e.g., infection, necrotic tissue, excessive exudate). Continuous moist gauze dressings are good for maintaining a moist ulcer bed.

The periulcer surface should be protected from moisture by a film or dressing to prevent maceration.

Mechanical, surgical, enzymatic, and autolytic debridement all effectively remove devitalized tissue. However, autolytic debridement is not appropriate for infected
wounds. Forceful irrigation with warm normal saline (through a 35 mL syringe fitted with a 19-gauge angiocatheter, generating 8 psi) is a good method of mechanical debridement that removes devitalized tissue and debris without injuring granulation tissue.

Systemic antibiotics are only indicated in the presence of sepsis, advancing cellulitis, or osteomyelitis.

Swab cultures are not appropriate for determining infection at wound sites because all open wounds are colonized by bacteria.

Venous leg ulcers require treatments that increase the venous return. Therapies include

- compression bandages with 20 to 40 mm Hg pressure at the ankle that gradually decreases toward the knee,
- elevation of legs above the level of the heart, and
- surgery as needed to repair superficial and perforating veins.

2.4.2 Lack of Consensus

There is a lack of consensus on several aspects of treating chronic wounds.

**Topical Antibiotics and Antiseptics**—Some of the guidelines that address the use of topical antimicrobials do not address treating local infection, cleansing the wound, or moistening the gauze dressing.

Frantz and Gardner recommend topical antimicrobial therapy for infected wounds that are otherwise free of nonviable tissue and debris. They recommend against the use of antiseptics (e.g., povidone iodine, Dakin’s solution, hydrogen peroxide) for wound cleansing or moistening dressings. They also suggest that several commercially prepared wound cleansers (e.g., Shur Clens, Biolex, Puri-Clens) are toxic to cells essential for wound healing. WOCN and the University Hospital Consortium (UHC) recommend using topical antimicrobial agents. WOCN recommends topical therapy to keep the wound surface clean, moist, and free from secondary infection. Although it notes the possible harm from povidone iodine, hydrogen peroxide, Dakin’s solution, and acetic acid, WOCN does not specifically recommend against their use. In fact, WOCN recommends Dakin’s solution to control odor, help liquefy necrotic tissue, and combat staphylococcal and streptococcal infections. However, in its 1993 guideline for the treatment of venous, arterial, and neuropathic leg ulcers, WOCN notes that “… controversy exists regarding the deleterious effects of
various solutions[antiseptics, antibiotics] in open wounds. . .” and that caregivers should review the current literature before reaching a decision about topical treatment. The UHC guideline states that topical antiseptics may be used for $\leq 1$ week; topical antibiotics may be used for fixed durations to avoid sensitization, selection of resistant organisms, and systemic toxicity.

Smith’s$^{80}$ guideline for pressure ulcers recommends against topical antibiotic agents. The Douglas & Simpson$^{81}$ guideline for venous leg ulcers states that there is little evidence that bacteria impair ulcer healing. The Goldman & Fronek$^{82}$ guideline for venous leg ulcers recommends against topical antibiotics. The 1995 AHCPR$^{83}$ guideline recommends against cleansing wounds with antiseptics or skin cleansers. The other guidelines do not address antimicrobial treatment.

**Grafting and Operative Closure**—There are no specific recommendations for candidate selection or use of grafting. Douglas & Simpson recommend it for patients with venous leg ulcers that have not healed after 1 year of properly applied support and compression bandaging. They prefer mesh grafting over split-skin or pinch grafting. However, Goldman & Fronek recommend split-skin and pinch grafting for non-healing ulcers. UHC recommends split thickness grafting or myocutaneous flaps, but does not specify selection criteria. AHCPR recommends operative repair of clean stage III or IV ulcers that do not respond to optimal treatment (as defined in its guideline) using direct closure, skin grafting, skin flaps, musculocutaneous flaps, and free flaps.

**Hyperbaric Oxygen (HBO) Therapy**—The 1992 British Columbia Office of Health Technology Assessment (BCOHTA) concludes that HBO therapy for chronic osteomyelitis (COM) and osteoradionecrosis (ORN) is questionable. At that time, only 1 small randomized controlled trial of HBO therapy for ORN had been published. More recent guidelines offer conflicting views. The 1992 AHCPR guideline states that there is inconclusive evidence. On the other hand, WOCN recommends HBO therapy for venous leg ulcers but acknowledges that it is controversial.

**Other Topical Pharmacologic Agents**—Many topical agents, such as sugar, antacids, vitamins A and D, growth factors, and hormones, have been proposed to aid wound healing. None of the guidelines recommend these adjuvant treatments. AHCPR’s 1992 technology assessment$^{84}$ of Procuren (PDGF-BB) concluded that results were uninterpretable because the 3 existing trials were small and because 2 of them were uncontrolled.

**Other Systemic Pharmacologic Agents**—AHCPR, Douglas & Simpson, and Goldman & Fronek guidelines state that pentoxiphylline (a vasodilator) has not been shown to be an effective therapy for chronic wounds.
**Irradiation**—Infrared, ultraviolet, and low-energy laser irradiation have been proposed as adjuvant therapies for chronic wounds. AHCPR found inadequate evidence to recommend any of these treatments for pressure ulcers.

**Hydrotherapy**—The 1995 AHCPR guideline recommends whirlpool treatment for ulcers with thick exudate, slough, or necrotic tissue.

**Ultrasound (US) Therapy**—AHCPR does not recommend US therapy. However, Goldman & Fronek suggest that it may be a useful treatment for venous leg ulcers.

**Electrical Stimulation**—The UHC guideline considers ES an unproven adjunctive therapy for wound healing. On the other hand, AHCPR recommends ES for recalcitrant stage II to IV pressure ulcers (based on ≥2 controlled clinical trials).

### 2.4.3 Practice Patterns

Summaries of reports of practice patterns for the treatment of wounds are presented in Table 2.3.

In 1994, Roe et al. surveyed 146 community nurses (primary caregivers for chronic leg ulcers) in England. The survey revealed that

- 51% routinely cleansed sites,
- 1% never cleansed sites,
- 79% used an antiseptic cleaner,
- 17% used an antibiotic tulle,
- 18% used an antibiotic cream,
- 65% used a dry dressing,
- 6% never used a dry dressing,
- 91% applied compression bandages,
- 66% applied compression bandages exclusively, and
- 23% used products providing 20 to 40 mm Hg compression at ankle graduated to 50% at the knee.
Margolis & Cohen\textsuperscript{86} analyzed the methodology sections of all English language RCTs (since 1966), evaluating therapies for venous leg ulcers to determine the standard of care. Forty-six percent of studies cleansed wounds with saline, 8\% with water, and 22\% with antiseptics and/or disinfectants.

Frantz et al.\textsuperscript{87} collected data from all patients treated for pressure ulcers at a Veterans Administration hospital between 1983 and 1988. Sixty-three percent of ulcers were treated with antiseptics, 48\% with topical agents (e.g., antacids), 18\% with antiseptic impregnated gauze, and 8\% with dry packing strips. One-third received no dressing at all.
## 2.5 Tables

### Table 2.1. Summary of Guidelines for Wound Healing Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Ulcer Types</th>
<th>Recommended</th>
<th>NOT Recommended</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Douglas & Simpson\(^8\) (1995) | Venous (leg) | • support or compression bandaging  
• leg elevation  
• if skin grafting, use mesh grafting rather than pinch or split-skin grafting  
• superficial vein surgery if deep veins are competent | • routine swabbing for bacterial culture  
• crêpe or elastic tubular bandages, except shaped bandages  
• oxpentiphylline or other drug therapy, including enhancers of fibrinolysis  
• grafting with cultured keratinocytes | No specifics on dressings, antiseptics, antibiotics. |
| WOCN\(^9\) (1992)         | Pressure    | • pressure relief/reduction devices  
• position changes, at least every 2 hours for bedfast patient  
• friction/shear force relief/reduction devices  
• reduce excessive moisture  
• nutrition — tissue hydration and positive nitrogen balance  
• remove impediments to healing, including infection, necrotic tissue, and excessive or pooled exudate  
• debridement: conservative instrumental debridement of clearly necrotic tissue; enzymatic; autolytic using a moisture-retentive dressing; mechanical using wet-to-dry dressings and/or water propulsion therapy  
• forceful irrigation of dirty wounds (35 mL syringe with 19-gauge needle)  
• gentle flushing with noncytotoxic solution for clean/granulating wounds  
• absorption dressings  
• wound cleansing at each dressing change  
• topical therapy to keep wound surface clean, moist, and free from secondary infection  
• evaluation of healing on a regular basis  
• referral to surgical consultation in nonhealing wounds  
• educate the patient  
• follow-up | • debride non-infected, dry ischemic wounds  
• debride dry eschar  
• occlusive dressings in infected wounds or in wounds with potential for anaerobic infection  
• tight wound packing  
Authors do not actually recommend against the following, but they emphasize the adverse qualities:  
• surgical debridement involves surgical and anaesthesia risks (but it is rapid and effective)  
• improperly diluted povidone iodine inhibits and/or destroys macrophages and fibroblasts  
• H\(_2\)O\(_2\) is a nonselective debriding agent (destroys fibroblasts)  
• Dakin's solution destroys fibroblasts unless properly diluted (but controls odor, may be used against staphylococcal and streptococcal infections, and helps liquefy necrotic tissue)  
• acetic acid destroys fibroblasts | Nursing guideline. |
Table 2.1. Summary of Guidelines for Wound Healing Therapy (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Ulcer Types</th>
<th>Recommended</th>
<th>NOT Recommended</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOCN® (1993)</td>
<td>Arterial (leg)</td>
<td>• optimize blood flow: to lower extremities by maintaining legs in a dependent or neutral position (arterial + neuropathic);^d for venous return by keeping legs elevated above the heart (venous); avoid crossing legs (a + v) or sitting with acute angulation (v); avoid exposure to cold (a + n); avoid smoking (a); avoid constrictive clothing (all) • reduce pressure for bony prominences (all) • orthotics consult for patient with altered gait (n) • moisturize skin after bathing with nonirritating agent such as petrolatum and xipamide (all) • ambulate patient to tolerance (a + v) • avoid standing for prolonged periods (v) • use of vascular support devices (v) • prevent moisture between toes (a + n) • avoid friction (a + n) • maintain routine foot care for toenails, corns, and calluses; avoid self-treatment of corns and calluses (a + n) • use of proper footwear (a + n) • evaluate diabetes management (n): blood glucose control, nutritional status, compliance • remove impediments to healing, including infection, necrotic tissue, and excessive or pooled exudate (all) • debridement: surgical consult for sharp debridement (n); enzymatic (all); autolytic using moisture vapor permeable transparent dressings (all), hydrogels (all), hydrocolloid dressings (all), or foam dressings (v); mechanical using wet-to-dry dressings (all) or water propulsion therapy (v) • gentle wound cleansing at each dressing change for non-necrotic ulcers (all)</td>
<td>• debride dry gangrene</td>
<td>Nursing guideline.</td>
</tr>
<tr>
<td></td>
<td>Venous (leg)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Neuropathic (leg)</td>
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</table>

^d The specific wound type for which a particular treatment is recommended by the authors is in parenthesis, abbreviated as arterial (a), venous (v), or neuropathic (n).
Table 2.1. **Summary of Guidelines for Wound Healing Therapy (continued)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Ulcer Types</th>
<th>Recommended</th>
<th>NOT Recommended</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Frantz & Gardner* (1994) | Not specific, but including pressure and venous ulcers | • absorption dressing for non-necrotic wounds with crater formation or pooled exudate (n)  
• dressings: moisture vapor permeable transparent adhesive dressings (all), hydrocolloid dressings (all), hydrogel dressings | • swab culture to diagnose a wound infection  
• autolytic debridement in immune compromised individuals  
• wet-to-dry dressings (mechanical debridement) once the wound begins to granulate  
• vigorous cleansing for wound with granulation tissue  
• antiseptic solutions to cleanse wounds or moisten gauze dressings  
• polyvinyl or hydrocolloid dressings on wounds that are infected and/or full thickness  
• sterile technique for dressing application  
• body weight in detecting malnourishment | • remove nonviable tissue, such as necrotic tissue and slough, and foreign debris, such as residual material from dressings  
• debridement: autolytic; biochemical (enzymes); mechanical; or sharp (surgical)  
• cleansing: vigorous technique confined to wounds with large segments of foreign debris or nonviable tissue; gentle irrigation (8 psi, equivalent to solution forced through 35 mL syringe with 19-gauge angiocath) for wounds with granulation tissue; using a gentle patting technique with a soft, moist gauze  
• physiologically compatible solutions, such as normal saline and lactated Ringer's, for cleansing and moistening gauze dressings  
• topical antimicrobial therapy (e.g., Silvadene) to treat wound infections  
• dressings that provide a moist healing environment and do not disrupt the skin surrounding the wound: moist gauze; polyvinyl or hydrocolloid dressings on partial-thickness wounds free of infection; absorptive dressings (e.g., calcium alginate) on wounds with large amounts of drainage.  
• positioning techniques for pressure ulcers  
• pressure-reducing devices for pressure ulcers  
• supportive boots, foam wedges, and specially fitted shoes, especially for diabetics with pressure ulcers  
• compressive stocking, Unna's paste boots, and pneumatic compression devices to enhance venous return for venous insufficiency ulcers |
<table>
<thead>
<tr>
<th>Study</th>
<th>Ulcer Types</th>
<th>Recommended</th>
<th>NOT Recommended</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>UHC® (1990)</td>
<td>Pressure</td>
<td>• maintain adequate nutrition, particularly protein; Vitamin C 500 mg orally twice daily; zinc sulfate 220 mg orally 3 times daily may be helpful for recalcitrant ulcers &lt;br&gt;• rehabilitative measures to improve mobility &lt;br&gt;• repositioning according to a regular schedule: turning the patients alternately from the 30° left side-lying position, the supine, and the 30° right sidelying positions; avoid positioning directly over greater trochanter; avoid prolonged sitting upright in a chair; avoid excessive elevation of upper torso &lt;br&gt;• carefully monitor bony prominences every 2 to 4 hours (development of stage I pressure ulcer requires more frequent monitoring) &lt;br&gt;• systemic antibiotics only if ulcers are complicated by cellulitis, osteomyelitis, bacteremia, or other sepsis &lt;br&gt;• bacterial endocarditis prophylaxis for persons with cardiac valvular lesions &lt;br&gt;• surgical debridement of all necrotic tissue with appropriate antibiotic therapy for sepsis &lt;br&gt;• surgical debridement of lesions totally covered by eschar accompanied by use of moist dressing &lt;br&gt;• enzymatic debridement &lt;br&gt;• topical antiseptics (povidone-iodine, acetic acid, Dakin's solution, H₂O₂) may be used for periods of 1 week or less</td>
<td>• routine swab cultures to diagnose infection &lt;br&gt;• foam pads less than 4” thick</td>
<td>Guideline focus is pressure relief/reduction devices.</td>
</tr>
</tbody>
</table>
Table 2.1. Summary of Guidelines for Wound Healing Therapy (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Ulcer Types</th>
<th>Recommended</th>
<th>NOT Recommended</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith (1995)</td>
<td>Pressure</td>
<td>• 4” to 6” deep solid foam mattresses are the most inexpensive and effective pressure-relieving products</td>
<td>• foam pads less than 4” thick</td>
<td>Guideline restricted to nursing home patients aged 65 years or older.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• polyurethane dressings can protect area from friction (i.e., for stage I ulcers), and are more effective for saline wet-to-dry dressings for stage II ulcers</td>
<td>• donut-type devices or ring cushions</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• necrotic material must be removed — enzymatic debridement in good for smaller eschars; polyurethane and hydrocolloid dressings (autolytic) are more effective for stage III ulcers; hydrogels for dry deep stage III and stage IV ulcers; hydrophilic foam, alginites, or saline-impregnated gauze for packing deep wounds with significant exudate</td>
<td>• wet-to-dry dressings can damage granulation tissue</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• surgical debridement for stage IV ulcers</td>
<td>• the is no consensus on the use of low air-loss and air-fluidized beds</td>
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<tr>
<td></td>
<td></td>
<td>• higher protein intake and vitamin C supplements</td>
<td>• swabs to establish clinical infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• topical antibiotic agents</td>
<td></td>
</tr>
<tr>
<td>Wiseman et al. (1992)</td>
<td>Leg ulcers</td>
<td>• occlusive nonabsorbent dressings for stage I ulcers and stage II ulcers with light (1-2 mL/day) drainage</td>
<td>• hydrogels</td>
<td>Book chapter about wound dressings.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• nonadherent absorbent dressings for stage II ulcers with light drainage</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• hydrocolloid dressings for stage II ulcers with light to moderate (3-5 mL/day) drainage and stage III-IV ulcers with moderate to heavy (&gt;5 mL/day) drainage</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• occlusive absorbent composite dressings for stage III-IV ulcers</td>
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</tbody>
</table>
Table 2.1. Summary of Guidelines for Wound Healing Therapy (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Ulcer Types</th>
<th>Recommended</th>
<th>NOT Recommended</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Edlich et al. (1992)   | Not specified                       | • cleanse wounds at high pressure — 35 mL syringe with 19-gauge needle, normal saline (= 8 psi) — ONLY for heavily contaminated wounds                                                                 | • regard occlusive arterial disease as an absolute contraindication for compression therapy  
• topical pharmacologic agents (e.g., antibiotics)  
• surgical or systemic pharmacologic treatments as stand-alone therapy  
• vein valve transplants  
• valvuloplasty  
• venous transposition                                                                 | Book chapter about surgical management of wounds.                                                                                         |
| Goldman & Fronek (1992)| Venous (leg)                        | • elevate legs above the level of the heart while at rest  
• compression therapy with stockings or bandages: should exert a resting pressure of at least 20 to 30 mm Hg at the ankle; should be applied to produce a pressure gradient where the pressure is higher at the ankle and lower at the knee  
• encourage walking and exercise  
• ultrasound therapy and intermittent pneumatic compression may also be beneficial  
• cover ulcer with a local dressing that should reduce pain and pruritus; allow excess fluid and exudate to escape without permitting desiccation; not cause an allergic reaction; be easy to change with the least discomfort possible; not leave dressing material in the wound when changed  
• surgical correction of venous insufficiency of superficial veins, perforating veins, and insufficiency of deep veins  
• split-skin or pinch grafting  
• sclerotherapy for venous hypertension in some patients  
• systemic antibiotics only in patients with cellulitis  
• diuretics only as a short course in cases with severe edema                                                                 | Consensus paper.                                                                                                                                |                                                                                                         |
| Rodeheaver et al. (1994)| Pressure + vascular insufficiency   | • mechanical/surgical debridement of necrotic tissue of ulcers in the lower extremity  
• sharp surgical debridement                                                                                                                                                                           | • debridement with wet-to-dry dressings                                                                                                                                                                      | Interdisciplinary roundtable.                                                                 |
### Table 2.1. Summary of Guidelines for Wound Healing Therapy (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Ulcer Types</th>
<th>Recommended</th>
<th>NOT Recommended</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>• autolytic debridement</td>
<td>• massage over bony prominences</td>
<td>Focus is on prediction and prevention.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• enzymatic debridement</td>
<td>• donut-type ring cushions</td>
<td></td>
</tr>
<tr>
<td>AHCPR98 (1992)</td>
<td>Pressure (stage I)</td>
<td>• systematic skin inspection at least once daily, paying particular attention to bony prominences</td>
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<td></td>
<td></td>
<td>• routine cleansing: avoid hot water; use a mild cleansing agent; minimize force and friction against skin</td>
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<tr>
<td></td>
<td></td>
<td>• minimize factors leading to dry skin (&lt;40% humidity, exposure to cold); moisturize dry skin</td>
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<td></td>
<td></td>
<td>• protect skin from excessive moisture (e.g., due to incontinence)</td>
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<td>• minimize friction and shear forces on skin: proper positioning, transferring, and turning techniques (avoid dragging by using trapeze or bed linen); lubricants (e.g., corn starch, creams); protective films; protective dressings (e.g., hydrocolloids); protective padding</td>
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<tr>
<td></td>
<td></td>
<td>• maintain adequate nutrition, especially in terms of calories, protein, and iron</td>
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<td>• maintain physical activity, when possible</td>
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<td></td>
<td></td>
<td>• reposition at least every 2 hours; avoid positioning directly on the trochanter</td>
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<td></td>
<td></td>
<td>• pillows or foam wedges to keep bony prominences from direct contact with one another</td>
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<td></td>
<td></td>
<td>• use device that totally relieves pressure on the heels in people who are completely immobile</td>
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<tr>
<td></td>
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<td>• maintain head of bed at lowest possible elevation</td>
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<td></td>
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<td>• pressure-reducing mattress: foam, static air, gel, or water</td>
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<tr>
<td></td>
<td></td>
<td>• patient education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHCPR99 (1995)</td>
<td>Pressure (stages II-IV)</td>
<td>• avoid positioning on a pressure ulcer</td>
<td>• donut-type ring cushions</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• follow same procedures as in AHCPR 1992 for repositioning</td>
<td>• autolytic debridement of infection ulcers</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• static support surface (e.g., foam overlay) if a patient can assume a variety of positions without bearing weight on an ulcer and without bottoming out</td>
<td>• debride heel ulcers with dry eschar that do not have edema, erythema, fluctuance, or drainage</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• cleanse wounds with skin cleansers or antiseptics</td>
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</tbody>
</table>
Table 2.1. Summary of Guidelines for Wound Healing Therapy (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Ulcer Types</th>
<th>Recommended</th>
<th>NOT Recommended</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>• dynamic support surface if patient cannot assume a variety of positions without bearing weight on an ulcer or without bottoming out, or if the ulcer does not heal&lt;br&gt;• low-air-loss or air-fluidized bed for patient with large stage III or IV pressure ulcers on multiple turning surfaces (may also help avoid excessive moisture on skin)&lt;br&gt;• debride devitalized tissue: sharp debridement if need is urgent (e.g., advancing cellulitis or sepsis); mechanical, enzymatic, and autolytic may be used when there is no urgent need&lt;br&gt;• cleanse wounds at each dressing change: use minimal mechanical force; use normal saline&lt;br&gt;• safe and effective irrigation pressures range from 4 to 15 psi&lt;br&gt;• whirlpool treatment for ulcers with thick exudate, slough, or necrotic tissue&lt;br&gt;• dressings that keep ulcer bed continuously moist; protect surrounding skin dry&lt;br&gt;• eliminate dead space by loose packing&lt;br&gt;• electrotherapy for stage III and IV ulcers that have proved unresponsive to conventional therapy or recalcitrant stage II ulcers (as an adjunctive therapy)&lt;br&gt;• systemic antibiotic therapy for bacteremia, sepsis, advancing cellulitis, or osteomyelitis&lt;br&gt;• protect ulcers from exposure to feces&lt;br&gt;• follow body substance isolation procedures&lt;br&gt;• use sterile instruments to debride&lt;br&gt;• use clean dressings, rather than sterile ones&lt;br&gt;• operative repair of clean stage III or IV ulcers that do not respond to optimal patient care: direct closure; skin grafting; skin flaps; musculocutaneous flaps; free flaps&lt;br&gt;• education</td>
<td>• systemic antibiotics for local infection&lt;br&gt;• hyperbaric oxygen&lt;br&gt;• infrared, ultraviolet, or low-energy laser irradiation&lt;br&gt;• ultrasound&lt;br&gt;• miscellaneous topical agents (e.g., sugar, vitamins, elements, hormones, other agents)&lt;br&gt;• growth factors&lt;br&gt;• skin equivalents&lt;br&gt;• systemic agents other than antibiotics (e.g., vasodilators, pentoxiphylline)&lt;br&gt;• use swab cultures to diagnose infection&lt;br&gt;• prophylactic ischiectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2.2. Summary of Technology Assessments for Wound Healing Therapies

<table>
<thead>
<tr>
<th>Study</th>
<th>Technology Assessed</th>
<th>Conditions/Diseases</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHCPR101 (1992)</td>
<td>Procuren (PDGF-BB)</td>
<td>Unhealed wounds</td>
<td>The existing trials are small, and 2 out of 3 are uncontrolled, making any interpretation impossible. There is insufficient evidence.</td>
</tr>
<tr>
<td>BCOHTA102 (1992)</td>
<td>Hyperbaric Oxygen (HBO)</td>
<td>Chronic osteomyelitis (COM) Osteoradionecrosis (ORN)</td>
<td>COM — There is conflicting data regarding HBO efficacy. Case series data report fairly high recovery rates, while the 1 RCT showed no beneficial (possibly deleterious) effect. Proponents of HBO say it is an adjunct therapy. ORN — HBO for ORN of the mandible is supported by the 1 small published RCT. Possibly useful in this situation, HBO is still an adjunct therapy.</td>
</tr>
<tr>
<td>NCHSR103 (1981)</td>
<td>Ultraviolet (UV) radiation</td>
<td>Pressure ulcers</td>
<td>The effectiveness of UV radiation in treating pressure ulcers has not been satisfactorily demonstrated. All data are from case studies; there are no controlled trials. Data is confounded by, for example, UV radiation treatment started simultaneously with more vigorous local measures.</td>
</tr>
<tr>
<td>NCHSR104 (1981)</td>
<td>Hydrotherapy/whirlpool (WP)</td>
<td>Pressure ulcers</td>
<td>Hydrotherapy (whirlpool bath) is a safe and effective treatment for pressure ulcers.</td>
</tr>
</tbody>
</table>
Table 2.3. Summary of Reports of Practice Patterns for the Treatment of Chronic Wounds

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type (Locale)</th>
<th>Ulcer Type</th>
<th>Practice Pattern</th>
</tr>
</thead>
</table>
| Brandeis et al.105 (1995) | Survey (U.S.)       | Pressure   | 2,011 nursing home residents ≥60 years of age in 270 nursing facilities  
• 79% of patients with stage II - IV were on a repositioning program  
• 72.8% received protective/preventive skin care  
• 72.8% had a pressure-relieving bed |
• 26% of studies used a multilayer inelastic bandage, 26% used a two-layer or thinner inelastic bandage, 20% used a single-layer elastic bandage, 4% used elastic stockings, and 2% used a combination of compression pump and stocking  
• 58% of studies did not indicate if debridement was performed, 8% used surgical debridement, 12% used enzymatic debridement, and 12% debrided the patients but did not specify which technique  
• 46% of studies used saline as a cleansing agent (most did not mention sterility), 8% used water, and 22% used disinfectants and antiseptics (including cetrimide, acetic acid, mercurochrome, chlorhexidine, gentian violet, hydrogen peroxide, and potassium permanganate)  
• 30% of studies used occlusive dressings (hydrocolloids, paraffin, foam), 20% used zinc-impregnated gauze, and 4% used saline-soaked gauze |
### Table 2.3. Summary of Reports of Practice Patterns for the Treatment of Chronic Wounds (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type (Locale)</th>
<th>Ulcer Type</th>
<th>Practice Pattern</th>
</tr>
</thead>
</table>
| Roe et al.107  | Survey (G.B.)       | Chronic leg ulcers associated with venous disease, arterial disease, rheumatoid arthritis, and diabetes | **Survey of 146 community nurses opinions.**  
• 68 (47%) sometimes cleanse, 74 (51%) routinely cleanse, and 2 (1%) never cleanse a leg ulcer  
• 78 (53%) use saline, 104 (71%) use warmed saline; 38 (26%) use either exclusively  
• 94 (64%) never use cetrimide  
• 115 (79%) never use hypochlorite  
• 69 (47%) never use H2O2  
• 98 (67%) never use chlorhexidine  
• 26 (18%) never use potassium permanganate, 82 (56%) use it (significantly higher rate of use in 1 of the 3 health authorities)  
• 128 (88%) use a combination of different dressings layered over the ulcer  
• 53 (36%) had used all of the dressing listed on the survey at one time or another:  
  • 133 (91%) use hydrocolloid dressings, 5 (3%) never use them  
  • 127 (87%) use alginate dressings, 2 (1%) never use them  
  • 81 (55%) use hydrogel dressings, 5 (4%) never use them  
  • 50 (34%) use foam dressings, 16 (11%) never use them  
  • 25 (17%) use an antibiotic tulle, 54 (37%) never do  
  • 27 (18%) use an antibiotic cream, 38 (26%) never do  
  • 73 (50%) use some other tulle, 30 (21%) never do  
  • 98 (67%) use polysaccharide beads, 3 (2%) never do  
  • 60 (41%) use a semipermeable film, 21 (14%) never do  
  • 27 (18%) use an odor absorbing dressing, 5 (3%) never do  
  • 95 (65%) use a dry dressing, 9 (6%) never do  
  • 90 (62%) use impregnated NA, 4 (3%) never do  
  • 84 (58%) use flamazine, 5 (3%) never do  
  • 76 (52%) use an enzymatic agent, 9 (6%) never do  
  • 105 (72%) use paste bandage, 3 (2%) never do  
• 133 (91%) apply compression bandages to venous ulcers, but only 93 (66%) do so exclusively, and only 33 (23%) used products that could provide an adequate level of compression (20 to 40 mm Hg at the ankle, graduated to 50% of that pressure at the knee) |
Table 2.3. Summary of Reports of Practice Patterns for the Treatment of Chronic Wounds (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type (Locale)</th>
<th>Ulcer Type</th>
<th>Practice Pattern</th>
</tr>
</thead>
</table>
| Frantz et al.108 (1992) | Retrospective (Iowa, U.S.) | Pressure   | Veterans Administration facility charts; part also from prospective study of ES.  
• 118 (49.4%) of ulcers were treated with enzyme debriding treatments, 112 (95%) of these by trypsin enzymatic spray  
• 69 (28.9%) of ulcers were treated with cleansing treatments, 52 (75.4%) of these with soap, and 16 (23.2%) of these with normal saline  
• 152 (63.6%) of ulcers were treated with some type of antiseptic: 131 (86.2%) of these with H2O2, 39 (25.7%) of these with povidone-iodine, and 22 (14.5%) of these with sodium hypochlorite  
• 105 (43.9%) of ulcers were treated with hydrocolloid dressings, 79 (33.1%) of ulcers were dressed with gauze squares, 56 (23.4%) of ulcers were treated with polyurethane dressings  
• 80 (33.5%) of ulcers were treated on a no-dressing protocol, 20 (8.4%) of ulcers were dressed with dry packing strips and dry gauze-type dressings applied to wound with no topical agents, 14 (5.9%) of ulcers were treated with Dakin's dressings, 11 (4.6%) with acetic acid dressings, 9 (3.8%) with saline dressings, 8 (3.3%) with povidone-iodine dressings, 1 (0.4%) with a H2O2 dressing, and 1 (0.4%) with iodoform gauze packing strips  
• 115 (48.1%) of ulcers were treated with topical treatments, 40 (34.8%) of these with antacids, and 35 (30.4%) of these with silver sulfadiazine  

* Frequency is printed as 69 (out of 239) ulcers, or 28.9% in the first sentence of the paragraph, and 89 (out of 239), or 28.9% in the last sentence of the paragraph. Assuming 28.9% is the correct percentage, 69 out of 239 ulcers is the correct proportion.
3.0 Electrical Stimulation for Wound Healing

3.1 Basic Description

Living cells produce electrical potentials by piezoelectric, pyroelectric, and streaming mechanisms. Piezoelectric potentials are generated by stress, typically at the interface between bone and surrounding ion-containing fluid. Pyroelectric potentials are created from the heating of fluids. Streaming potentials are created by charged liquids flowing next to each other.

Human skin itself may act as a battery capable of driving substantial currents into a wound. If so, this electrical current may accelerate wound healing.

Preclinical studies have shown that externally applied ES can

- increase ATP (adenosine triphosphate) concentrations in tissues,
- increase DNA synthesis,
- promote healing of soft tissue or ulcers,
- cause migration of epithelial and fibroblasts into a wound site,
- accelerate the recovery of damaged neural tissue,
- reduce edema, and
- inhibit the growth of various pathogens.

Examples of preclinical studies of electrical stimulation are presented in Table 3.1.

ES has been used or studied for many different therapeutic applications. ECRI has conducted extensive technology assessments on Electrical Bone Growth Stimulation for the Lower Leg, Electrical Bone Growth Stimulation for the Spine, Electrical Bone Growth Stimulation for the Wrist, and Spinal Cord (Dorsal Column) Stimulation for Chronic Intractable Pain. Studies have also been conducted to test the efficacy of ES for healing jaw fractures, reducing pain and swelling in soft tissue injuries, alleviating spinal cord lesions, eliminating intermittent claudication, improving healing from assorted hand injuries, reducing cerebral edema in cases of head trauma, reducing swelling in grades I and II ankle sprains, and accelerating healing after foot surgery, dental surgery, and oral surgery.
3.2 Types of Electrical Stimulation and Treatment Protocols

All electrical stimulators are not the same. We classified ES devices for chronic wound healing into several basic categories:

- direct current (DC) [which we also refer to as low-intensity direct current (LIDC) throughout this report],
- pulsed current (PC),
- alternating current (AC),
- pulsed electromagnetic induction (PEMI), and
- spinal cord stimulation (SCS).

These categories are primarily based on the type of electrical current.

Just as all ES studies do not use the same type of current, the types of devices within each category may not be the same. Devices categorized within each group may differ technically and/or by mode of action. We did not assume *a priori* that all devices within a category are homogeneous. We used these categories to describe and present the diversity of ES devices for chronic wound healing.

3.2.1 Direct Current Applications

Some electrical stimulators used DC, which is a continuous, unidirectional, constant current. **Table 3.2** displays therapy synopses for DC stimulation for wound healing.

The published studies of DC stimulation for the treatment of wound healing used low-intensity direct current (LIDC).f (One study, however, {Akers & Gabrielson138} used an unspecified level of DC.) Clinicians applied 20 to 100 microamps (µA) of current at low voltage (<8 volts). The cathode (negative electrode) was usually wrapped in saturated saline-gauze and placed directly over the wound site; the anode (positive electrode) was placed on the skin surface near the wound. Patients underwent 2-hour sessions 2 or 3 times daily. After several days or if the wound apparently stopped healing, clinicians reversed (switched) the polarity of the electrode by placing the anode directly over the

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f We use the term “low-intensity direct current” (LIDC) throughout this report. Although the term low-intensity may be redundant because all studies in this report used a microamperage current, this nomenclature reminds the reader that these devices use very low currents, that are unlikely to cause electrolytic tissue destruction.
wound and the cathode at a nearby site. They reversed polarity 1 or more times (depending on the regimen) to stimulate healing if the wound had not improved or reached a “growth plateau.”

The regimen used by Wolcott et al. appears typical of published DC therapies for wound healing.

Representative LIDC Regimen: Wolcott et al. 1969

(1) The ulcer base was covered with dry sterile gauze. The negative electrode was placed on gauze packing, covered with additional gauze, and secured by waterproof tape. The positive electrode was placed on gauze 15 cm proximal to lesion. Both electrode packs were saturated with Ringer’s solution.

(2) A 600 µA current was applied for ≥2 hours.

(3) If there was extensive ulcer drainage without bleeding, the current was increased to 800 µA for 1 or 2 hours. If the ulcer bled, the current was reduced to 400 µA.

(4) In subsequent treatments, current was maintained 200 µA below level producing bleeding in ulcer.

(5) The daily cycle consisted of 2 hours current on, then 4 hours current off. (6 hours of stimulation delivered in 2-hour sessions TID {3 times daily}.)

(6) If the ulcer was not infected after 3 days, polarity was reversed. (The positive electrode was placed over the lesion, and the negative electrode was placed proximally.) If the ulcer was infected, therapy continued at same polarity, but was reversed 3 days after the infection cleared.

(7) Daily procedures consisted of (a) substituting fresh gauze; (b) cleansing the ulcer; (c) adjusting the current as needed; (d) evaluating for granulation tissue formation and re-epithelialization at ulcer margins; and (e) evaluating for possible growth cessation (“growth plateau”), usually 14 to 21 days after treatment onset.

(8) If the ulceration had reached the growth plateau, polarity was reversed (negative electrode over lesion).

(9) If another growth plateau in ulceration occurred, polarity was reversed again (positive electrode over lesion).
Thereafter, polarity was reversed every 24 hours until the lesion healed.

### 3.2.2 Pulsed Current Applications

Some electrical stimulators used PC, which is a periodic, nonsinusoidal pulsed wave current. Table 3.3 displays therapy synopses for PC stimulation for wound healing.

We classified published studies of PC stimulation for the treatment of wound healing into 2 subcategories: (a) pulsed direct current (PDC), in which the delivered current has a DC component and (b) high-voltage pulsed current (HVPC), in which the delivered current has little or no DC component.

Pulsed DC studies generally used 30 to 40 mA (generated by a 6 to 12 V battery) at 128 pulses per second (Hz), although 1 study (Wood et al.140) used 300 to 600 µA at only 0.8 Hz. PDC studies include Wood et al.,141 Gentzkow et al.,142 Feedar et al.,143 Mulder,144 and Weiss et al.145 (The study reported by Mulder appears to be a duplicate of results reported by Feedar et al. based on the study size, outcomes, regimen, device, and an editorial.146)

Regimens used by Feedar et al. and Wood et al. appear typical of published PDC therapies for wound healing.

**Representative PDC Regimen: Feedar et al. 1991**147

1. The wound bed was irrigated with saline solutions before and between treatments. Saline-soaked gauze sponges were applied on or in wounds.

2. A 16 × 16 cm moistened electrode was applied ≥30.5 cm from the wound. A 7.5 × 7.5 cm saline-soaked gauze covered electrode was applied onto the wound.

3. Stimulation was set for 35 mA at 128 Hz, with the negative electrode over the wound. Therapy was a minimum of 4 hours, with a maximum of 8 hours between treatment sessions.

4. Some patients received surgical or whirlpool (WP) debridement as needed.

5. The negative electrode was kept over the wound for 3 days after serosanguineous drainage.
(6) Thereafter, the polarity of active (wound) electrode was reversed every 3 days until the lesion decreased to stage II. (Polarity changed an average of 6 times in 28 days.)

(7) At the first polarity reversal, the pulse frequency was decreased to 64 Hz. When lesions reached stage II, the polarity was reversed daily.

Representative PDC Regimen: Wood et al. 1993

(1) Stimulation was 600 µA with a 0.8 Hz pulse frequency administered from electrodes placed 2 cm on opposite sides of lesion.

(2) Stimulation was applied 3 times weekly.

[The investigators did not specify the duration of treatment sessions.]

HVPC studies generally used 100 to 250 V at 80 to 100 pulses per second (Hz). HVPC studies include Fitzgerald & Newsome, Gogia et al., Griffin et al., Unger, Kloth & Feedar, and Feedar & Kloth.

Regimens used by Griffin et al. and Kloth & Feedar appear typical of published HVPC therapies for wound healing.

Representative HVPC Regimen: Griffin et al. 1991

(1) The ulcer site was packed with sterile 0.9% saline-soaked gauze. The active electrode was placed over the site and covered by wet gauze, aluminum foil, and plastic. The inactive (dispersive) electrode was placed on the medial thigh.

(2) The stimulator was initially set at 100 Hz frequency. The voltage intensity was gradually increased to 200 V or maximal voltage that did not produce visible muscular contraction, producing approximately 500 µA of total current.

(3) Daily treatment sessions were 1 hour and continued for 28 days or until the site healed. The polarity was not reversed.

(4) Ancillary care included (a) wound cleansing using Cara-Klenz, (b) Carrington gel topical medication, (c) dry dressings, (d) mechanical debridement if needed, (e) turning patients every 2 hours, and (f) continuing use of pressure-relieving devices.
Representative HVPC Regimen: Kloth & Feedar 1988

1. Before ES treatment, the ulceration site was debrided mechanically, with proteolytic enzyme ointment (Elase®) and collagenase enzyme ointment (Biozyme-C®). The site was packed with saline-soaked gauze to absorb enzymatic debridement, then flushed with saline solution before placement of electrodes.

2. Electrical intensity was set at 100 V (below amount needed to produce visible muscular contraction) at 105 Hz frequency with 100 µs intraphase interval (from monophasic twin-pulsed generator). This produced a single-phase charge of 1.6 µC with a total-pulse charge of 342 µC/sec. The anode (positive electrode) was placed directly over wound in saline-soaked gauze; the cathode was placed 15 cm distal to anode.

3. Daily sessions lasted 45 minutes and were continued 5 days per week for 4 to 16 weeks or until sites healed.

4. Polarity (electrode placement) was maintained unless wounds exhibited growth (healing) plateau.

3.2.3 Alternating Current Applications

Some devices used AC delivered in a variety of waveforms. Table 3.4 displays therapy synopses for AC stimulation for wound healing.

We classified published studies of AC stimulation for the treatment of wound healing into 2 sub-categories: (a) TENS and (b) biphasic pulsed.

Studies of TENS generally used small, portable devices capable of generating square-wave pulses at 80 to 90 Hz with 0.1 to 0.2 ms pulse widths. TENS studies include Lundeberg et al.,158,159 Frantz,160 Kjartansson & Lundeberg,161 Kaada & Emru,162 Alon et al.,163 Barron et al.,164 Kaada,165 and Westerhof & Bos.166

Regimens used by Lundeberg et al. and Frantz are indicative of protocols reported in published TENS studies for wound healing.

Representative TENS Regimen: Lundeberg et al. 1992

1. Patients used an electrical nerve stimulation (ENS) unit capable of producing alternating constant current square-wave pulses (pulse width = 1 ms). Each ENS unit was applied just beyond ulcer surface area and was set to produce intensity-evoking paresthesia from the active (4 × 6 cm) electrode.
(2) Patients underwent 20-minute daily sessions for 12 weeks or until the site healed. They underwent treatment at a clinic for the first week, then used the unit at home for 11 weeks or until healing.

(3) Polarity was changed after each session.

Representative TENS Regimen: Frantz 1990

(1) Conventional therapy was packing the ulcer with 0.9% normal saline gauze and changing the dressing TID.

(2) One set of surface electrodes was applied with the cathode between the 1st and 2nd metacarpal on one hand and the anode in a corresponding position on the other hand.

(3) The other set of surface electrodes was applied with the cathode placed immediately distal to ulceration and the anode placed immediately proximal to the ulcer.

(4) The TENS unit delivered 85 Hz (standard low-frequency) with 150 µs pulse width at a 30 mA amplitude.

(5) Sessions were 30 minutes TID.

(6) Patients underwent 2-hour turning schedules while laying on 4-inch foam mattresses.

Biphasic AC studies used 15 to 25 mA with 0.25 ms pulses at 40 Hz frequency. Biphasic AC studies include Stefanovska et al. and Karba et al.

Representative Biphasic AC Regimen: Stefanovska et al. 1993

(1) A biphasic, charge-balanced AC stimulus was applied with a 0.25 ms pulse duration at 40 Hz. Four-second stimulation trains were rhythmically alternated with 4-second pauses. The AC amplitude was kept between 15 and 25 mA to prevent damage to newly formed tissue and to minimize tetanic contraction of stimulated tissues.

(2) Daily sessions lasted 2 hours and were continued until lesions healed.
3.2.4 Pulsed Electromagnetic Applications

Some electrical stimulators use generators which create energy in what is commonly referred to as the “radio frequency” or RF band (a few tens of megahertz [MHz]). They typically deliver energy by noncontacting means (e.g., coils) rather than by leads and surface electrodes typical of the three previous categories (DC, PC, and AC). We call this group of ES stimulators pulsed electromagnetic induction (PEMI). **Table 3.5** displays therapy synopses for PEMI stimulation for wound healing.

We classified published studies of PEMI stimulation for the treatment of wound healing into 2 sub-categories: (a) those using PEMF devices containing electromagnetic coils capable of generating a magnetic field and (b) those using PEE devices capable of generating a high peak wattage. Both types of devices are applied externally on top of dressings; both types are also nonthermal. Neither uses electrodes wrapped in wet gauze.

PEMF studies generally used a low-level magnetic field that induced a low-level nonthermal electrical field. PEMF studies include Stiller et al., Todd et al., Ieran et al., and Jeran et al. (Jeran et al. appears to be a preliminary report of results reported by Ieran et al.; Ieran and Jeran also appear to be different spellings of the same name.)

Representative PEMF Regimen: Stiller et al.

1. The device consisted of an electromagnetic transducer (attached to a generator powered by a 9 V battery) containing coils for generating magnetic fields. The transducer unit induced a low-level, nonthermal electrical field of 0.06 mV/cm, 3-part pulse (3.5 ms total width), and 25% duty cycle. It was capable of generating 22 Gauss.

2. The device was applied externally (by velcro strapping) over existing wound dressing (elastic compression wrap) and used by patients at home.

3. Patients were instructed to use the device 3 hr/day for 8 weeks or until the lesion healed.

4. Ancillary treatment consisted of Duoderm® hydroactive dressing ± gentamicin ointment, mupirocin ointment + Vigilon® or nonadherent gauze, Elase® debridement ointment + gauze, or Unna boot beneath Ace® bandage compression wrap.

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The acronym “PEE” was used in the Salzberg et al. 1995 study. The device is also known as pulsed radio frequency energy.
PEE Regimen:

PEE studies used Diapulse® devices exclusively. These devices emit a nonthermal pulsed high-frequency high peak power electromagnetic energy delivered at 27.12 MHz, with a pulse repetition rate of 80 to 600 pulses/second, 65 µsec pulse width, and produce 273 to 975 W per pulse, with a 0.5% to 4.0% duty cycle. Energy is induced at the wound site by a 9” drum-shaped treatment head placed in light contact with the dressing and tuned to resonance with the wound site. Recommended treatment consists of 30 minutes, twice daily, until the lesion is healed. As with PEMF devices, the device is applied externally over existing dressings. PEE studies include Salzberg et al., Tung et al., Itoh et al., and Goldin et al. Therapies generally consisted of 30-minute sessions twice daily for 8 to 12 weeks or until the lesion healed.

3.2.5 Spinal Cord Stimulation Applications

Spinal cord stimulators are primarily designed to reduce intractable pain in patients with failed back syndrome and other chronically painful disorders. [See ECRI Technology Assessment “Spinal Cord (Dorsal Column) Stimulation for Chronic Intractable Pain.”] These devices significantly differ from the types of electrical stimulators previously mentioned for wound healing because spinal cord stimulators are (a) invasive and (b) not primarily intended to increase the rate of wound healing.

However, several case reports (Meglio et al., Richardson et al., and Cook et al.) and 2 small case series (Graber et al., Jivegard et al.) reported increased healing of ulcers in patients following implantation of epidural spinal cord stimulators.

Basic Procedure for Spinal Cord Stimulator Implantation (Percutaneous Epidural Type)

1. A Touhy needle is used to introduce the electrode into the epidural space at the appropriate spinal level for stimulation. The needle should be inserted at the most shallow angle possible (<40°) and close to the anatomical midline.

2. A good epidural entry point is between the 1st and 2nd lumbar vertebrae. The process begins with a stab incision at the appropriate spinal level using a #11 blade, followed by insertion of the lead into the epidural space while ensuring electrode contact with the dura mater.

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Diapulse refers to their device as a nonthermal pulsed high-frequency high peak power electromagnetic energy device (NT/PHF). This acronym does not appear in the literature.
The lead is advanced (using fluoroscopy) into the area of the spinal cord to create a channel for subsequent insertion of active electrodes. Spinal cord leads are then bent and maneuvered into the desired position as needed.

After the active electrodes are properly positioned, they can be connected to an external generator (for testing), an implanted receiver, or a totally implanted (inductively powered) pulse generator. The receiver or generator may then be inserted and anchored (sutured) to the appropriate site.

SCS systems often use 4 (quadripolar) or 8 (octopolar) electrodes with an external or internal power source.

“Multichannel” programmable SCS systems have been developed. These minimize the need for a clinician to surgically revise an implanted electrode’s position and enable the patient to noninvasively select the best electrode orientation for pain relief. Patients may program amplitude, pulse width, frequency, wave type, electrode array, and polarity on an external transmitter to achieve the optimal pain relief.

Patients may use these stimulators an average of 14 hours per day.
3.3 Safety

3.3.1 Reports from Published Studies

General contraindications include use in the presence of: metallic implants, neoplasms, osteomyelitis; or on patients with demand-type cardiac pacemakers.\(^{188}\)

**Direct Current Stimulators**—No complications or adverse reactions were reported in any DC studies of wound healing.

**Pulsed Current Stimulators**—Minor complications included 7 cases of uncomfortable tingling, 1 case of excessive bleeding at the ulcer site, and 1 case of skin irritation were reported in 2 studies.\(^{189,190}\) No other complications or adverse reactions reported in any other PC studies for wound healing.\(^{191,192,193}\)

**Alternating Current Stimulators**—No complications or adverse reactions were reported in any AC study of wound healing. None of the studies specified any contraindications for therapy.

**Pulsed Electromagnetic Induction Stimulators**—No complications or adverse reactions were reported in any PEMF or PEE study of wound healing.\(^{194,195,196,197}\)

**Spinal Cord Stimulators**\(^{198}\)—Percutaneous SCS complications include a 5% to 11% infection rate, skin erosion, pain at the incision site, and cerebrospinal fluid fistula. [See ECRI Technology Assessment on “Spinal Cord (Dorsal Column) Stimulation for Intractable Chronic Pain.”] The safety of these devices has not been established for young children or pregnant women. Spinal cord stimulators are contraindicated for patients who do not experience pain relief during preimplant percutaneous testing.

3.3.2 Contraindications and Warnings from Product Literature

There are several contraindications and warnings common to all types of stimulators evaluated in this assessment. These include not applying stimulation over the carotid sinus or on patients with demand-type pacemakers, advanced cardiac disease, epilepsy, osteomyelitis, or neoplasms. All stimulators may interfere with cardiac or fetal monitoring. In addition, neuromuscular stimulation is contraindicated in patients prone to seizures and following surgical procedures when muscle contraction may disrupt the healing process. Stimulation should not be delivered over the eyes, transcerebrally, or over the pharyngeal area. Pregnancy is considered a contraindication for neuromuscular
stimulation. Although some TENS units have been marketed to manage labor pain, most vendors note that the effects of using TENS units during pregnancy have not been determined. Caution is advised when delivering TENS therapy to patients taking narcotic medications.

### 3.3.3 ECRI Health Device Alerts Database

We searched our Health Device Alerts database using the following key words:

- (Wound or ulcer or sore) and (heal or improve or reduce or current or treat) and (stimulator or electromagnetic or electrothermal or diathermal or TENS or neuromuscular or ultrasonic or transcutaneous).

We found no reported patient injuries associated with ES devices for wound healing (excluding spinal column stimulators) as of December 14, 1995.\(^1\)

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\(^1\) Despite the apparent lack of reported patient injuries in the medical literature and within the FDA databases, ECRI, through its accident and forensic investigations, is directly aware of several incidents of skin burns and adverse outcomes during such ES use for wound healing. However, in these very few cases, injury was the result of the healthcare practitioner’s inappropriate technique when using the device, sometimes combined with inappropriate use despite the presence of written contraindications for that use.
3.4 Manufacturers and Costs

This section lists devices that are (or may be) used for ES to promote wound healing. The published literature may not fully reflect the range of devices used and/or their manufacturer(s).

ECRI contacted many manufacturers of EC devices. A comprehensive list of devices is presented in Table 3.6. Data presented in the table was based on information provided by the respective manufacturers.

We obtained the following information and specifications provided by device manufacturers and distributors:

- Manufacturer
- Model
- Waveforms
- Voltage
- Amperage
- Delivery Mode
- Frequency Range
- Pulse Width
- Number of Channels
- Programmability
- Intended Applications
- Price
- Type of Unit

**Neuromuscular Stimulators**—Specific applications claimed include

- increasing local blood circulation,

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This table does not include vendors of discontinued stimulators.
• reducing edema,
• accelerating metabolic activity,
• Preventing and/or retarding muscle atrophy,
• Relaxing muscle spasms or inhibiting spasticity,
• Maintaining and increasing range of motion,
• Strengthening muscles, and
• Preventing postoperative venous thrombosis.

Infrequent applications include accelerating wound healing, enhancing tissue repair, and gait training.

**Pain Management Devices**—Specific applications include

• relief from acute pain,
• relief from chronic pain, and
• relief from postoperative pain.

Types of Devices—The classification of devices reported in the product literature is inconsistent. Some electrical stimulators are recognized by the names of their inventors or by names designated by vendors (examples: Galvanic, faradic, diadynamic, high voltage, low voltage, low frequency, medium frequency, etc.). TENS (transcutaneous electrical nerve stimulation) has been used to refer to both a specific type of stimulator used for pain management and all devices that stimulate peripheral nerves transcutaneously through surface electrodes. Because of this inconsistency, we classified them into 2 groups: (a) electrical stimulators (first part of Table 3.6), which included combination ultrasound unit/electrical stimulators, and (b) pulsed electromagnetic energy devices (second part of Table 3.6). (Vendor classification of device and recommendations for intended use are reported in the “type of unit” and “indications” columns, respectively.) Devices cited in referenced articles are presented in the third part of Table 3.6.

Universal Medical Device Nomenclature System™ (UMDNS™)—We used ECRI’s UMDNS to identify stimulators listed in the tables. The Universal Medical Device Nomenclature System (UMDNS) is an ECRI-developed and maintained system of classifying medical devices for indexing, storing, and retrieving device-related information. The scope of UMDNS covers all medical devices,
including capital equipment, implants, clinical laboratory equipment and reagents, and selected hospital furniture, systems, and test equipment.

UMDNS terms and the corresponding 5-digit codes are widely incorporated into publications, databases, information systems, and software used by government agencies, healthcare systems and facilities, medical information systems, hazard alerting systems, and other parties and other functions worldwide. UMDNS has also been incorporated into the U.S. National Library of Medicine’s (NLM) Unified Medical Language System (UMLS), a long-term NLM research and development effort designed to facilitate the retrieval and integration of information from multiple machine-readable biomedical information sources. Links are being established between UMDNS and other biomedical vocabularies and classifications such as NLM MeSH, SNOMED, CPT, and ICD, and HPCS.

13762 Stimulators

Definition: Devices that generate and apply a current (stimulus) used to identify or evoke a response from nerves, muscles, tissues, or discrete areas of the central nervous system. Stimulators consist of an energy source, a delivery system (usually electrodes, lead wires, or a probe), an amplitude controller and/or circuit interrupter to prevent excessive energies from damaging the tissues. Stimulators permit control of specific duration, intensity, frequency, and waveform of the applied stimulus. Stimulators may be external, hard-wired percutaneous, transcutaneously coupled, or totally implantable. Implantable devices typically include an enclosure to prevent the biological environment from damaging the circuit components and vice versa.

13775 Stimulators, Neuromuscular

Definition: External stimulators that ameliorate muscle dysfunction through electrically-elicited muscle contraction. Neuromuscular stimulators may deliver low-intensity direct current, low-frequency pulsed current, high-voltage pulsed current, or a pulsed electromagnetic field.

16255 Stimulators, Neuromuscular, Therapeutic

Definition: Neuromuscular stimulators that activate muscle through stimulation of the intact peripheral nerve. Applications include delaying or reducing disuse atrophy, muscle re-education, and increasing range of motion.

16250 Stimulators, Neuromuscular, Functional

Definition: Neuromuscular stimulators that stimulate paralyzed muscle. These devices may enhance the function of a patient’s paralyzed or weak muscles, eliminating the need for orthoses. This type of stimulation may also aid the
return of a functional sill such as walking or grasping, but does not treat the underlying dysfunction.

13782 Stimulators, Electroanalgesic, Transcutaneous Electrical Nerve

Definition: Stimulators used to manage acute and chronic pain. These devices block the transmission of pain impulses by delivering a series of electrical impulses to large-diameter sensory fibers. Transcutaneous electrical stimulation (TENS) units may be single or dual channel, use various types of electrodes, may be monophasic or biphasic, and may deliver a variety of waveforms. Applications include the management of postsurgical, posttraumatic, and labor-induced pain.

17908 Ultrasound Units/Neuromuscular Stimulators, Physical Therapy

Definition: Single units that combine therapeutic ultrasound with neuromuscular stimulation capabilities in which either modality can be used alone or in combination with the other.

Abbreviations Used in Table 3.6—
LIDC: Low-intensity Direct Current
MENS: Microcurrent Electrical Neuromuscular Stimulation
NMES: Neuromuscular Electrical Stimulator
PC: Pulsed Current
TENS: Transcutaneous Electrical Nerve Stimulator

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k Devices labelled or described by manufacturers as high-voltage pulsed galvanic are categorized as pulsed current (PC) and, when available, subcategorized as pulsed direct current (PDC) or high-voltage pulsed current (HVPC).
### 3.5 Tables

**Table 3.1. Examples of Preclinical Studies Evaluating the Effects of Electrical Stimulation on Wound Healing**

<table>
<thead>
<tr>
<th>Study</th>
<th>Investigators' Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carey &amp; Lepley(^{199}) (1962)</td>
<td>Cellular migration around positive pole after DC stimulation: dense infiltration with leukocytes and lymphocytes; predominant cell present was polymorphonuclear leukocyte</td>
</tr>
<tr>
<td>Assimacopoulos(^{200}) (1968)</td>
<td>Improved healing of rabbit skin defects by electrical stimulation</td>
</tr>
<tr>
<td>Fenn(^{201}) (1969)</td>
<td>PEE energy resolved hematomas faster than controls in rabbits</td>
</tr>
<tr>
<td>Barranco et al.(^{202}) (1974)</td>
<td>DC inhibits growth of <em>S. aureus</em> in vitro</td>
</tr>
<tr>
<td>Wilson &amp; Jagadeesh(^{203}) (1975)</td>
<td>PEMF stimulation induced nerve-fiber regeneration across scars in rats</td>
</tr>
<tr>
<td>Konikoff(^{204}) (1976)</td>
<td>DC current promoted soft tissue healing in rats</td>
</tr>
<tr>
<td>Cheng et al.(^{205}) (1982)</td>
<td>DC increases ATP (adenosine triphosphate) concentrations in tissue and stimulates amino acid incorporation into the proteins of rat skin</td>
</tr>
<tr>
<td>Alvarez et al.(^{206}) (1983)</td>
<td>Improved epithelialization of superficial skin wounds in pig by DC current; suggests that proliferative and/or migratory capacity of epithelial and connective tissue cells involved in repair and regeneration can be affected by an electrical field</td>
</tr>
<tr>
<td>Raji &amp; Bowden(^{207}) (1983)</td>
<td>PEMF stimulation accelerated recovery of damaged nerves and reduced epi-, peri-, and intraneural fibrosis in rats</td>
</tr>
<tr>
<td>Foulds &amp; Barker(^{208}) (1983)</td>
<td>Human skin acts as battery; Identified negative electrical potentials from the stratum corneum with respect to the dermis at all sites examined; avg potential overall all sites and subjects was -23 mV ±9 mV (SD)</td>
</tr>
<tr>
<td>Korenstein et al.(^{209}) (1984)</td>
<td>Pulsed ES caused changes in intracellular level of cAMP (cyclic adenosine monophosphate) and enhanced DNA synthesis in rat embryos</td>
</tr>
<tr>
<td>Young(^{210}) (1984)</td>
<td>PEMF stimulation reduced Ca(^{2+}) accumulation in spinal cords of injured cats</td>
</tr>
<tr>
<td>Murray et al.(^{211}) (1985)</td>
<td>PEMF increased production of collagen in fibroblasts (possibly by altering cAMP metabolism)</td>
</tr>
<tr>
<td>Jayakumar et al.(^{212}) (1986)</td>
<td>PEMF reduced cerebral edema in rats</td>
</tr>
<tr>
<td>Bourguignon &amp; Bourguignon(^{213}) (1987)</td>
<td>HVPC produced increased rate of protein and DNA synthesis and migration of human fibroblasts in tissue culture</td>
</tr>
<tr>
<td>Kjartansson et al.(^{214}) (1988)</td>
<td>Improved survival of ischemic musculocutaneous flaps by TENS stimulation in rats</td>
</tr>
<tr>
<td>Yen-Patton et al.(^{215}) (1988)</td>
<td>PEMF produced 20% to 40% improvement in growth rate of partially denuded endothelial cells in vitro</td>
</tr>
<tr>
<td>Dunn et al.(^{216}) (1988)</td>
<td>DC produced fibroblast ingrowth and collagen fiber alignment in vitro</td>
</tr>
<tr>
<td>Politis et al.(^{217}) (1989)</td>
<td>DC on full-thickness grafts in rat skin and found that orienting the anode above the graft yielded significantly more healing than the cathode above the graft or no current at all</td>
</tr>
<tr>
<td>Kincaid et al.(^{218}) (1989)</td>
<td>HVPC produced inhibition of <em>S. aureus, E. coli</em>, and <em>Pseudomonas aeruginosa</em></td>
</tr>
</tbody>
</table>
Table 3.1. Examples of Preclinical Studies Evaluating the Effects of Electrical Stimulation on Wound Healing (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Investigators' Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reger et al.219 (1991)</td>
<td>Improved pressure-ulcer healing by AC or DC therapy in pigs</td>
</tr>
<tr>
<td>Akai et al.220 (1991)</td>
<td>DC applied to severed rabbit ligament produced higher tensile stiffness and earlier changes of collagen types in newly formed tissues</td>
</tr>
<tr>
<td>Szuminsky et al.221 (1994)</td>
<td>HVPC produced antimicrobial effects in vitro against E. coli, Klebsiella, Pseudomona aeruginosa, and S. aureus</td>
</tr>
</tbody>
</table>

DC = direct current; HVPC = high-voltage pulsed current; PEE = pulsed electromagnetic energy; PEMF = pulsed electromagnetic field; TENS = transcutaneous electrical nerve stimulator
### Table 3.2. Synopses of Direct Current (DC) Stimulation Therapies for Wound Healing

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Direct Current Stimulation</th>
<th>Therapy Synopsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katelaris et al.222 (1987)</td>
<td>LIDC</td>
<td>20 µA current with cathode over ulceration; otherwise similar to Wolcott et al. [Device manufacturer not specified]</td>
</tr>
<tr>
<td>Carley &amp; Wainapel223 (1985)</td>
<td>LIDC</td>
<td>2 hr sessions BID of 300 to 700 µA with cathode initially over ulceration (with wet gauze) and regimen otherwise similar to Wolcott et al.; current density 30 to 110 µA/cm² [Device manufacturer not specified]</td>
</tr>
<tr>
<td>Akers &amp; Gabrielson224 (1984)</td>
<td>(Unspecified) DC</td>
<td>Not specified</td>
</tr>
</tbody>
</table>
| Gault & Gatens225 (1976)     | LIDC                              | Regimen similar to Wolcott et al., except polarity reversed only once  
Device Manufacturers: Tri-tonics Laboratory, Inc. (Euless, TX); Prototype of Vitron Unit by Ritter Sybron Corp. (Rochester, NY)                                                                                                                                                                                                   |
| Wolcott et al.226 (1969)     | LIDC                              | 2 hr sessions (2 hrs on, 4 hrs off) TID of 600 to 800 µA with cathode initially over ulceration (with wet gauze) and anode proximal; electrodes switched (polarity reversed) after 3 days (if not infected) or until infection cleared + 3 days (if infected); polarity reversed if healing does not improve ("growth plateau") and/or every 24 hours  
[Device manufacturer not specified]                                                                                                                                                                                                                   |
| Assimacopoulos227 (1968)     | LIDC                              | 50 to 100 µA at 0.25 to 0.80 V with negative electrode (cathode) over ulceration site and positive electrode (anode) lateral to lesion  
[Device manufacturer not specified]                                                                                                                                                                                                                                                                                     |

**TID** = 3 times a day
### Table 3.3. Synopses of Pulsed Current (PC) Stimulation Therapies for Wound Healing

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Pulsed Current Stimulation</th>
<th>Therapy Synopsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wood et al.228 (1993)</td>
<td>PDC</td>
<td>300 μA followed by 600 μA from electrodes placed on opposite sides of wound with current pulsed at 0.8 Hz. Device Manufacturer: MEMS CS 600 (Harbor Medical Inc., Minneapolis, MN)</td>
</tr>
<tr>
<td>Fitzgerald &amp; Newsome229 (1993)</td>
<td>HVPC</td>
<td>100 to 120 V @ 80 to 100 Hz (100 μs interpulse interval); 1-hr session/day (20 minutes at negative polarity, 40 minutes positive polarity) 5 days/ wk. Device Manufacturer: PGS 200 Pulsed Galvanic Stimulator (Universal Technology Systems, Jacksonville, FL)</td>
</tr>
<tr>
<td>Gogia et al.230 (1992)</td>
<td>HVPC</td>
<td>250 V (pulse width 5 to 8 μs) @ 100 Hz for 20 minute daily sessions; negative polarity (in wet gauze) directly over lesion (first 4 sessions), then polarity reversed (last 16 sessions). Device Manufacturer: HVGS (Chattanooga Corp., Chattanooga, TN)</td>
</tr>
<tr>
<td>Gentzkow et al.231 (1991)</td>
<td>PDC</td>
<td>35 mA (from 6 V battery) pulsed at 128 Hz for 30-minute sessions BID; negative polarity (in wet gauze) directly over lesion, then polarity reversed every 3 days after site debrided; reduced to 64 Hz when ulcer decreased to stage II lesion; delivered charge of 0.89 Coulombs/tx (1.78 C/day). Device Manufacturer: Dermapulse® (Staodyn, Inc., Longmont, CO)</td>
</tr>
<tr>
<td>Griffin et al.232 (1991)</td>
<td>HVPC</td>
<td>200 V intensity @ 100 Hz for 1-hr daily session for 20 days; negative polarity (in wet gauze) directly over lesion for duration (no polarity change); produced total current of 500 μA. Device Manufacturer: Intelect 500 HVPC (Chattanooga Corp., Chattanooga, TN)</td>
</tr>
<tr>
<td>Feedar et al.233 (1991)</td>
<td>PDC</td>
<td>35 mA @ 128 Hz (rectangular pulses of 29.2 mA and 132 μs duration) for 30-minute sessions BID with 4 to 8 hrs between sessions; treatment for 7 days/week; negative electrode on lesion; polarity reversed every 30-minute sessions BID 3 days after wound debrided up to 15 weeks. Device Manufacturer: Vara/Pulse® (Staodynamics, Inc., Longmont, CO)</td>
</tr>
<tr>
<td>Mulder234 (1991)</td>
<td>PDC</td>
<td>30, 35, or 40 mA (from 6 V battery) @ 128 Hz for 30-minute sessions BID with 4 to 8 hrs between sessions; negative (or positive) polarity (in wet gauze) directly over lesion; pulse width of 140 μs and charge/pulse of 4.2, 4.9, and 5.6 μC. Device Manufacturer: Dermapulse® (Staodynamics, Inc., Longmont, CO)</td>
</tr>
<tr>
<td>Unger235 (1991) [Abstract]</td>
<td>HVPC</td>
<td>150 V (750 mA peak current) @ 50 Hz; negative polarity (wrapped in tin foil) directly over wound; after 6 days, polarity reversed with 100 V intensity (500 mA peak current) @ 80 Hz. [Device not specified]</td>
</tr>
<tr>
<td>Unger et al.236 (1991) [Abstract]</td>
<td>HVPC</td>
<td>Same as Unger [Device not specified]</td>
</tr>
<tr>
<td>Study</td>
<td>Type of Pulsed Current Stimulation</td>
<td>Therapy Synopsis</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Weiss et al.237 (1989)</td>
<td>PDC</td>
<td>35 mA @ 128 Hz for 30-minute sessions BID with 4 to 8 hrs between sessions; treatment for 7 days/week; positive polarity on surgically induced wound Device Manufacturer: Vara/Pulse® (Staodynamics, Inc., Longmont, CO)</td>
</tr>
<tr>
<td>Kloth &amp; Feedar238 (1988)</td>
<td>HVPC</td>
<td>100 V @ 105 Hz (from monophasic twin-pulsed generator with 100 µs intraphase interval); results in single-phase charge at 1.6 µC with total-pulse charge of 342 µC/s; once daily 45-minute sessions, 5 days/wk for 4 to 16 wks; positive electrode (anode) on lesion for 3 days, then polarity reversed (cathode on wound) if healing plateau reached Device Manufacturer: DynaWave® Model 12 (DynaWave Corp., Geneva, IL)</td>
</tr>
<tr>
<td>Feedar &amp; Kloth239 (1985)</td>
<td>HVPC</td>
<td>100 V @ 105 Hz (100 µs intraphase interval); daily 45-minute sessions, 5 days/wk; negative electrode, then polarity reversed after 3 days Device Manufacturer: DynaWave® Model 12 (DynaWave Corp., Geneva, IL) 240</td>
</tr>
<tr>
<td>Ross &amp; Segal241 (1981)</td>
<td>HVPC</td>
<td>[Voltage not specified] Negative polarity on wound site, 4 Hz pulses for 15 minutes, then polarity reversed with 80 Hz pulses Device Manufacturer: Galvanator Model 700 (Avra Tronics Corp., Greenvale, NY)</td>
</tr>
<tr>
<td>Thurman &amp; Christian242 (1971)</td>
<td>“High-frequency” DC</td>
<td>Not specified</td>
</tr>
</tbody>
</table>

* Nomenclature used by investigators of study
### Table 3.4. Synopses of Alternating Current (AC) Stimulation Therapies for Wound Healing

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Alternating Current Stimulation</th>
<th>Therapy Synopsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stefanovska et al.243 (1993)</td>
<td>Biphasic AC</td>
<td>Biphasic AC current of 15 to 25 mA with charge-balanced current stimuli with 0.25 ms pulse duration @ 40 Hz; 2 hr daily sessions [Device not specified]</td>
</tr>
<tr>
<td>Lundeberg et al.244 (1992)</td>
<td>Electrical nerve stimulation (ENS) unit</td>
<td>AC (alternating constant-current square-wave pulses) of 1 ms pulse width @ 80 Hz applied just outside ulcer surface area—at current sufficient to produce paresthesia—for 20-minute sessions BID; polarity changed after each session Device Manufacturer: Delft Instruments, The Netherlands and/or Henley International, Houston, TX</td>
</tr>
<tr>
<td>Karba et al.245 (1991)</td>
<td>Biphasic AC</td>
<td>Biphasic AC current of 15 to 25 mA with charge-balanced current stimuli with 0.25 ms pulse duration @ 40 Hz; amplitude adjusted for each individual patient; 60-minute daily sessions [Device not specified]</td>
</tr>
<tr>
<td>Frantz246 (1990)</td>
<td>TENS</td>
<td>Constant square-wave pulses of 30 mA @ 85 Hz (150 μs pulse width); 1 set of electrodes on hands, other set proximal (anode) or distal (cathode) to lesions; applied for 30-minute sessions TID Device Manufacturer: Medtronic Eclipse Plus Model 7723 TENS</td>
</tr>
<tr>
<td>Kjartansson &amp; Lundeberg247 (1990)</td>
<td>Electrical nerve stimulation (ENS) unit</td>
<td>Monopolar square wave pulses with duration of 0.2 ms @ 90 Hz Device Manufacturer: TENS unit (Delta, U.K.)</td>
</tr>
<tr>
<td>Kaada &amp; Emru248 (1988)</td>
<td>TENS</td>
<td>Pocket stimulator delivering pulse trains (to electrodes in gauze around lesion) @ 2 Hz, 25 to 50 mA stimulation intensity, delivering constant square-wave pulses at 100 Hz internal frequency and 0.1 to 0.2 ms duration Device Manufacturer: Viking Single (Medi-Stim A/s, Oslo, Norway)</td>
</tr>
<tr>
<td>Lundeberg et al.249 (1988)</td>
<td>Electrical nerve stimulation (ENS) unit</td>
<td>Alternating square-wave pulses 0.4 ms duration @ 80 Hz; stimulus intensity set to 3 times threshold in which tingling sensation felt by patient; 2 hr sessions BID Device Manufacturer: ENS unit (Enraf-Nonius, Netherlands)</td>
</tr>
<tr>
<td>Alon et al.250 (1986) [Abstract]</td>
<td>TENS</td>
<td>Continuous mode @ 80 Hz; positive electrode (in sterile gauze) over ulcer site [Device not specified]</td>
</tr>
<tr>
<td>Barron et al.251 (1985)</td>
<td>Percutaneous low-energy non-galvanic stimulator [TENS]</td>
<td>Modified biphasic square wave: 600 μA, 50 V @ 0.5 Hz administered percutaneously across ulcer surface; 3 sessions TID for 3 wks Device Manufacturer: Micro-Electro Medical Stimulation</td>
</tr>
</tbody>
</table>
Table 3.4. Synopses of Alternating Current (AC) Stimulation Therapies for Wound Healing (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Alternating Current Stimulation</th>
<th>Therapy Synopsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaada^252 (1983)</td>
<td>TENS</td>
<td>Constant square wave pulses of 15 to 30 mA (intensity increased until local contraction of adjacent muscles without producing pain), each stimulus consisting of bursts of 5 pulses with 100 Hz internal frequency; 30- to 45-minute sessions TID; 1 set of electrodes on hands, other set proximal (anode) or distal (cathode) to lesions; all applied from pocket stimulator [Device not specified]</td>
</tr>
<tr>
<td>Westerhof &amp; Bos^253 (1983)</td>
<td>TENS</td>
<td>120 Hz, 250 µs pulse width, 0.5 sec pulse train envelope, 0.5 pulse train interval; 30-minute sessions TID Device Manufacturer: Bio-Medical Research P8 unit</td>
</tr>
</tbody>
</table>

BID = two times a day; TID = three times a day
Table 3.5. Synopses of Pulsed Electromagnetic Induction (PEMI) Stimulation Therapies for Wound Healing

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Electromagnetic Stimulation</th>
<th>Therapy Synopsis</th>
</tr>
</thead>
</table>
| Salzberg et al.254 (1995) | PEE                                 | Pulsed, nonthermal, high-frequency, high peak power electromagnetic energy delivered at 27.12 MHz, pulse repetition rates of 80 to 600 pulses/sec, 65 µs pulse width, 293 to 975 W per pulse peak, 0.5 to 3.9% duty cycle; treatment head placed in contact with wound site and tuned to resonance in area of wound; 30-minute sessions BID  
Device Manufacturer: Diapulse® (Diapulse Corp. of America, Great Neck, NY) |
| Tung et al.255 (1995)   | PEE                                 | Same device parameters as Salzberg et al.; applied in case reports  
Device Manufacturer: Diapulse® (Diapulse Corp. of America, Great Neck, NY) |
| Stiller et al.256 (1992) | PEMF                                | Electromagnetic transducer (attached to signal generator 9 V battery) containing coils for magnetic focusing strapped over wound dressing with elasticized Velcro strap; induces low level, nonthermal electrical field of approx. 0.06 mV/cm; has 3-part pulse of 3.5 ms total width, 25% duty cycle, 22 Gauss; applied (at home) 3 hrs/day on top of dressing for 8 to 12 wks (or healing)  
Device Manufacturer: PELUT* System (Geomed, Inc.) |
| Todd et al.257 (1991)   | PEMF                                | Active coils in Helmholtz arrangement; ulcer placed between coils connected to magnetic field generator; field strength = 60, intensity = 5 Hz; 15-minute sessions performed twice/week for 5 wks after initial 2 wks on standard ulcer therapy  
[Device not specified] |
| Itoh et al.258 (1991)   | PEMF                                | Same device parameters as Salzberg et al.; applied directly through dressings at 600 pulses/sec and 6 peak power; 30-minute sessions BID (8 hour separation between sessions) until healed  
Device Manufacturer: Diapulse® (Diapulse Corp. of America, Great Neck, NY) |
| Jeran et al.259 (1990)  | PEMF                                | Stimulators supplied electromagnetic coils with a single pulse of electrical current generating magnetic field of 2.8 mT @ 75 Hz and 1.3 ms pulse width; patients instructed to use stimulators at home 3-4 hrs/day for 90 days or until healed  
Device Manufacturer: Dermagen, Igea (Carpi, Italy) |
| Jeran et al.260 (1987)  | PEMF                                | Stimulation parameters in electromagnetic coils: maximum magnetic field = 2.7 mT, 75 Hz, 1.3 ms pulse width; patients instructed to use stimulators at home 4 hrs/day for 90 days or until healed  
Device Manufacturer: Dermagen, Igea (Carpi, Italy) |
Table 3.5. Synopses of Pulsed Electromagnetic Induction (PEMI) Stimulation Therapies for Wound Healing (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Electromagnetic Stimulation</th>
<th>Therapy Synopsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldin et al.261 (1981)</td>
<td>Pulsed “radio energy”</td>
<td>Peak output of 975 W @ 400 pulses/sec, 65 µs average pulse duration, mean energy output with 3 cm depth penetration; 30-minute application to graft donor site at time of premedication and 6 hours postoperatively. Device Manufacturer: Diapulse® (Diapulse Corp. of America, Great Neck, NY)</td>
</tr>
</tbody>
</table>

*PELUT = pulsed electromagnetic limb ulcer therapy  
BID = 2 times a day
Table 3.6. Manufacturers, Models, and Device Specifications of Electrical Stimulators
(Data in this table was based on information from respective manufacturers.)

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Model</th>
<th>Waveforms</th>
<th>Voltage, Volts</th>
<th>Amperage</th>
<th>Delivery Modes</th>
<th>Frequency Range, Hz.</th>
<th>Pulse Width, microseconds</th>
<th>No. of Channels</th>
<th>Programmable</th>
<th>Intended Application</th>
<th>Price</th>
<th>Type of Unit</th>
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<tr>
<td>Electrical Stimulators</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>3M Health Care</td>
<td>Dual Channel TENS 6880202</td>
<td>Biphasic</td>
<td>60 mA peak (1000 Ohm load)</td>
<td>Pulsed, burst</td>
<td>2-140</td>
<td>25-250</td>
<td>2</td>
<td>No</td>
<td>Pain management</td>
<td>TENS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3M Health Care</td>
<td>Dual Channel TENS 6820203</td>
<td>Biphasic</td>
<td>80 mA peak (500 Ohm load)</td>
<td>Pulsed, burst</td>
<td>2-170</td>
<td>24-250</td>
<td>2</td>
<td>No</td>
<td>Pain management</td>
<td>TENS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advance</td>
<td>Araddin204</td>
<td></td>
<td>0-10 mA (1000 Ohm load)</td>
<td>Pulsed</td>
<td>40</td>
<td>100</td>
<td>1</td>
<td>No</td>
<td>Pain management</td>
<td>TENS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avra Tronics</td>
<td>Galvanator 770205</td>
<td>Monophasic</td>
<td>0-500</td>
<td></td>
<td>Pulsed</td>
<td>1</td>
<td>1</td>
<td>No</td>
<td>Neuromuscular stimulation</td>
<td>PC, NMES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Imex</td>
<td>A-TENS206</td>
<td>Biphasic</td>
<td>0-100</td>
<td></td>
<td>Pulsed, burst, pulse width modulation</td>
<td>2-110</td>
<td>100</td>
<td>2</td>
<td>No</td>
<td>Pain management</td>
<td>TENS</td>
<td></td>
</tr>
<tr>
<td>American Imex</td>
<td>Easy TENS207</td>
<td>Biphasic</td>
<td>0-100</td>
<td></td>
<td>Pulsed</td>
<td>2-110</td>
<td>100</td>
<td>2</td>
<td>No</td>
<td>Pain management</td>
<td>$520</td>
<td>TENS</td>
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<tr>
<td>American Imex</td>
<td>MES f208</td>
<td>Biphasic, interferential</td>
<td>60 peak 10-600 microamps</td>
<td>Pulsed, interventional beat wave</td>
<td>0-1000</td>
<td>2</td>
<td>No</td>
<td>Pain management</td>
<td>Microcurrent, medium freq.</td>
<td></td>
<td></td>
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<tr>
<td>American Imex</td>
<td>Premier TENS209</td>
<td>Biphasic</td>
<td>0-68</td>
<td></td>
<td>Pulsed, burst, pulse width modulation</td>
<td>2-160</td>
<td>40-250</td>
<td>2</td>
<td>No</td>
<td>Pain management</td>
<td>$595</td>
<td>TENS</td>
</tr>
<tr>
<td>American Imex</td>
<td>Ultima X2010</td>
<td>Biphasic</td>
<td>60 peak 10-600 microamps</td>
<td>Pulsed</td>
<td>0.5 and 100</td>
<td>2</td>
<td>No</td>
<td>Pain management</td>
<td>$795</td>
<td>Microcurrent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amrex</td>
<td>Synchrosonic UHVGS2021</td>
<td>Monophasic, biphasic</td>
<td>0-500</td>
<td>0-10 mA</td>
<td>Constant, pulsed</td>
<td>1-160</td>
<td>30</td>
<td>2</td>
<td>No</td>
<td>Pain management, neuromuscular stimulation</td>
<td>$3295</td>
<td>PC, LIDC, NMES, ultrasound</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Model</th>
<th>Waveforms</th>
<th>Voltage, Volts</th>
<th>Amperage</th>
<th>Delivery Modes</th>
<th>Frequency Range, Hz.</th>
<th>Pulse Width, microseconds</th>
<th>No. of Channels</th>
<th>Programmable</th>
<th>Intended Application</th>
<th>Price</th>
<th>Type of Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amrex</td>
<td>Synchrosonic US/50272</td>
<td>Low volt, biphasic, asymmetrical</td>
<td>100 peak (1K Ohm load); 28 peak (100 Ohm load)</td>
<td>Pulsed</td>
<td>1-80</td>
<td>200 (at 50% V max)</td>
<td>1</td>
<td>No</td>
<td>Pain management</td>
<td>$1850</td>
<td>Low voltage, ultrasound</td>
<td></td>
</tr>
<tr>
<td>Amrex</td>
<td>Synchrosonic US/54273</td>
<td>Low volt, biphasic, asymmetrical</td>
<td>110 peak (1K Ohm load); 28 peak (100 Ohm load)</td>
<td>Pulsed</td>
<td>1-80</td>
<td>200 (at 50% V max)</td>
<td>2</td>
<td>No</td>
<td>Pain management</td>
<td>$2100</td>
<td>Low voltage, ultrasound</td>
<td></td>
</tr>
<tr>
<td>Amrex</td>
<td>Synchrosonic US/752274</td>
<td>Biphasic</td>
<td>0-500</td>
<td>Pulsed</td>
<td>1-160</td>
<td>10, 20, 30</td>
<td>2</td>
<td>No</td>
<td>Pain management, neuromuscular stimulation</td>
<td>$2695</td>
<td>PC, ultrasound</td>
<td></td>
</tr>
<tr>
<td>Biomedical Life Systems</td>
<td>BioMed Plus275</td>
<td>Biphasic</td>
<td>120</td>
<td>0-58 mA peak</td>
<td>Pulsed, burst, pulse width modulation</td>
<td>10, 50-250</td>
<td>2</td>
<td>No</td>
<td>Pain management</td>
<td>TENS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biomedical Life Systems</td>
<td>EMS 2000278</td>
<td>Biphasic</td>
<td>120 max</td>
<td>0-95 mA</td>
<td>Pulsed, interrupted</td>
<td>2-40</td>
<td>300</td>
<td>2</td>
<td>No</td>
<td>Neuromuscular stimulation</td>
<td>NMES</td>
<td></td>
</tr>
<tr>
<td>Biomedical Life Systems</td>
<td>Gentle Touch277</td>
<td>Biphasic</td>
<td>0-80 mA</td>
<td>Pulsed, burst</td>
<td>14, 120</td>
<td>150</td>
<td>2</td>
<td>No</td>
<td>Pain management</td>
<td>TENS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biomedical Life Systems</td>
<td>MFIII</td>
<td>Biphasic</td>
<td>0-50 mA</td>
<td>Pulsed</td>
<td>2-200, 8000-12000</td>
<td>20-250, 5-40</td>
<td>2</td>
<td>No</td>
<td>Pain management</td>
<td>TENS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biomedical Life Systems</td>
<td>Systems 2000278</td>
<td>Biphasic</td>
<td>120</td>
<td>0-80 mA peak</td>
<td>Pulsed, burst, pulse rate/width modulation</td>
<td>2-120</td>
<td>50-250</td>
<td>2</td>
<td>No</td>
<td>Pain management</td>
<td>TENS</td>
<td></td>
</tr>
<tr>
<td>Biomedical Life Systems</td>
<td>Systems Plus279</td>
<td>Biphasic</td>
<td>120 peak</td>
<td>0-80 mA peak</td>
<td>Pulsed, burst, pulse rate/width modulation</td>
<td>2-120</td>
<td>50-250</td>
<td>2</td>
<td>No</td>
<td>Pain management</td>
<td>TENS</td>
<td></td>
</tr>
<tr>
<td>Biorem</td>
<td>Compact 100280</td>
<td>Monophasic, biphasic, interferential</td>
<td>0-100 mA</td>
<td>Continuous, pulsed, interferential beat wave, modulated Kotz current, interrupted</td>
<td>4-400, 4000-4250 (interfer)</td>
<td>50-200</td>
<td>2</td>
<td>Yes</td>
<td>Neuromuscular Stimulation</td>
<td>TENS, Kotz, medium frequency, PC, NMES</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Table 3.6. Manufacturers, Models, and Device Specifications of Electrical Stimulators (continued)

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Model</th>
<th>Waveforms</th>
<th>Voltage, Volts</th>
<th>Amperage</th>
<th>Delivery Modes</th>
<th>Frequency Range, Hz.</th>
<th>Pulse Width, microseconds</th>
<th>No. of Channels</th>
<th>Programmable</th>
<th>Intended Application</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biorem</td>
<td>Ergon281</td>
<td>Biphasic</td>
<td>0-160 (1000 Ohm load)</td>
<td>0-100 mA</td>
<td>Continuous, interrupted</td>
<td>2500</td>
<td>8</td>
<td>Yes</td>
<td>Neuromuscular stimulation</td>
<td>Kotz, medium frequency</td>
<td></td>
</tr>
<tr>
<td>Biorem</td>
<td>Expert282</td>
<td>Monophasic, biphasic, interferential</td>
<td>0-100 mA</td>
<td>Continuous, differentiated, interrupted</td>
<td>4-400, 4000-4250 (interfer)</td>
<td>50-200</td>
<td>2</td>
<td>Yes</td>
<td>Neuromuscular stimulation</td>
<td>TENS, Kotz, medium frequency, PC, NMES</td>
<td></td>
</tr>
<tr>
<td>Biorem</td>
<td>Expert Mini283</td>
<td>Monophasic, biphasic, interferential</td>
<td>0-100 mA</td>
<td>Continuous, differentiated, interrupted</td>
<td>4-400, 4000-4250 (interfer)</td>
<td>50-200</td>
<td>2</td>
<td>Yes</td>
<td>Neuromuscular stimulation</td>
<td>TENS, Kotz, medium frequency, PC, NMES</td>
<td></td>
</tr>
<tr>
<td>Biorem</td>
<td>Expert Plus284</td>
<td>Monophasic, biphasic, interferential</td>
<td>0-80 mA</td>
<td>Continuous, differentiated, interrupted</td>
<td>4-400, 4000-4250 (interfer)</td>
<td>50-200</td>
<td>2</td>
<td>Yes</td>
<td>Neuromuscular stimulation</td>
<td>TENS, Kotz, medium frequency, PC, NMES</td>
<td></td>
</tr>
<tr>
<td>Bloomex Intl</td>
<td>BX-400C285</td>
<td>Biphasic</td>
<td>80 peak (1000 Ohm load)</td>
<td>Pulsed, interrupted</td>
<td>90</td>
<td>250</td>
<td>4</td>
<td>No</td>
<td>Pain management, neuromuscular stimulation</td>
<td>NMES, low voltage</td>
<td></td>
</tr>
<tr>
<td>Bloomex Intl</td>
<td>BX-600C286</td>
<td>Monophasic, biphasic</td>
<td>55 peak (1000 Ohm load)</td>
<td>Pulsed, interrupted</td>
<td>4-190</td>
<td>30-250</td>
<td>4</td>
<td>No</td>
<td>Pain management, neuromuscular stimulation</td>
<td>NMES, low voltage</td>
<td></td>
</tr>
<tr>
<td>Bloomex Intl</td>
<td>BX-1000287</td>
<td>Monophasic, biphasic</td>
<td>70 peak (1000 Ohm load)</td>
<td>Pulsed, interrupted</td>
<td>4-120</td>
<td>20-340</td>
<td>10</td>
<td>Yes</td>
<td>Neuromuscular stimulation</td>
<td>NMES, LIDC</td>
<td></td>
</tr>
<tr>
<td>Bloomex Intl</td>
<td>BX-200SC288</td>
<td>Biphasic</td>
<td>80 peak (1000 Ohm load)</td>
<td>Pulsed, interrupted</td>
<td>1-180</td>
<td>50-300</td>
<td>2</td>
<td>No</td>
<td>Pain management, neuromuscular stimulation</td>
<td>NMES</td>
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<tr>
<td>Brudermueller</td>
<td>DoloTENS 1289</td>
<td>Biphasic</td>
<td>0-60 mA</td>
<td>Pulsed</td>
<td>2-150</td>
<td>50-250</td>
<td>2</td>
<td>No</td>
<td>Pain management</td>
<td>DM 325</td>
<td>TENS</td>
</tr>
<tr>
<td>Brudermueller</td>
<td>DoloTENS 2290</td>
<td>Biphasic</td>
<td>0-60 mA</td>
<td>Pulsed, burst</td>
<td>2-150</td>
<td>50-250</td>
<td>2</td>
<td>No</td>
<td>Pain management</td>
<td>DM 545</td>
<td>TENS</td>
</tr>
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Table 3.6. Manufacturers, Models, and Device Specifications of Electrical Stimulators (continued)

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Model</th>
<th>Waveforms</th>
<th>Voltage, Volts</th>
<th>Amperage</th>
<th>Delivery Modes</th>
<th>Frequency Range, Hz.</th>
<th>Pulse Width, microseconds</th>
<th>No. of Channels</th>
<th>Programmable</th>
<th>Intended Application</th>
<th>Price</th>
<th>Type of Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brudermueller</td>
<td>DoloTENS EMS</td>
<td>Biphasic</td>
<td>0-60 mA</td>
<td>Pulsed, burst</td>
<td>2-150</td>
<td>50-250</td>
<td>2</td>
<td>No</td>
<td>Pain management</td>
<td>DM 595</td>
<td>TENS</td>
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<tr>
<td>Brudermueller</td>
<td>Medimoll 1000</td>
<td>Biphasic</td>
<td>0-60 mA</td>
<td>Pulsed</td>
<td>2-100</td>
<td>50-250</td>
<td>1</td>
<td>No</td>
<td>Pain management</td>
<td>DM 395</td>
<td>TENS</td>
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<tr>
<td>Brudermueller</td>
<td>Medimoll 2000</td>
<td>Biphasic</td>
<td>0-60 mA</td>
<td>Pulsed, burst</td>
<td>2-100</td>
<td>50-250</td>
<td>2</td>
<td>No</td>
<td>Pain management</td>
<td>DM 595</td>
<td>TENS</td>
<td></td>
</tr>
<tr>
<td>Carin</td>
<td>Interferential 94</td>
<td>Biphasic, interferential</td>
<td></td>
<td></td>
<td>Pulsed, interrupted, interferential beat wave</td>
<td>1,000-10,000</td>
<td>2</td>
<td>Yes</td>
<td>Pain management, neuromuscular stimulation</td>
<td></td>
<td>NMES, medium frequency</td>
<td></td>
</tr>
<tr>
<td>Carin</td>
<td>Megasonic 90</td>
<td>Monophasic, biphasic</td>
<td>75 mA peak (3000 Ohm load)</td>
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<td>1.5 and 80</td>
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<td>Pain management, neuromuscular stimulation, wound healing</td>
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<td>D-83²²⁴</td>
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<td>0-500 (3,000 Ohm load)</td>
<td>1.2 mA (at 500 V and 80 Hz)</td>
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<td>Pulsed, interrupted</td>
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<td>Biphasic, interferential</td>
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<td>Pain management, treatment of edema, increasing circulation</td>
<td>Interferential</td>
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<td>NMES, MENS, microcurrent</td>
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<td>TENS, medium frequency, ultrasound</td>
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<td>TENS, microcurrent, medium frequency, ultrasound</td>
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<td>TENS, HVPG, ultrasound</td>
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<td>No</td>
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<td>Accu-O-Matic VM2³²⁹</td>
<td>Monophasic, biphasic (“Tsunami”)</td>
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Table 3.6  Manufacturers, Models, and Device Specifications of Electrical Stimulators (continued)

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<th>Manufacturer</th>
<th>Model</th>
<th>Waveforms</th>
<th>Voltage, Volts</th>
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<th>Intended Application</th>
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<td>0-140 mA peak</td>
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<td>Pulsed, interrupted</td>
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### Table 3.6. Manufacturers, Models, and Device Specifications of Electrical Stimulators (continued)

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<th>Manufacturer</th>
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<th>Pulse Width, microseconds</th>
<th>No. of Channels</th>
<th>Programmable</th>
<th>Intended Application</th>
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<td>0-70 mA</td>
<td>Pulsed, burst, pulse rate/width modulation</td>
<td>2-120</td>
<td>40-200</td>
<td>2</td>
<td>No</td>
<td>Pain management</td>
<td>TENS</td>
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<tr>
<td>Medical Devices</td>
<td>Mentor 159390</td>
<td>Biphasic</td>
<td>0-60 mA</td>
<td>Pulsed, burst</td>
<td>2.5-110</td>
<td>60-200</td>
<td>2</td>
<td>No</td>
<td>Pain management</td>
<td>$500</td>
<td>TENS</td>
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<tr>
<td>Medical Devices</td>
<td>Mentor 259391</td>
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<td>0-60 mA</td>
<td>Pulsed, burst, pulse rate/width modulation</td>
<td>2.5-145</td>
<td>36-200</td>
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<td>Pain management</td>
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<td>Medical Devices</td>
<td>Ultrapac II SX382</td>
<td>Biphasic</td>
<td>0-70 mA (500 Ohm load)</td>
<td>Pulsed, burst, pulse rate/width modulation</td>
<td>2-120</td>
<td>40-250</td>
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<td>Pain management</td>
<td>$575</td>
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<td>40-250</td>
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<td>Mettler Electronics</td>
<td>Sonicator Plus394</td>
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<td>0-500</td>
<td>0-2500 mA</td>
<td>Pulsed</td>
<td>0-120</td>
<td>2</td>
<td>Yes</td>
<td>Pain management</td>
<td>PC, ultrasound</td>
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<tr>
<td>Mettler Electronics</td>
<td>SysStim 206395</td>
<td>Monophasic, biphasic</td>
<td>0-102</td>
<td>30 mA peak (Continuous), 100 mA peak (Pulsed)</td>
<td>Pulsed, continuous</td>
<td>1-83</td>
<td>500-1500</td>
<td>1</td>
<td>No</td>
<td>Neuromuscular stimulation</td>
<td>NMES</td>
<td></td>
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Table 3.6. Manufacturers, Models, and Device Specifications of Electrical Stimulators (continued)

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Model</th>
<th>Waveforms</th>
<th>Voltage, Volts</th>
<th>Amperage</th>
<th>Delivery Modes</th>
<th>Frequency Range, Hz.</th>
<th>Pulse Width, microseconds</th>
<th>No. of Channels</th>
<th>Programmable</th>
<th>Intended Application</th>
<th>Price</th>
<th>Type of Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mettler Electronics</td>
<td>SysStim 206A</td>
<td>Monophasic, biphasic</td>
<td>0-102</td>
<td>0-30 mA (continuous), 0-200 mA (Pulsed) (500 Ohm load)</td>
<td>Pulsed, continuous, interrupted</td>
<td>1-83</td>
<td>500-1500</td>
<td>2</td>
<td>No</td>
<td>Neuromuscular stimulation</td>
<td></td>
<td>NMES</td>
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<tr>
<td>Mettler Electronics</td>
<td>SysStim 207A</td>
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<td>0-102</td>
<td>0-30 mA (continuous), 0-200 mA (Pulsed) (500 Ohm load)</td>
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<td>1-120, 2500</td>
<td>500-1500</td>
<td>2</td>
<td>No</td>
<td>Neuromuscular stimulation, medium frequency</td>
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<td>NMES, medium frequency</td>
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<tr>
<td>Mettler Electronics</td>
<td>SysStim 220</td>
<td>Biphasic, interferential</td>
<td>0-60 mA</td>
<td>Pulsed, interferential beat wave, interrupted</td>
<td>4000</td>
<td>2</td>
<td></td>
<td>2</td>
<td>No</td>
<td>Neuromuscular stimulation, medium frequency</td>
<td></td>
<td>NMES, medium frequency</td>
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<tr>
<td>OMS Medical Supplies</td>
<td>TX-3 TENS</td>
<td>Biphasic</td>
<td>0-40 (500 Ohm load)</td>
<td>0-60 mA (500 Ohm load)</td>
<td>Pulsed, burst</td>
<td>2-20</td>
<td>50-250</td>
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<td>Pain management</td>
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<td>OMS Medical Supplies</td>
<td>Dr Pulse</td>
<td>Biphasic</td>
<td>0-60 (500 Ohm load)</td>
<td>0-120 mA (500 Ohm load)</td>
<td>Pulsed</td>
<td>1.5-27</td>
<td>250</td>
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<td>Pain management</td>
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<td>OMS Medical Supplies</td>
<td>HP-707</td>
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<td>0-30 (500 Ohm load)</td>
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<td>Pulsed</td>
<td>2</td>
<td>80</td>
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<td>OMS Medical Supplies</td>
<td>Mstim-2000</td>
<td>Biphasic</td>
<td>0-30 (500 Ohm load)</td>
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<td>Pulsed, interrupted</td>
<td>2-100</td>
<td>230</td>
<td>2</td>
<td>No</td>
<td>Neuromuscular stimulation</td>
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<td>NMES</td>
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<td>Preston</td>
<td>Health Pulse</td>
<td>Biphasic</td>
<td>0-55</td>
<td>0-130 mA peak</td>
<td>Pulsed</td>
<td>0-100</td>
<td></td>
<td>1 or 2</td>
<td>No</td>
<td>Pain management</td>
<td>$130, $160</td>
<td>TENS</td>
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<td>Preston</td>
<td>Portamax</td>
<td>Monophasic</td>
<td>0-500</td>
<td>Pulsed, interrupted</td>
<td>1-140</td>
<td>1</td>
<td></td>
<td>No</td>
<td></td>
<td></td>
<td>$1395</td>
<td>PC</td>
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<tr>
<td>Preston</td>
<td>Ultramax III</td>
<td>Monophasic</td>
<td>0-500</td>
<td>1.0 mA (at 500 V, 140 Hz)</td>
<td>Pulsed, interrupted</td>
<td>1-140</td>
<td></td>
<td>1</td>
<td>No</td>
<td></td>
<td>$2195</td>
<td>PC</td>
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Table 3.6. Manufacturers, Models, and Device Specifications of Electrical Stimulators (continued)

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Model</th>
<th>Waveforms</th>
<th>Voltage, Volts</th>
<th>Amperage</th>
<th>Delivery Modes</th>
<th>Frequency Range, Hz.</th>
<th>Pulse Width, microseconds</th>
<th>No. of Channels</th>
<th>Programmable</th>
<th>Intended Application</th>
<th>Price</th>
<th>Type of Unit</th>
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<tbody>
<tr>
<td>PTI</td>
<td>Omnistim 500</td>
<td>Monophasic, biphasic, interferential, Russian</td>
<td>0-250</td>
<td>Pulsed, burst, interrupted, interferential beat wave</td>
<td>0.1-999, 2000-5000 (Interfer)</td>
<td>30-500</td>
<td>2</td>
<td>No</td>
<td>Pain management, neuromuscular stimulation, treatment of edema</td>
<td>5000 (Interfer)</td>
<td>TENS, PC, NMES</td>
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<tr>
<td>PTI</td>
<td>Omnisound 2500C</td>
<td>Monophasic, biphasic, interferential, Russian</td>
<td>Pulsed, burst, interrupted interferential beat wave</td>
<td>0.1-999, 2000-5000</td>
<td>30-500</td>
<td>2</td>
<td>No</td>
<td>Pain management</td>
<td>5000</td>
<td>PC, medium frequency, ultrasound</td>
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<tr>
<td>Rich-Mar</td>
<td>HV II SP</td>
<td>Monophasic</td>
<td>Pulsed, interrupted</td>
<td>2-120</td>
<td>No</td>
<td>Pain management</td>
<td>PC, ultrasound</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Rich-Mar</td>
<td>V</td>
<td>Biphasic</td>
<td>Pulsed, interrupted</td>
<td>No</td>
<td>Pain management</td>
<td>NMES, ultrasound</td>
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<td></td>
<td></td>
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<td>Rich-Mar</td>
<td>V I HV</td>
<td>Monophasic</td>
<td>Pulsed, interrupted</td>
<td>5-80</td>
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<td>Pain management</td>
<td>PC, ultrasound</td>
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<td>Rich-Mar</td>
<td>Theratouch 3.3</td>
<td>Monophasic, biphasic, interferential, Russian</td>
<td>Pulsed, interferential beat wave</td>
<td>4</td>
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<td>Pain management, neuromuscular stimulation</td>
<td>TENS, NMES, microcurrent, medium frequency</td>
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<td>Rich-Mar</td>
<td>Theratouch 4.7</td>
<td>Monophasic, biphasic, interferential, Russian</td>
<td>Pulsed, interferential beat wave</td>
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<td>TENS, NMES, microcurrent, medium frequency</td>
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<tr>
<td>Rich-Mar</td>
<td>III</td>
<td>Biphasic</td>
<td>Pulsed, interrupted</td>
<td>1-60</td>
<td>2</td>
<td>No</td>
<td>Neuromuscular stimulation</td>
<td>NMES</td>
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<tr>
<td>Rich-Mar</td>
<td>III-G</td>
<td>Monophasic, biphasic</td>
<td>Pulsed, interrupted</td>
<td>0-40 mA (monophasic)</td>
<td>1-60</td>
<td>800, 1400 (monophasic)</td>
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<td>No</td>
<td>Denervated muscle stimulation, neuromuscular stimulation</td>
<td>NMES</td>
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<td>Manufacturer</td>
<td>Model</td>
<td>Waveforms</td>
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<td>Amperage</td>
<td>Delivery Modes</td>
<td>Frequency Range, Hz</td>
<td>Pulse Width, microseconds</td>
<td>No. of Channels</td>
<td>Programmable</td>
<td>Intended Application</td>
<td>Price</td>
<td>Type of Unit</td>
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<td>ST-Electromedicina</td>
<td>Sarria ST-120[3]</td>
<td>Monophasic, biphasic</td>
<td>270 max</td>
<td>70 mA peak (3500 Ohm load)</td>
<td>Pulsed</td>
<td></td>
<td></td>
<td>4</td>
<td>Yes</td>
<td>Pain management, neuromuscular stimulation</td>
<td></td>
<td>TENS, NMES</td>
</tr>
<tr>
<td>Staodyn</td>
<td>Dermapulse[4]</td>
<td>Monophasic</td>
<td>0-42 mA peak</td>
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<td></td>
<td>64, 128</td>
<td>140</td>
<td>4</td>
<td>No</td>
<td>Wound management, accelerated healing</td>
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<td>PC (PDC)</td>
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<tr>
<td>Staodyn</td>
<td>EMS+2[5]</td>
<td>Monophasic, biphasic</td>
<td>0-100 mA (0-500 Ohm load)</td>
<td>Pulsed, interrupted, burst, pulse rate/width modulation</td>
<td>4-8</td>
<td>5-300</td>
<td></td>
<td>2</td>
<td>No</td>
<td>Neuromuscular stimulation</td>
<td>$645</td>
<td>NMES</td>
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<tr>
<td>Staodyn</td>
<td>Maxima [6,7]</td>
<td>Biphasic</td>
<td>75</td>
<td>0-80 mA peak (500 Ohm load)</td>
<td>Pulsed</td>
<td>2-150</td>
<td>50-250</td>
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<td>No</td>
<td>Pain management</td>
<td>$645</td>
<td>TENS</td>
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<tr>
<td>Staodyn</td>
<td>Maxima III[8,9,10]</td>
<td>Biphasic</td>
<td>130</td>
<td>0-100 mA (1300 Ohm load)</td>
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<td>2-160</td>
<td>50-400</td>
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<td>Pain management</td>
<td>$665</td>
<td>TENS</td>
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<tr>
<td>Staodyn</td>
<td>Nuwave[11,12]</td>
<td>Biphasic</td>
<td>100</td>
<td>100 mA peak (500 Ohm load)</td>
<td>Pulsed</td>
<td>278</td>
<td>60</td>
<td>2</td>
<td>No</td>
<td>Pain management</td>
<td>$795</td>
<td>TENS</td>
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<tr>
<td>Staodyn</td>
<td>Tuwave[13]</td>
<td>Biphasic, triphasic</td>
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<td>100 mA peak (500 Ohm load)</td>
<td>Pulsed</td>
<td>278, 222</td>
<td>60</td>
<td>2</td>
<td>No</td>
<td>Pain management, treatment of edema, increasing circulation</td>
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<td>PC, TENS</td>
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<tr>
<td>Titan Electronics</td>
<td>Compact-TENS[14]</td>
<td>Biphasic</td>
<td>0-60 mA (1000 Ohm load)</td>
<td>Pulsed, pulse rate/width modulation</td>
<td>1-200</td>
<td>30-300</td>
<td></td>
<td>2</td>
<td>No</td>
<td>Pain management</td>
<td></td>
<td>TENS</td>
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<tr>
<td>Titan Electronics</td>
<td>TCI-EL[15]</td>
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<td>0-50 (1000 Ohm load)</td>
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<td>100</td>
<td>100</td>
<td>1</td>
<td>No</td>
<td>Management of menstrual pain</td>
<td></td>
<td>TENS</td>
</tr>
</tbody>
</table>

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### Table 3.6. Manufacturers, Models, and Device Specifications of Electrical Stimulators (continued)

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Model</th>
<th>Waveforms</th>
<th>Voltage, Volts</th>
<th>Amperage</th>
<th>Delivery Modes</th>
<th>Frequency Range, Hz.</th>
<th>Pulse Width, microseconds</th>
<th>No. of Channels</th>
<th>Programmable</th>
<th>Intended Application</th>
<th>Price</th>
<th>Type of Unit</th>
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<tbody>
<tr>
<td>Ultraschall Dr. Born GmbH</td>
<td>M 200²²¹</td>
<td>Monophasic</td>
<td>0-500 (10000 Ohm load)</td>
<td>Pulsed</td>
<td></td>
<td>2-150</td>
<td></td>
<td>No</td>
<td>No</td>
<td>Pain management</td>
<td>PC, ultrasound</td>
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<tr>
<td>Universal Technology Systems</td>
<td>PGS-3000²²²</td>
<td>Monophasic</td>
<td>330</td>
<td>Pulsed</td>
<td></td>
<td>1-100</td>
<td></td>
<td>1</td>
<td>No</td>
<td>Neuromuscular stimulation</td>
<td>NMES, PC</td>
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<tr>
<td>Verimed</td>
<td>Veristim II²²²</td>
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<td>80 (1000 Ohm load)</td>
<td>Pulsed</td>
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<td>10-100</td>
<td>10-350</td>
<td>1</td>
<td>No</td>
<td>Neuromuscular stimulation</td>
<td>NMES</td>
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<tr>
<td>Verimed</td>
<td>Phyaction 780²²²</td>
<td>Monophasic, biphasic, interferential, Russian</td>
<td>140 mA peak (500 Ohm load)</td>
<td>Pulsed, burst, interrupted, interferential beat wave</td>
<td>1-500, 4000 (Interfer), 2500 (Russian)</td>
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<td>Yes</td>
<td>Pain management, neuromuscular stimulation</td>
<td>TENS, NMES</td>
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### Pulsed Electromagnetic Induction

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<th>Manufacturer</th>
<th>Model</th>
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<th>Generator Frequency</th>
<th>Pulse Duration</th>
<th>Programmable</th>
<th>Intended Application</th>
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<tr>
<td>Biorem</td>
<td>Maxima²²²</td>
<td>1-50 Gauss</td>
<td>1-100 Hz</td>
<td>Yes</td>
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<td>Increase circulation, reduce inflammation</td>
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<tr>
<td>Biorem</td>
<td>Micra²²²</td>
<td>48 Gauss</td>
<td>1-50 Hz</td>
<td>Yes</td>
<td></td>
<td>Increase circulation, reduce inflammation</td>
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<tr>
<td>Diapulse</td>
<td>D101³³³</td>
<td>293-975 W (radiated energy)</td>
<td>27.12 MHz</td>
<td>65 microseconds</td>
<td>Yes</td>
<td>Wound treatment</td>
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</tbody>
</table>

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Table 3.6. Manufacturers, Models, and Device Specifications of Electrical Stimulators (continued)

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Model</th>
<th>Waveforms</th>
<th>Voltage, Volts</th>
<th>Amperage</th>
<th>Delivery Modes</th>
<th>Frequency Range, Hz.</th>
<th>Pulse Width, microseconds</th>
<th>No. of Channels</th>
<th>Programmable</th>
<th>Intended Application</th>
<th>Price</th>
<th>Type of Unit</th>
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<tbody>
<tr>
<td>Electropharmacology</td>
<td>sofPulse\textsuperscript{125}</td>
<td>Monophasic</td>
<td>80-600</td>
<td>65 microseconds</td>
<td>No</td>
<td>Pain management, treatment of edema</td>
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<td></td>
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<td>Devices Cited in Referenced Articles</td>
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<td>Avra Tronics</td>
<td>Galvanator 770\textsuperscript{132}</td>
<td>Monophasic</td>
<td>0-500</td>
<td>Pulsed</td>
<td>4-80</td>
<td>1</td>
<td>No</td>
<td>Neuromuscular stimulation</td>
<td>PC, NMES</td>
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<tr>
<td>Chattanooga Group</td>
<td>Intelect 5005\textsuperscript{127}</td>
<td>Monophasic</td>
<td>0-500</td>
<td>0-2500 mA peak</td>
<td>Pulsed, interrupted</td>
<td>1-120</td>
<td>1</td>
<td>No</td>
<td>Neuromuscular stimulation</td>
<td>NMES, PC</td>
<td>(HVPC)</td>
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</tr>
<tr>
<td>Dynawave</td>
<td>Dynawave Model 12\textsuperscript{126}</td>
<td>Monophasic</td>
<td>0-500</td>
<td>Microamp</td>
<td>Pulsed, interrupted</td>
<td>1-1</td>
<td>2</td>
<td>No</td>
<td>Neuromuscular stimulation</td>
<td>Microcurrent, NMES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Empi</td>
<td>Eclipse\textsuperscript{439}</td>
<td>Biphasic</td>
<td>0-60 mA (200-1200 Ohm load)</td>
<td>Pulsed, burst, pulse rate/width/amplitude modulation</td>
<td>2-125</td>
<td>30-250</td>
<td>2</td>
<td>No</td>
<td>Pain management</td>
<td>$685</td>
<td>TENS</td>
<td></td>
</tr>
<tr>
<td>Herley</td>
<td>EMS 8100\textsuperscript{441}</td>
<td>Biphasic</td>
<td>0-80 mA</td>
<td>Pulsed, interrupted</td>
<td>20-100</td>
<td>60-800</td>
<td>2</td>
<td>No</td>
<td>Pain management</td>
<td>$829</td>
<td>TENS</td>
<td></td>
</tr>
<tr>
<td>Stadyn</td>
<td>Dermapulse\textsuperscript{441}</td>
<td>Monophasic</td>
<td>0-42 mA peak</td>
<td>Pulsed</td>
<td>64, 128</td>
<td>140</td>
<td>4</td>
<td>No</td>
<td>Wound Management, Accelerated healing</td>
<td>PC (PDC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Universal Technology Systems</td>
<td>PGS-3000\textsuperscript{442}</td>
<td>Monophasic</td>
<td>330</td>
<td>Pulsed</td>
<td>1-100</td>
<td>1</td>
<td>1</td>
<td>No</td>
<td>Neuromuscular stimulation</td>
<td>NMES, PC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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### Table 3.6. Manufacturers, Models, and Device Specifications of Electrical Stimulators (continued)

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Model</th>
<th>Waveforms</th>
<th>Voltage, Volts</th>
<th>Amperage</th>
<th>Delivery Modes</th>
<th>Frequency Range, Hz.</th>
<th>Pulse Width, microseconds</th>
<th>No. of Channels</th>
<th>Programmable</th>
<th>Intended Application</th>
<th>Price</th>
<th>Type of Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulsed Electromagnetic Energy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diapulse</td>
<td>D103</td>
<td>Radiated</td>
<td>Generator</td>
<td>Pulse Duration</td>
<td>Programmable</td>
<td>Intended Application</td>
<td>Price</td>
<td>593-975 W 293-975 W</td>
<td>27.12 MHz</td>
<td>65 microseconds</td>
<td>Wound treatment</td>
<td></td>
</tr>
</tbody>
</table>

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4.0 Quality of Electrical Stimulation Studies for Chronic Wound Healing

Our analysis of studies of electrical stimulation for the treatment of chronic wounds consisted of

- an analysis of the quality of the ES studies (section 4);
- a description of ES study procedures and outcomes (as reported by investigators) in evidence tables (section 5);
- a quantitative analysis and meta-analyses of healing rates and complete wound healing within ES studies (section 6);
- a comparative analysis of the quality of controlled ES studies with controlled studies of alternative therapies (section 7); and
- a comparative analysis of healing rate and complete wound healing of ES studies with outcomes reported in alternative therapies (section 8).

Our analysis of ES literature quality consisted of the following:

- Step 1: literature search (section 4.1) and collection of appropriate articles
- Step 2: an overall description of possible confounding factors that may arise from flaws in patient selection, randomization, or concomitant therapy that may lead to potentially biased outcomes (section 4.2)
- Step 3: a description of weaknesses in outcome reporting possibly leading to erroneous conclusions (section 4.2)
- Step 4: an assessment of the quality of individual ES studies (section 4.3)
4.1 Databases and Search Strategies for Electrical Stimulation Studies

ECRI searched the following databases:

- Ageline (1966 through December 1995)
- Biosis Previews (1969 through December 1995)
- Catline (1985 through December 28, 1995)
- Ei Compendex Plus (1970 through December 1995)
- Current Contents (January 1994 through January 4, 1996)
- Diogenes (1976 through January 4, 1996)
- Dirline (1985 through December 1995)
- Embase (1974 through November 11, 1995)
- Federal Research in Progress (January 1996; updated monthly)
- Health Care Standards (1990 through January 4, 1996)
- Health Device Alerts (1977 through January 4, 1996)
- Health Devices Sourcebook (January 1995; updated monthly)
- Health Planning and Administration (1975 through December 19, 1995)
- Health Services/Technology Assessment Research (1985 through December 19, 1995)
- INSPEC (1969 through December 1995)
- International Health Technology Assessment (1990 through January 4, 1996)
- MEDLINE (1966 through December 19, 1995)
- Nursing and Allied Health (1984 through December 19, 1995)
We also identified relevant literature by hand searching through

- journals,
- bibliographies of articles reviewed,
- material provided by experts contacted, and
- material provided by manufacturers contacted.

Our search strategies for identifying ES studies of chronic wound healing within these databases used the following subject areas (and keywords in parentheses):

- Chronic wounds, ulcers *(wounds; decubitus ulcer; skin ulcer; varicose ulcer; stasis ulcer; venous ulcer; pressure ulcer; pressure sore; diabetic foot; foot ulcer; leg ulcer; bedsore; ischemic ulcer; ischemia; soft tissue)*

- Wound healing *(wound healing; ulcer healing)*

- Electric stimulation *(electric stimulation; electric stimulation therapy; electrostimulation; electrostimulation therapy; pulsed electromagnetic frequency (PEMF); low-intensity direct current (LIDC); diathermy; electrocoagulation; monophasic; biphasic; radiowave; shortwave; diapulse; electromagnetics; electromagnetic therapy; electromagnetic energy; electromagnetic radiation; electromagnetic fields; electricity; electrotherapy; transcutaneous electric nerve stimulation; TENS; stimulators; equipment safety; equipment failure)*

- Randomized/controlled trials *(clinical trials; clinical trials, phase I; clinical trials, phase II; clinical trials, phase III; clinical trials, phase IV; randomized controlled trials; controlled clinical trials; multicenter studies; random allocation; single-blind method; double-blind method; placebos; mask; random; control; blind)*

[See section 7.1 for search strategies used for alternative therapies.]

A search of these databases yielded 41 studies of ES for the treatment of chronic wounds. They included

- 6 studies using DC stimulation *(2 randomized controlled trials (RCTs), 1 comparative, 2 case series (with embedded RCTs), and 1 case report);*
• 14 studies using PC stimulation (9 RCTs, 2 case series, and 3 case reports);
• 9 studies using AC or TENS stimulation (2 RCTs, 6 case series (1 with a very preliminary RCT), and 1 case report);
• 7 studies using PEE devices (5 RCTs, 1 case series, and 1 case report); and
• 5 studies using implanted SCS (2 case series, 3 case reports) + 1 background article (on SCS for amputations).

These studies form the basis of our qualitative and quantitative analyses.

We also identified 8 background studies of ES for wound or soft tissue healing including DC for healing of grafts following burn injuries;444 PC for evaluation of transcutaneous oxygen levels in spinal cord injury patients;445 TENS for the prevention of amputations,446 and for improved healing postoperative healing447 or for skin flaps;448 PEE for the healing of donor sites for grafts449 or soft tissue injuries;450 and SCS for improving limb salvage in patients with inoperable severe leg ischemia.451

Our only exclusion criteria was that these studies not explicitly state that they primarily used patients with lesions of less than 30-day duration. (Our definition of chronic was duration ≥30 days.)

Throughout our analyses, the terms “lesion,” “wound,” and “ulcer” are used interchangeably.

In addition we searched the literature for published studies of cost effectiveness of ES for wound healing. In this search we used the previously identified subject areas and keywords related to chronic wounds, wound healing and electrical stimulation in conjunction with the following keywords:

• Economics (economics; costs and cost analysis; cost allocation; cost-benefit analysis; cost control; cost savings; cost of illness; health care costs; direct service costs; drug costs; employer health costs; health expenditures; capital expenditures; economics, hospital; hospital charges; hospital costs; economics, medical; fees and charges)

The searches did not yield any relevant cost-effectiveness studies.
4.2 Possible Confounding Factors in Wound Healing Studies

Any investigator conducting a study on wound healing faces a daunting challenge—demonstrating that any observed effect (improvement in healing) is due exclusively to the therapeutic modality (e.g., dressing, ointment, device). This means that investigators must design studies that eliminate, or at least address, potential confounding factors. Failure to do so may compromise outcomes and lead investigators to erroneously conclude that the modality under study improves healing when it actually does not—or does not improve healing when it actually does. Investigators must also choose one or more outcome measures that are not intrinsically flawed and that adequately quantify the healing process. Therefore, any study of wound healing should answer the following basic questions:

- What is the study designed to measure?
- Is the study adequately designed?
- Does the study have a sufficiently large statistical power to detect which a difference in healing between ≥2 therapies?
- Does the study design eliminate confounding factors such as patient heterogeneity, differences in concomitant therapy, or variations within the modality being evaluated?
- Are the outcome measure(s) chosen intrinsically flawed, biased, or inappropriate to assess wound healing?

4.2.1 Study Types

Investigators may choose from many study designs including randomized controlled trials (RCTs), comparative controlled trials, case controlled, crossover, case series, and case reports.

A case report is an anecdotal presentation that cannot quantify the effect of a therapeutic modality. A case series is also inadequate because wounds may heal with little or no intervention, and any summary statistic may only be measuring outcomes for the particular sample of patients, not the effect of the therapeutic modality. For example, suppose investigators used the same modality to treat 2 sets of patients with leg ulcers—except that 1 group of patients had poor circulation and the other had excellent circulation. In this case, healing outcomes would probably differ because of heterogeneity in the sample population—not the treatment effect. A comparative controlled trial is an improvement, but again, differences in outcomes between groups of patients may be due to differences in patients rather than treatment.
An RCT is the optimal study design to evaluate wound healing because individuals are assigned to a treatment group by chance. This design maximizes the chances that any significant differences in outcome measurements are ascribable to treatment and minimizes the chances that the differences are due to characteristics of patients in the study.

RCTs for wound healing may control for treatment effect or patient selection.

In one type of RCT, a patient with similar bilateral lesions undergoes therapy A on one lesion and therapy B on the other lesion. This design controls for patient selection, but attempts to control for treatment effect. The advantage of this design is that there is no possible bias in patient selection. However, the investigator must conclusively demonstrate the effect of the therapy on one lesion is localized and does not affect healing of the other lesion. This is very difficult to prove. Also, it is difficult to blind investigators to treatment, which could lead to bias.

In the other design, investigators randomly allocate patients with similar lesions to different treatment groups. This design controls for treatment effect, but attempts to control for patient selection. The advantage of this design is that there is no bias in effect. However, even treatment groups with apparently randomly assigned patients may differ significantly from each other in 1 or more important patient characteristics. This can pose a problem in studies using only a few patients. Generally, this type of RCT is considered to be the “gold standard” for study design. It is used in most ES studies.

RCTs may be nonblind, single-blind, or double-blind. In a nonblind study, both patients and clinicians know which treatment group the patient has been assigned. (For example, in a study comparing ES and whirlpool therapy for wound healing, patients and clinicians are aware which therapy the patient receives.) Such RCTs may be biased by patients and/or clinicians. In a single-blind study, patients do not know which treatment they receive. (For example, in a study comparing ES device and a sham ES device, the patient may not be aware which therapy he receives, but the clinician knows.) Such RCTs may be unconsciously biased by the clinician. In a double-blind study, patients and clinicians do not know which treatment the patient receives. Such RCTs are unlikely to be biased by patients or clinicians, but are difficult to conduct. For some therapies, it may be technically and/or ethically infeasible to perform single- or double-blind studies.

An RCT of ES for wound healing may be designed to answer 1 or more of the following questions:

- Is ES therapy significantly different from no therapy at all for wound healing?
• Is ES therapy significantly different from conventional or standard therapy for wound healing?

• Is ES with conventional therapy significantly different from conventional therapy alone?

• Is ES therapy significantly different from the best available conventional therapy?

These are important distinctions. An RCT demonstrating that ES is significantly better than no therapy at all (e.g., ES versus a sham unit) does not show that it is as effective as standard therapy.

An RCT for wound healing must have a sufficient follow-up duration, particularly if it measures the percentage of patients who completely heal. The remodeling phase does not begin until at least 3 weeks after injury. Therefore, a study measuring the number of patients healed with only a 3-week follow-up may yield substantially different results than studies with 12- or 16-week follow-up durations.

An RCT should also have sufficient statistical power to demonstrate whether the investigators can detect the hypothesized effect on healing. If the study size is too small, there is probably insufficient power to ascertain whether the effect size is significant (i.e., reaches a specified p level). For example, a study of 10 patients (5 ES, 5 placebo) has insufficient statistical power to determine whether a 20% healing rate among patients receiving ES for 8 weeks is significantly greater than the 0% observed among patients receiving placebo. The same study using 200 patients would have sufficient power.

4.2.2 Confounding Sources

Outcomes of wound healing studies may be confounded by several types of confounding factors:

• Lack of homogeneity of study groups

• Failure to account for systemic or local medical conditions that can interrupt or alter wound healing

• Inconsistencies in regimen of primary wound therapy,

• Inconsistencies in concomitant wound therapy
Differences Between Study Groups—Designing proper RCTs to test a therapeutic modality for chronic wounds is difficult because of differences between patients. In an RCT, one wants to compare the outcomes of groups of patients that have similar characteristics entering the study. For example, if an RCT (with 2 groups of patients) yields significantly different outcomes and there is no (statistically) significant difference between the mean ages of patients in the groups, then one can be reasonably certain that the outcomes are not confounded by the age of the patients. On the other hand, if an RCT (with 2 groups of patients) yields significantly different outcomes and the mean ages of patients in the groups significantly differ, then the outcomes may be correlated to differences in patient ages, not therapy. Differences between patients also compromise case series outcomes.

Relevant patient characteristics include age, gender, and presence of underlying systemic medical conditions (e.g., diabetes mellitus, rheumatoid arthritis). Lesion characteristics include type of wound (e.g., venous, decubitus, diabetic), duration of wound, previous therapies, stage of wound, initial size of wound (e.g., surface area, volume), vascularization (perfusion) around wound site, and infection status.

Medical Conditions Affecting Wound Healing—Outcomes of wound healing studies can be confounded if investigators do not account for systemic medical conditions and local wound conditions that can severely impede or arrest wound healing. Potential factors include obesity, inadequate perfusion to the wound site, anemia, interstitial edema, repeated trauma at site, the presence of foreign bodies, infection, nutritional deficiencies (e.g., proteins, vitamins {A, B, C}, and trace elements {Zn, Fe, Cu}), smoking, radiation exposure, and medications (e.g., exogenous steroids). Diseases predisposing patients to chronic wounds include diabetes mellitus (leading to atherosclerosis, neuropathy, multiple disorders of the immune system, and metabolic abnormalities), chronic venous stasis ulceration, inherited disorders of wound healing (Ehlers-Danlos syndrome {inability to produce normal collagen}, epidermolysis bullosa {inherited failure of adhesion of epidermis, dermis, and basement membrane of skin}, and Marfan’s syndrome {abnormalities in collagen maturation and cross-linking}), connective tissue disorders (e.g., rheumatoid arthritis, osteoarthritis, scleroderma), hematologic disorders (e.g., sickle cell disease, thalassemia, myeloma, cryoglobulinemia, myeloid metaplasia, macroglobulinemia), lymphedema, malignancies, inflammatory bowel disease, and ulcerative necrobiosis lipoidica.

Inconsistencies in Primary Therapeutic Modality—If patients are not treated uniformly, then it is difficult to determine how the treatment affects outcome. For example, if a study of TENS therapy for chronic venous leg ulcerations permitted patients to undergo therapy from 1 to 14 hours per day, assuming that the outcome measurement is not flawed.
the outcomes would be compromised (unless reported per subject and regimen). Patient compliance also potentially confounds outcomes. [See section 5 for critique of individual ES study regimen flaws.]

**Inconsistencies in Concomitant Wound Therapy**—Patients undergoing ES for wound healing often undergo a concomitant standard (or minimal) therapy (e.g., saline-soaked gauze). Concomitant therapy may include debridement (e.g., mechanical/surgical, enzymatic), use of topical and/or cleansing agents, applications of dressings, use of pressure-relieving devices or regimens, and administration of topical or systemic antibiotics. In an RCT, if one group of patients receives a conventional therapy and another group receives ES with a similar concomitant therapy, then any significant difference in outcomes between the groups may be attributed to ES therapy (assuming patient groups do not otherwise differ). On the other hand, if some patients within a treatment group receive different types of dressings and/or debridement agents and/or topical agents, then outcomes may be biased. ES wound healing studies that do not maintain uniform concomitant therapies for patients may not accurately reflect the effect on healing by electrical stimulation.

**4.2.3 Outcome Measures**

Investigators can measure the surface area, depth, volume, or clinical appearance (e.g., granulation tissue, exudate) of an ulceration at any given time.

**Surface Area**—Measurement techniques include planimetry, direct tracing, and stereophotogrammetry. These methods generally employ photographing or tracing a wound and using a computer and/or digitized scanner to directly calculate the surface area. Surface area is the most frequently recorded measurements of wounds. Healing rates may be small, so accurate measurements are essential. If a wound was exactly circular, one could calculate the surface area based on a single accurate measure of the diameter \( (area = \pi \times (d/2)^2) \). If a wound was exactly rectangular, one could calculate the surface area based on 2 accurate measurements, length and width \( (area = length \times width) \). If a wound was exactly oval shaped, one could also calculate the surface area. However, wounds are rarely exact geometric shapes. Multiplying the length times the width of a wound often leads to inaccurate estimations of the surface area. Such systematic errors can lead to erroneous healing rates. Accurate planimetry is essential to properly measure surface area and calculate healing rates.

**Volume**—Ulcerations have 3 dimensions; ulcer depths vary. Surface area only measures 2 dimensions. Therefore, volume is a better measure of wound size than surface area. For example, if two wounds of 5 cm² surface area each undergo the same therapy and heal in 8 weeks, then the average (surface area) healing rate may be expressed as 62.5 mm²/week. If one lesion is 1 mm deep and
the other is 4 mm deep, then the volumetric healing rates substantially differ (62.5 mm³/week versus 250 mm³/week). Calculating the volume of a wound by linear measurements creates inaccuracies. Wounds are not precisely cylindrical (volume = \( \pi \times (d/2)^2 \times \text{depth} \)) or cubic solids (volume = length \( \times \text{width} \times \text{depth} \)). Using such formula can overestimate wound size by \( \geq 20\% \). Accurate volumetric assessment often requires clinical intervention such as filling the lesion with sterile saline and measuring the volume or temporarily molding substances such as Jeltrate (mixture of diatomaceous earth, potassium alginate, calcium sulfate, potassium titanium fluoride, magnesium oxide, tetrasodium pyrophosphate, and spearmint oil) into the wound and measuring the volume. Although some wound healing studies have reported ulcer depths, few, unfortunately, have reported ulcer volume.

**Types of Reported Outcomes**—The efficacy of any therapy for wound healing is based on how rapidly it promotes healing and the percentage of patients who are likely to heal. Investigators have described different outcomes, including:

- time required for all lesions to heal,

- the percentage of lesions healed during a specified period of time (e.g., 4 weeks, 8 weeks),

- mean (± some measure of variance) time for complete healing of lesions,

- mean (± some measure of variance) healing (or reduction) expressed as a percentage of surface area and/or volume of all lesions a specified period of time,

- healing rate (± some measure of variance) = total surface area or volume healed divided by a specified time,

- linear healing rate (± some measure of variance) = average of total surface area or volume healed at different times (e.g., 70 mm² healed at 2 weeks and 150 mm² healed at 5 weeks = average of 32.5 mm² healed/week),

- exponentially modeled healing rate (theta)[see section 6],

- mean (± some measure of variance) of treatment time and percentage of lesions healed,

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\(^m\) Measures of variance include standard deviation (SD), standard error (SE), 95% confidence interval (CI), or variance itself.

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• mean (± some measure of variance) of treatment time and percentage of total surface or volume healed, and

• subjective (clinically-based) grading system accounting for development of granulation tissue, rating of excellent/good/poor healing, etc.

Studies expressing outcomes for each subject provide the best data for analysis. Those providing means and some index of variance are also useful; those failing to provide variances are rarely useful.

Although outcomes reported in wound healing studies are often idiosyncratic and difficult to compare and contrast, they can be classified into several types:

• objective expressions of complete healing,

• objective expressions of the healing rate, and

• subjective assessments describing the healing process.

4.2.3.1 Objective Outcomes: Percentage of Patients Completely Healed

Many wound healing studies report the number (and/or percentage) of patients healed at given time intervals. One might assume that this is a straightforward, simple measurement of a therapy to promote healing. Unfortunately, the number (percentage) of patients healed is a flawed outcome measure because it depends on study follow-up duration and initial wound size.459

Problems with Percentage (or Number) of Patients Totally Healed—We illustrate by the following theoretical example. Suppose we have a 2-group, properly randomized, double-blind RCT: 15 patients in group A receive an experimental therapy and 15 patients in group B receive standard therapy. The surface areas of the lesions at the beginning of the study (i.e., initial size) are as follows:

Group A = 14 cm², 14 cm², 14 cm², 14 cm², 14 cm², 10 cm², 10 cm², 10 cm², 10 cm², 10 cm², 10 cm², 10 cm², 6 cm², 6 cm², 6 cm², 6 cm², 6 cm²

(n = 15 patients)
Group B = 12 cm², 12 cm², 12 cm², 12 cm², 12 cm², 10 cm², 10 cm², 10 cm², 10 cm², 10 cm², 10 cm², 10 cm², 8 cm², 8 cm², 8 cm², 8 cm², 8 cm², 8 cm²

(n = 15 patients)

Further assume that patients in both groups are similar, that there are no known systemic and local medical conditions which could interrupt wound healing, and that there are no inconsistencies in either the experimental or concomitant wound therapies. Group A mean surface area and standard error (SE) is 10.0 ±0.9 cm² (95% CI = 8.1 to 11.9 cm²); group B mean and SE is 10.0 ±0.4 cm² (95% CI = 9.1 to 10.9 cm²). There is no significant difference between these groups.

If the experimental and standard therapies both had a linear healing rate of 1 cm² per week, then after 6 weeks, the percentage of patients healed would be 33% for group A (5 of 15 healed) and 0% for group B. We would detect significantly different percentages of patients healed based exclusively on initial wound size. If the healing rate in the experimental group was 14 cm²/6 weeks and the rate in the control group was 12 cm²/6 weeks, we would observe 100% healing at 6 weeks for both groups. If the healing rate in the experimental group was 1 cm²/week and was 2 cm²/week in the control group, but the follow-up was only 3 weeks, we would observe 0% healing in both groups and erroneously conclude that there was no effect.

In this example, we have shown that a double-blind RCT using the percentage (or number) of healed patients is flawed by dependence on initial wound size and follow-up duration.

Wound healing investigators have considered the percentage of patients healed an important measure of wound healing, because of concerns that a therapy might only “partially” heal lesions—failing to completely heal them. Possible causes of arrested wound healing include inadequate perfusion to the wound site, blood dyscrasias (e.g., anemia), edema, repeated trauma, foreign body, infection, excessive necrotic tissue at wound site, nutritional deficiencies, metabolic disorders steroids, and topical agents inhibiting cell growth. If a wound is healing with a therapy, then appears to stop, it seems more likely that this is due to a physiologic cause rather than a deficiency in the therapy.

4.2.3.2 Objective Outcomes: Healing Rates

Most wound healing studies expressed healing as a rate, usually the percentage of ulcer healed per week.

Many other studies expressed the healing rate as the percentage difference between the initial size of a lesion and the final size divided by the time interval.
For example, if after 5 weeks, lesions were an average of 40% of their initial size, then the healing rate was:

\[
(100\% \text{ initial size} - 40\%) \div 5 \text{ weeks} = 12\%/\text{week}.
\]

This healing rate means little unless we know the initial size of a lesion. One might ask “12% of what?” Without knowing initial lesion size, 12% healing per week could represent 1 cm\(^2\) per week or 10 cm\(^2\) per week. Unfortunately, many wound healing studies neglected to specify initial lesion size.

Many studies provided the initial mean wound size, often with some measure of variance. They often provided healing rates as percentages of lesion healed or in cm\(^2\) healed from initial to final lesion size. In some studies, healing rates were obtained empirically at selected intervals between initial and final lesion sizes and averaged to yield a mean healing rate. Such healing rates assume that healing is linear. There is no evidence that this is true. We examined healing rate curves of ES and conventional therapy RCTs and the relationship often visually appears as an exponential decay. Pierard and Pierard-Franchimont\(^{461}\) recently concluded that chronic leg ulcers heal at uniform, nonlinear rates, following a proportional change process.

We used an exponential decay model to express healing rates for wound healing. [See Section 6 for explanation of the normalized healing rate (?).]

Wound healing rates are generally good measures of the healing process. Unfortunately, the results of nearly all wound healing studies are expressed in healing rates by surface area. These rates may substantially differ from volumetric healing rates which more accurately represent true healing.

### 4.2.3.3 Subjective Outcomes

Subjective, clinically-based rating systems score the development of granulation tissue, the degree of exudate, patient discomfort, and healing. Such rating systems qualitatively describe the healing process. However, they are not standardized and do not present a quantitative measure suitable for comparison with other wound healing studies.
4.3 Quality of Individual Electrical Stimulation Studies of Wound Healing

We evaluated the quality of ES studies for wound healing by study design, sources of confounding, and outcome measures. (Case reports and background studies were excluded.)

For study design, each trial was evaluated to determine the following:

- Type of study
- Whether randomization process was specified (if an RCT)
- Blinding of patients, or patients and clinicians
- Study size

For differences between study groups, each trial was evaluated to determine whether it accounted for the following:

- Patient age and whether it was specified by subject, group (without some measure of variance), or group with some measure of variance
- Gender
- Type of wound (venous, decubitus, mixed)
- Duration of wounds and whether these were specified by subject group (without variance), or group with variance
- Stage or grading of wounds
- Anatomical location of wounds
- Infective status of wounds

For medical conditions affecting wound healing, each trial was evaluated to determine whether it accounted for the following:

- Presence of peripheral arterial or peripheral vascular disease and/or performed pre-therapy vascular perfusion testing
- Presence of rheumatoid arthritis
- Exogenous steroid use by patients
• Nutritional status of patients

For inconsistencies in concomitant wound therapy, each trial was evaluated to determine whether it accounted for possible confounding by the following:

• Debridement
• Use of topical and/or cleansing agents
• Use of dressings
• Use of pressure devices or turning therapy (if applicable)
• Use of topical or systemic antibiotics

For outcome measures, each trial was evaluated to determine whether it
• specified initial wound size by surface area and/or volume, and
• specified initial wound size by subject, group (without some measure of variance), or group with some measure of variance.

Quality assessments for individual ES studies are presented by stimulation type in Table 4.1 (Direct Current), Table 4.2 (Pulsed Current), Table 4.3 (Alternating Current), and Table 4.4 (Pulsed Electromagnetic Induction).

Summaries of flaws and/or deficiencies in ES controlled studies by stimulation type are presented in sections 4.3.1 through 4.3.4. [See section 5 for more details of individual studies.]

4.3.1 Direct Current Controlled Studies

(1) Katelaris et al. (1987)\textsuperscript{462}—A controlled study in which patients were not randomly assigned for LIDC with povidone solution versus povidone solution alone, and LIDC with normal saline dressing versus saline alone for venous lesions

• Small study (average 6 patients per treatment group)
• Duration of lesions not specified
• Lesion size expressed in surface area alone
• No vascular perfusion testing before therapy
• Did not specify whether patients with infected lesions, with peripheral arterial disease, or with rheumatoid arthritis were included or excluded from study

• Did not specify steroid use or nutritional status of patients

(2) Carley & Wainapel (1985)\textsuperscript{463}—RCT of LIDC therapy versus control (saline-soaked gauze) for unspecified lesions

• Did not specify lesion type (e.g., venous, decubitus, diabetic) and therefore may have examined several types of ulcers

• Randomization method not specified

• Lesion size expressed in surface area alone

• No vascular perfusion testing before therapy

• Did not specify whether patients with infected lesions, with peripheral arterial or venous disease, or with rheumatoid arthritis were included or excluded from study

• Did not specify steroid use or nutritional status of patients

• Possibly confounded by dressings used in concomitant therapy

(3) Akers & Gabrielson (1984)\textsuperscript{464}—Comparative (nonrandomized) controlled study of DC with whirlpool (WP) versus DC alone versus WP alone for decubitus lesions

• Small study (average <5 patients per treatment group)

• Did not specify number of patients per treatment group

• Did not specify important patient and lesion characteristics: patient age, gender, anatomical location and duration of lesions, stage of lesions

• Did not provide initial or final size of lesions, so not possible to determine healing rate

• No vascular perfusion testing before therapy

• Did not specify whether patients with infected lesions, with peripheral arterial or venous disease, with diabetes, or with rheumatoid arthritis were included or excluded from study
• Did not specify steroid use or nutritional status of patients

4.3.2 Pulsed Current Controlled Studies

(1) Wood et al. (1993)\textsuperscript{465}—Double-blind RCT of PDC versus sham (placebo) unit for decubitus lesions

• Randomization method not specified
• Lesion expressed in surface area; can only determine crude approximation of volume (surface area multiplied by depth)
• No vascular perfusion testing before therapy
• Did not specify whether patients with infected lesions, with peripheral arterial or venous disease, with diabetes, or with rheumatoid arthritis were included or excluded from study
• Did not adequately specify nutritional status of patients

(2) Gogia et al. (1992)\textsuperscript{466}—RCT of HVPC with WP versus WP alone for lesions of mixed etiology

• Small study (6 patients per treatment group)
• Mixed etiology including diabetic, venous, and decubitus
• Heterogeneous sample population
• Randomization method not specified
• Lesion expressed in surface area alone
• No vascular perfusion testing before therapy
• Did not specify whether patients with infected lesions, with peripheral arterial disease, or with rheumatoid arthritis were included or excluded from study
• Did not adequately specify nutritional status of patients
• Possibly confounded by inclusion of diabetic patients in study
• Possibly confounded by debridement therapy used in study

(3) Gentzkow et al. (1991)\textsuperscript{467}—Double-blind RCT of PDC versus sham (placebo) unit for decubitus lesions

• Randomization method not specified
• Lesion expressed in surface area alone
• No vascular perfusion testing before therapy
• Did not specify whether patients with infected lesions, with peripheral arterial or venous disease, with diabetes, or with rheumatoid arthritis were included or excluded from study
• Did not adequately specify nutritional status of patients
• Possibly confounded by debridement and/or whirlpool (cleansing) therapy used in study

(4) Griffin et al. (1991)\textsuperscript{468}—Single-blind RCT of HVPC versus sham (placebo) unit for decubitus lesions

• Small study (<10 patients per treatment group)
• Randomization method not specified
• Did not specify gender of patients
• No vascular perfusion testing before therapy
• Did not specify whether patients with infected lesions, with peripheral arterial or venous disease, with diabetes, or with rheumatoid arthritis were included or excluded from study
• Did not specify steroid use or nutritional status of patients

(5) Feedar et al. (1991)\textsuperscript{469}—Double-blind RCT of PDC versus sham (placebo) unit for lesions of mixed etiology

• Mixed etiology including decubitus, surgical, vascular, and traumatic
• Heterogeneous sample population
• Randomization method not specified
• Lesion expressed in surface area alone

• Systematic inaccuracies in measurement of surface area because determined as product of length x width

• No vascular perfusion testing before therapy

• Did not specify whether patients with infected lesions or with rheumatoid arthritis were included or excluded from study

• Did not adequately specify nutritional status of patients

• Possibly confounded by debridement and/or whirlpool (cleansing) therapy used in study

(6) Mulder (1991)\textsuperscript{470}—Double-blind RCT of PDC versus sham (placebo) unit for lesions of mixed etiology. This study is an apparent duplication of the study by Feedar et al. (1991). Any discrepancies in the quality assessment between this article and Feedar et al. are due to reporting inconsistencies in the Mulder article.

(7) Unger et al. (1991)\textsuperscript{471}; Abstract—Double-blind RCT of HVPC versus sham (placebo) unit for decubitus lesions

• Small study (<10 patients per treatment group)

• Insufficient data for determining homogeneity of study population

• Did not specify important patient and lesion characteristics: patient age, gender, anatomical location or duration of lesions, stage of lesions

• Did not provide initial or final size of lesions, so not possible to determine healing rates

• No vascular perfusion testing before therapy

• Did not specify whether patients with infected lesions, with peripheral arterial or venous disease, with diabetes, or with rheumatoid arthritis were included or excluded from study

• Did not specify steroid use or nutritional status of patients

• Did not specify any concomitant therapy (e.g., debridement, use of topical or cleansing agents, dressings, antibiotics)
(8) **Kloth & Feedar (1988)**—Single-blind RCT of HVPC versus sham (placebo) unit for decubitus lesions

- Small study (<10 patients per treatment group)
- Differences in patient characteristics
- Lesion expressed in surface area alone
- No vascular perfusion testing before therapy
- Did not specify whether patients with infected lesions or with rheumatoid arthritis were included or excluded from study
- Did not specify steroid use or nutritional status of patients
- Possibly confounded by inclusion of patients with peripheral vascular disease or diabetes in study
- Possibly confounded by debridement therapy used in study

(9) **Feedar & Kloth (1985)**; **Abstract**—Single-blind RCT of HVPC versus sham (placebo) unit for decubitus lesions

- Small study (≤5 patients per treatment group)
- Randomization method not specified
- Did not specify important patient and lesion characteristics: patient age, gender, anatomical location and duration of lesions
- Did not provide initial or final size of lesions, so not possible to determine healing rates
- No vascular perfusion testing before therapy
- Did not specify whether patients with infected lesions, with peripheral arterial or venous disease, with diabetes, or with rheumatoid arthritis were included or excluded from study
- Did not specify steroid use or nutritional status of patients
- Possibly confounded by debridement therapy used in study
4.3.3 Alternating Current and TENS Controlled Studies

(1) Stefanovska et al. (1993)\textsuperscript{474}—RCT of Biphasic AC versus LIDC versus conventional therapy for decubitus lesions

- Randomization method not specified
- Stage of lesions not specified
- Lesions expressed in surface area alone
- No vascular perfusion testing before therapy
- Did not specify whether patients with infected lesions, with diabetes, or with rheumatoid arthritis were included or excluded from study
- Did not specify steroid use or nutritional status of patients
- Did not specify any concomitant therapy (e.g., debridement, use of topical or cleansing agents, dressings, antibiotics)

(2) Lundeberg et al. (1992)\textsuperscript{475}—Double-blind RCT of TENS versus sham (placebo) unit for diabetic ulcerations

- Did not specify patient age or duration of lesions
- Lesions expressed in surface area alone
- Did not specify whether patients with infected lesions were included or excluded from study
- Did not specify steroid use or nutritional status of patients

4.3.4 Pulsed Electromagnetic Induction Controlled Studies

(1) Salzberg et al. (1995)\textsuperscript{476}—Double-blind RCT of PEE device versus sham (placebo) unit for decubitus ulcers

- Randomization method not specified
- Did not specify patient age, anatomical location of lesions, or duration of lesions
• Lesions expressed in surface areas alone
• No vascular perfusion testing before therapy
• Did not specify whether patients with peripheral arterial or venous disease, with diabetes, or with rheumatoid arthritis were included or excluded from study
• Did not specify steroid use of patients

(2) Stiller et al. (1992)\textsuperscript{477}—Double-blind RCT of PEMF device versus sham (placebo) unit for venous ulcers

• Lesions expressed in surface areas alone
• Did not specify whether patients with infected lesions or with rheumatoid arthritis were included or excluded from study
• Did not specify steroid use of patients
• Possibly confounded by debridement therapy, use of dressings, and antibiotic therapy

(3) Todd et al. (1991)\textsuperscript{478}—Double-blind RCT of PEMF versus sham (placebo) unit for venous ulcers

• Small study (≤10 patients per treatment group)
• Randomization method not specified
• Lesion expressed in surface area alone
• Did not specify whether patients with diabetes or with rheumatoid arthritis were included or excluded from study
• Did not specify steroid use or nutritional status of patients

(4) Ieran et al. (1990)\textsuperscript{479}—Double-blind RCT of PEMF versus sham (placebo) unit for venous ulcers

• Lesions expressed in surface area alone
• Did not specify whether patients with infected lesions or with rheumatoid arthritis were included or excluded from study
• Did not specify nutritional status of patients
• Possibly confounded by inclusion of patients with diabetes in study
• Possibly confounded by antibiotic therapy used in study

(5) Jeran et al. (1987)\textsuperscript{480}—Double-blind RCT of PEMF versus sham (placebo) unit for venous ulcers

• Randomization method not specified
• Did not specify patient age or gender
• Lesions expressed in surface area alone
• No vascular perfusion testing before therapy
• Did not specify whether patients with peripheral arterial disease, with diabetes, or with rheumatoid arthritis were included or excluded from study
• Did not specify steroid use or nutritional status of patients
• Possibly confounded by inclusion of infected lesions in study
• Possibly confounded by antibiotic therapy used in study

4.3.5 ES Study Quality: General Findings

All of the controlled trials of ES for the treatment of wound healing have flaws. However, these may or may not be typical for all RCTs for wound healing. See section 7 for a comparison of the quality of ES studies with non-ES studies for wound healing.
### 4.4 Tables

**Table 4.1. Assessment of Quality of Direct Current Stimulation Studies of Wound Healing**

<table>
<thead>
<tr>
<th>Study Specified...</th>
<th>Katelaris(^{481})</th>
<th>Carley(^{482})</th>
<th>Akers(^{483})</th>
<th>Gault(^{484})</th>
<th>Wolcott(^{485})</th>
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<td>Stimulation Type</td>
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<td>DC</td>
<td>LIDC</td>
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Table 4.1. Assessment of Quality of Direct Current Stimulation Studies of Wound Healing (continued)

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<tr>
<th>Study Specified...</th>
<th>Katelaris(^{481})</th>
<th>Carley(^{482})</th>
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Embedded RCT (study comparing bilateral lesions on same patient) not applicable to quality assessment
Group + variance = study specified some measure of variance
Excluded: Fakhri & Amin\(^{486}\) (background study)
Assimacopoulos\(^{487}\) (case report)
### Table 4.2. Assessment of Quality of Pulsed Current Stimulation Studies of Wound Healing

<table>
<thead>
<tr>
<th>Study Specified...</th>
<th>Wood⁴⁸⁸</th>
<th>Gogia⁴⁸⁹</th>
<th>Gentzkow⁴⁹⁰</th>
<th>Griffin⁴⁹¹</th>
<th>Feedar⁴⁹²</th>
<th>Mulder⁴⁹³</th>
<th>Unger, Eddy⁴⁹⁴ [Abstract]</th>
<th>Kloth⁴⁹⁵</th>
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Table 4.2. Assessment of Quality of Pulsed Current Stimulation Studies of Wound Healing (continued)

<table>
<thead>
<tr>
<th>Study Specified...</th>
<th>Wood 488</th>
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Group + variance = study specified some measure of variance

Excluded:
- Fitzgerald & Newsome 497 (case report)
- Weiss et al. 498 (background study)
- Unger 499 (abstract on wounds?)
Table 4.2. Assessment of Quality of Pulsed Current Stimulation Studies of Wound Healing (continued)

Mawson et al.\textsuperscript{500} (background study)
Ross & Segal\textsuperscript{501} (case report)
Thurman & Christian\textsuperscript{502} (case report)
Table 4.3. Assessment of Quality of Alternating Current Stimulation Studies of Wound Healing

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Table 4.3. **Assessment of Quality of Alternating Current Stimulation Studies of Wound Healing** (continued)

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*Group + variance = study specified some measure of variance*
*Excluded: Finsen et al.510 (background study)*
*Lundeberg et al.511 (background study)*
Table 4.3.  **Assessment of Quality of Alternating Current Stimulation Studies of Wound Healing**
(continued)

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286961.WGE
### Table 4.4. Assessment of Quality of Pulsed Electromagnetic Induction Studies of Wound Healing

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286961.WGE
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Group + variance = study specified some measure of variance
Excluded: Wilson\textsuperscript{521} (background study)
Tung et al.\textsuperscript{522} (case report)
Goldin et al.\textsuperscript{523} (background study)
5.0 Electrical Stimulation Study Descriptions and Outcomes

The second part of our analysis of ES for the treatment of wound healing consists of basic study descriptions and outcomes as reported by investigators.

ECRI's analysis included all published studies of ES for the treatment of chronic wound healing. We defined a chronic wound as a (non-burn-induced) lesion of \( \geq 30 \) days duration. [See section 4.1.] Many studies did not specify wound duration. (The absence of lesion duration data is specified in Tables 4.1 through 4.4.) [See section 4.3.]

Published studies were categorized as

- direct current (DC) stimulators,
- pulsed current (PC) stimulators,
- alternating current (AC), including TENS, stimulators,
- pulsed electromagnetic induction (PEMI) stimulators, and
- spinal cord stimulators (SCS).

Studies within each category were classified as

- uncontrolled (case series or case reports), or
- controlled (randomized controlled (RCT), case-controlled, or comparative controlled).

Properly designed RCTs are the most important type of studies for evaluating wound healing therapies because they determine whether differences between 2 or more treatments are due to the treatments—without confounding by patient heterogeneity. [See section 4.2.1.] Uncontrolled studies, on the other hand, either report outcomes from case reports or outcomes that may reflect characteristics of the patients being studied—not the effect of therapy. [Uncontrolled ES studies of wound healing presented in the following sections cannot be used to quantitate efficacy. We present them merely as background studies.]
5.1 Direct Current Studies

Outcomes of DCS of wound healing (as reported by study investigators) are presented in Table 5.1. Studies in sections 5.1.1 and 5.1.2 are presented in chronological order.

5.1.1 Uncontrolled Studies

Assimacopoulos\textsuperscript{524} conducted the first clinical study (case reports) of low intensity direct current (LIDC) on 3 patients with chronic venous ulcers. Each patient received between 50 and 100 µA and 0.25 to 0.80 V with the negative electrode (cathode) over the ulceration site and the positive electrode (anode) placed on the lateral thigh. All ulcers completely healed 32, 40, and 42 days after therapy.

Wolcott et al.\textsuperscript{525} treated 83 ischemic ulcers (including paraplegic, venous stasis, and peripheral arteriosclerotic etiology) on 67 patients with LIDC. Before ES therapy, nonviable tissue surrounding the lesions was debrided and scrubbed with antibacterial detergent. Details of this ES protocol are discussed in section 3.2. Briefly, it consisted of giving patients three 2-hour sessions of 600 to 800 µA daily (2 hours therapy on and 4 hours off) and switching electrode polarity after 3 days for noninfected ulcers or, if infected, 3 days after the infection healed. Fresh gauze was placed in the site daily with cleansing and adjustments in current flow as deemed appropriate. (The investigators did not specify specific current adjustments, which could affect outcomes, making it difficult for subsequent investigators to reproduce them.) When there was no apparent improvement ("growth plateau"), electrode polarity was switched every 24 hours until sites completely healed. Lesion size was assessed before therapy and at weekly intervals afterward by measuring the volume of normal saline needed to fill the wound. Therapy was discontinued after 16 weeks or if the wound healed. The study consisted of 2 parts: a case series evaluation of 75 ischemic lesions, and an "embedded" RCT\textsuperscript{a} using 8 patients with contralateral lesions. In the case series evaluation, 53 paraplegic lesions had an 80.5% mean decrease in volume (9.3% weekly decrease) in a mean of 8.7 weeks; 15 arteriosclerotic lesions had an 82.2% volume decrease (14.0% weekly decrease) in 5.9 weeks; and venous stasis ulcers had an 85.0% volume decrease (14.4% weekly decrease) in 5.9 weeks. Forty percent of the ulcerations healed, but the investigators did not specify the time required for them to heal. The weighted mean decrease of ulcer volume was 81.8% during a mean of 7.7 weeks, which the investigators presented as a mean (linear) healing rate of 13.4% per week. There was insufficient data presented to verify whether healing was, indeed, linear. These healing rate outcomes as reported are not useful for

\textsuperscript{a} Patients with bilateral lesions (within a case series) treated by ES on one lesion and a non-ES therapy (control therapy) on the contralateral lesion.
comparison with other therapies because the investigators did not specify initial wound sizes. [See sections 4 and 6.]

Gault and Gatens\textsuperscript{526} treated 76 patients who had 106 ischemic lesions (including sequelae of quadriplegia, paraplegia, cerebral vascular accident brain tumor, cardiac disease, peripheral vascular disease, burns, diabetes, tuberculosis, fractures, and amputations) using a similar LIDC regimen to Wolcott et al., except that they reversed the polarity only once. The investigators did not specify whether they measured lesion volume and/or surface area. The study consisted of 2 parts: a case series evaluation of 100 ischemic lesions, and an embedded RCT using 6 patients with contralateral lesions. In the case series evaluation, 100 ulcers were treated over a range of 3 days to 24 weeks. After a mean of 4.7 weeks, 80.5\% of the ulcers treated had healed. The mean healing rate was 28.4\% per week. Outcomes reported by these investigators cannot be readily compared with other therapies because the investigators combined outcomes of different types of ischemic ulcers (e.g., vascular, diabetic) and did not specify initial lesion size for normalization.

Fakhri & Amin\textsuperscript{527} used a Baghdad elastoplast device (1 cm wide aluminum foil sandwiched between 2 cm wide lint and 3 cm wide adhesive plaster) delivering 10 to 20 mA current and 10 to 25 V on 20 patients with full-, mixed-, or partial-thickness burns that had failed to respond to conventional therapy. The reported regimen was an indeterminate treatment setting and duration twice weekly. The investigators reported that all burn sites healed in 2 weeks to 4 months. They provided no data on initial lesion size.

5.1.2 Controlled Studies

Wolcott et al.\textsuperscript{528} randomized some of the patients from the case series [see section 5.1.1], using 8 patients (6 paraplegics, 1 with chronic varicosities, 1 with rheumatoid arthritis) with contralateral lesions in an “embedded RCT.” Patients underwent LIDC therapy on 1 lesion and saline-soaked gauze therapy on the other. Three-quarters of LIDC-treated lesions healed after 15.4 weeks compared to none of the conventionally treated. All patients had greater healing of 1 lesion (volumetric measurement) by LIDC than by conventional therapy. The weekly healing rate (volumetric decrease in lesion size per week) was 27.0\% for LIDC therapy compared to 5.0\% for controls. This study suffers from 2 major weaknesses. First, because the investigators did not specify initial lesion sizes, we cannot be certain that bilateral lesions on patients were the same size. Substantial differences in lesion size, even on the same patient, can lead to substantially different healing rates expressed as percentages [see section 4]. Second, the investigators did not demonstrate that the effect of LIDC is localized to the treatment site and has no effect on the contralateral lesions. This may confound outcomes.
Gault and Gatens\textsuperscript{529} also randomized 6 patients from their case series) [see section 5.1.1] with contralateral lesions. Patients underwent LIDC therapy on one lesion and conventional therapy on the other lesion. After a mean of 4 weeks, the mean percentage of lesion healed was 74.0\% for LIDC-treated lesions and 27.3\% for conventionally treated lesions. The mean healing ratio (percentage of lesion healed per week) was 30.0\% for LIDC- and 14.7\% for conventionally-treated lesions. This study suffers from 4 major weaknesses. First, the investigators did not specify initial lesion size. Second, they did not specify whether lesion size was measured by surface area and/or volume. Healing rates by surface area may substantially differ from healing rates by volume. Third, they did not demonstrate that the effect of stimulation is localized to the treatment site. Fourth, they did not specify the type of ulcer (e.g., venous, decubitus, diabetic), which also influences the percentage of patients healing and healing rates.

Akers & Gabrielson\textsuperscript{530} conducted a controlled comparison among patients with decubitus ulcers undergoing high-voltage direct current (galvanic) stimulation (DC) with whirlpool (WP) therapy twice daily, DC alone, and WP once daily. The investigators found no significant difference between the healing rates of these therapies. However, this study has several weaknesses. First, the investigators did not specify treatment regimen or ES parameters. Second, they did not specify the number of patients in each treatment group. Third, they did not provide any patient characteristics (e.g., age) or lesion data (e.g., duration, stage). Fourth, they did not specify initial lesion sizes.

In an RCT, Carley & Wainapel\textsuperscript{531} treated 15 patients who had unspecified lesions by a regimen similar to Wolcott et al. (2-hour daily sessions of 300 to 700 \textmu A twice daily) and 15 by conventional therapy. They matched patients in each treatment group by age, diagnosis, wound size, and wound etiology. They reported patients undergoing LIDC healed 1.5 to 2.5 times faster than those treated conventionally. Wounds were significantly smaller by LIDC therapy than conventional therapy after 3 weeks (LIDC = 1.11 \pm 0.42 cm\(^3\) {SD}, control = 2.62 \pm 0.98 cm\(^3\)\(^\text{3}\); 4 weeks (LIDC = 0.69 \pm 0.26 cm\(^3\), control = 2.48 \pm 0.85 cm\(^3\)\(^\text{3}\)); and 5 weeks (LIDC = 0.50 \pm 0.20 cm\(^3\), control = 2.16 \pm 0.88 cm\(^3\)). This study suffers from 3 flaws. First, the most important shortcoming is that the investigators did not specify the types of lesions treated. We cannot determine whether these outcomes pertain to venous, decubitus, and/or diabetic ulcerations. Second, the follow-up duration is only 5 weeks. [See section 4.2.1.] From data provided, we cannot determine whether LIDC-treated wounds completely heal faster than controls. Third, the outcomes may be confounded because of differences in concomitant therapy. Some patients received saline-damped gauze whereas others received “... various absorption gels daily...” The investigators did not demonstrate that these differences did not bias outcomes from the LIDC- and/or conventionally treated groups.
Katelaris et al.\textsuperscript{532} conducted a comparative (nonrandomized) controlled trial on 24 patients with venous leg ulcers. Four patients received LIDC with povidone-iodine soaked gauze, 11 received povidone-iodine therapy alone, 5 received LIDC with saline-soaked gauze, and 4 received saline-soaked gauze alone. LIDC therapy was 20 \( \mu \)A current using a regimen similar to Wolcott et al. The investigators observed no significant difference in healing between the groups. LIDC with povidone-treated patients healed in 85.3 ±7.2 days (mean ± SE) compared to 49.2 ±4.3 days for those treated by povidone alone; LIDC with saline-treated patients healed in 45.9 ±6.4 days compared to 46.1 ±7.2 days. This study has 2 flaws. First and foremost, the sample size is very small. The study suffers from lack of statistical power. Three of the 4 treatment groups have \( \leq 5 \) patients. This study would not be able to detect any significant difference between groups unless there was a huge effect size. Second, patients were apparently not randomly assigned to groups.
5.2 Pulsed Current Studies

Outcomes of PC studies of wound healing (reported by study investigators) are presented in Table 5.2. Studies in sections 5.2.1 and 5.2.2 are presented in chronological order.

5.2.1 Uncontrolled Studies

Thurman & Christian\textsuperscript{533} treated a diabetic patient who had a draining abscess to a “high frequency” direct current once or twice daily for 4 weeks. The lesion healed within 4 months.

Ross & Segal\textsuperscript{534} reported treating 2 patients following foot surgery with HVPC (negative polarity at wound site, 4 Hz pulses for 15 minutes, then reversed polarity with 80 Hz pulses). Patients reported minimal postoperative pain and swelling.

Weiss et al.\textsuperscript{535} treated donor skin graft sites of 4 patients with pulsed current stimulation (peak current = 35 mA, frequency = 128 Hz, pulse width = 150 $\mu$s) with positive polarity for two 30-minute sessions for a week. They observed reduced scar thickness and hypertrophic scar formation.

Unger\textsuperscript{536} reported treating 223 wounds (average duration 2.4 months) with HVPC (150 V or 750 mA peak current at 50 Hz, negative polarity initially over wound for 6 days). They reported 200 wounds (89.7\%) healed in a mean healing time of 10.85 weeks (54.25 days). However, the investigators did not specify wound type and omitted important specifics of the regimen (length of treatment sessions, number of session per day, duration of treatment).

Fitzgerald & Newsome\textsuperscript{537} treated a quadriplegic patient who had a large wound overlying the thoracic spine to monophasic HVPC (100 to 200 V, 80 to 100 Hz) for daily 1-hour sessions (switching polarity after 20 minutes). The ulcer healed after 10 weeks.

Mawson et al.\textsuperscript{538} found that HVPC (75 V, 10 Hz) increased the typically low levels of sacral transcutaneous oxygen tension in patients with spinal cord injuries.

5.2.2 Controlled Studies

In a single-blind RCT, Feedar & Kloth\textsuperscript{539} treated patients who had stage IV decubitus ulcers to HVPC (100 V, 105 Hz, 100 $\mu$s intraphase interval, polarity reversed after 3 days) or a sham device for daily 45-minute sessions (5 sessions per week, 4 to 16 weeks). Five patients underwent HVPC therapy; 3 received placebo therapy. All HVPC patients healed (in a mean of 7.3 weeks).
HVPC-therapy wounds decreased a mean of 25.3% per week whereas placebo-therapy wounds increased a mean of 13.8% per week (in a mean of 10.6 weeks). The investigators did not provide initial lesion sizes.

In a subsequently published study, Kloth & Feedar used the same therapeutic regimen on 16 patients with stage IV decubitus ulcers (9 HVPC, 7 sham). All HVPC-therapy lesions had healed after 16 weeks, but none of the placebo-therapy lesions had healed after 17 weeks. The mean (and SD) healing rate of HVPC-treated wounds decreased 44.8% ±22.6% per week compared to an 11.6% ±18.6% increase per week for placebo-treated wounds. This study has 2 flaws. First, lesion etiologies of the study groups are dissimilar (heterogeneous). The primary diagnoses of the treatment group includes 3 patients with diabetes, 2 with cerebrovascular accidents, 2 with peripheral vascular disease, 1 with a pilonidal cyst, and 1 with a lower extremity fracture; primary diagnoses of the control group include 1 patient with diabetes, 2 with cerebrovascular accidents, 0 with peripheral vascular disease, 1 with a pilonidal cyst, 0 with a lower extremity fracture, 1 with a stasis ulcer, 1 with anemia, and 1 with senile dementia. Adequate perfusion and nutrition are essential for wound healing. The differences between these groups includes patients with substantially different levels of perfusion and nutrition (e.g., diabetes, peripheral vascular disease, anemia), which can affect wound healing. Such heterogeneity in conjunction with small study groups may confound outcomes. Second, some patients underwent additional debridement by Biozyme-C®. Unless we know which patients (or at least the proportional number) in each group who received Biozyme-C debridement, the outcome may be confounded by this inconsistency in concomitant therapy.

Unger et al. performed a double-blind RCT on patients with pressure ulcers. Nine patients received the same HVPC therapy specified by Unger in section 5.2.1; 8 patients underwent placebo-therapy with a sham device. Eight HVPC-treated patients (88.9%) healed, whereas 3 placebo-treated patients (37.5%) healed. HVPC-treated wounds healed in an average of 51.2 days compared to 77.0 days for those treated by sham devices. This study has several weaknesses. (Some of these shortcomings may be reporting omissions because this was an abstract.) First, the study is small and therefore has low statistical power. Second, the study did not provide sufficient patient and lesion characteristic data to ascertain whether these groups are similar (homogeneous). The investigators did not specify lesion stage which can affect healing rates and percentage of patients who completely heal. Third, the study did not provide initial lesion size. Fourth, the investigators did not specify any elements of concomitant therapy (e.g., debridement, dressings). Unless one knows that the concomitant therapy did not vary within or between treatment groups, one cannot be certain that inconsistencies in this therapy did not confound outcomes.

In a double-blind RCT, Feedar et al. treated 50 patients who had stages II through IV decubitus ulcerations of mixed etiologies. Twenty-six patients
(22 stage III, 4 stage IV) received PDC therapy (30-minute sessions BID of 35 mA at 128 Hz every day for 4 to 16 weeks, polarity reversed every 3 days after wound debrided); 24 patients (2 stage II, 17 stage III, 5 stage IV) received sham-therapy. The frequency was reduced to 64 Hz when stage III or IV lesions improved to stage II. After 4 weeks, none of the patients had healed in either group. The investigators reported a significantly greater reduction in the percentage of wound size after 4 weeks with PDC therapy (43.9% of original size) than sham therapy (67.2%). PDC-treated lesions healed an average of 14%/week compared to 8.25%/week for sham-treated lesions. Mulder also reported outcomes from this study, noting that, after 4 weeks, 38.5% of PDC-treated lesions exhibited excellent healing (<25% of their original size) versus 20.8% for sham-treated, 53.8% exhibited good healing (50% to 75% of original size) versus 33.3%, and 7.7% exhibited poor healing (≥75% of original size) versus 45.8%. Fourteen patients in the sham group “crossed over” to PDC; 6 (42.9%) of these completely healed. This study has many potential shortcomings. First, the study groups combined patients with acute duration lesions (<1 month) with long-standing lesions (>12 months). Although the percentages of these patients do not significantly differ among the groups, combining these patients makes it difficult to interpret outcomes. Second, the groups combined patients with different etiologies: decubitus (65% of PDC group, 75% of control group); postoperative (23% of PDC, 13% of controls); vascular (0% of PDC, 4% of controls); and traumatic (12% of PDC, 8% of controls). These may not confound the outcomes, but unless outcomes are provided separately for these different types of lesions, the results may be difficult to interpret. Third, the investigators expressed surface area of lesions as the product of length multiplied by width. As stated previously [see section 4], length times width is an accurate measurement of surface area only if the wound is exactly rectangular. This introduces a systematic error in all outcome measurements. Fourth, the investigators changed the pulse rate from 128 Hz to 64 Hz when lesions improved to stage II. However, they did not provide individual patient or summary data for these changes in ES therapy. Without such data, it is difficult to interpret whether the change in frequency altered the healing rate or confounded PDC outcomes. Fifth, the follow-up duration of most patients in the study was too short. Only 12 patients (46%) of the PDC group were followed for at least 8 weeks. Six patients of the 14 patients followed for <8 weeks had lesions ≤20% of their original size, indicating that a longer follow-up time might have yielded substantially different total healing rates. Sixth, some patients received surgical or whirlpool debridement. Although 10% of both patient groups received debridement, this therapy was not consistent because surgical debridement may have been used predominantly in one group compared to whirlpool debridement. This could confound outcomes.

In a single-blind RCT, Griffin et al. treated 17 patients who had grade II through IV decubitus ulcers. Eight patients (2 grade II, 5 grade III, 1 grade IV) received HVPC therapy (1 hr daily sessions of 200 V at 100 Hz for 20 days, no polarity reversal) and 9 patients (2 grade II, 6 grade III, 1 grade IV) received...
sham therapy. After 20 days, 3 HVPC lesions (37.5%, including 2 grade II and 1 grade III) and 2 sham-therapy lesions (22.2%, both grade II) had healed. This study had 3 major shortcomings. First, study groups were small. There is insufficient statistical power for concluding the efficacy of HVPC for grade II decubitus lesions, much less more severe ulcerations. Second, the follow-up duration is short. The last phase of healing does not normally begin until 3 weeks after injury. The follow-up time is probably inadequate to observe complete healing of grade II lesions, let alone more severe lesions extending through subcutaneous tissue. Third, the investigators only provided the median initial lesion size. A median is often an inadequate measure of distribution, especially in nonnormal distributions (e.g., bimodal).

In a double-blind RCT, Gentzkow et al. treated 21 patients who had decubitus ulcers. Twenty-one stage IV patients received an PDC therapy nearly identical to Feedar et al. (1991); 19 patients (1 stage III, 18 stage IV) received sham-therapy. The investigators reported a significantly greater healing in the percentage of wound size after 4 weeks with PDC therapy (49.8%) than by sham therapy (23.4%). PDC-treated lesions healed an average of 12.5%/week compared to 5.8%/week for sham-treated lesions. Fifteen patients in the sham group “crossed over” to PDC; after 4 weeks of stimulation, the percentage of surface area healed was 47.9%, significantly greater than with previous sham therapy. This study had outcomes and shortcomings similar to Feedar et al. (1991). First, the study groups combined patients having acute duration lesions (<1 month) with long-standing lesions (>12 months), which makes it difficult to generalize outcomes. Second, the investigators expressed surface area of lesions as the product of length multiplied by width, introducing a systematic error in all outcome measurements. Third, the investigators changed the pulse rate from 128 Hz to 64 Hz when lesions sufficiently improved without providing individual patient or summary data for these changes. Fourth, the investigators reported on the percentage of ulcers healed at 1, 2, 3, and 4 weeks after initiating therapy and found significant differences between PDC and sham therapy at 1, 2, and 4 weeks. However, it appears that they used repeated t-tests between these intervals. If so, this is invalid. A more proper test would have been an analysis of variance (ANOVA) to reduce the risk of finding a statistically significant result that was due to chance.

In an RCT, Gogia et al. treated 12 patients who had stage III lesions (full-thickness skin loss) of mixed etiologies on the leg or foot. Six patients (3 diabetic, 2 decubitus, 1 venous stasis) received HVPC therapy (daily 20-minute sessions of 250 V at 100 Hz for 20 days, negative polarity for 4 days, positive polarity for

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Grade II: a break in or blistering of the epidermis, surrounded by erythema and induration; Grade III: a shallow, irregular defect extending through the dermis to the subcutaneous fat junction; Grade IV: ulcer extending through the full thickness of the skin into the subcutaneous tissue, fascia, or muscle.

Medians are often reported when data are highly variable.
16 days) and 6 patients (2 diabetic, 3 decubitus, 1 venous stasis) received whirlpool therapy. After 20 days, 37.4% of HVPC-treated lesions had healed compared to 27.2% for control lesions. The healing rates did not significantly differ. This study has several weaknesses. First, these study groups are small, so this study has little statistical power. Second, lesion etiologies are heterogeneous. Patients in these groups have substantially different degrees of tissue perfusion. (Diabetics would be expected to have worse tissue perfusion than patients with venous stasis ulcerations.) Although there is no significant difference between the types of patients in each treatment group, such differences can confound interpretation of outcomes, particularly in studies with such small sample sizes. Third, the investigators did not provide a measure of variance for interpreting healing rates. Fourth, the follow-up time was only 20 days, which is inadequate to observe complete healing. Fifth, some patients had debridement, which may confound outcomes by inconsistencies in concomitant therapy.

In a double-blind RCT, Wood et al. treated 78 patients who had stage II or III decubitus ulcerations. Forty-three patients underwent PDC therapy (300 µA followed by 600 µA at 0.8 Hz, 3 times weekly, initial negative polarity) and 31 patients received sham therapy. Three patients (2 PDC and 1 sham therapy) were lost to follow-up. After 8 weeks, 25 (58%) of the PDC-treated ulcers healed compared to one (3%) of the sham-treated ulcers. Seventy-three percent of PDC ulcers decreased 80% within 8 weeks compared to 13% of sham-treated ulcers. Surface area and ulcer depth healing rates were significantly greater with PDC therapy than sham therapy. The major flaw of this study was that the investigators did not specify the duration of each treatment session.
5.3 Alternating Current (and TENS) Studies

Outcomes of alternating current studies of wound healing (reported by study investigators) are presented in Table 5.3. Studies in sections 5.3.1 and 5.3.2 are presented in chronological order.

5.3.1 Uncontrolled Studies

Westerhof & Bos\textsuperscript{548} treated a patient who had severe (trigeminal) neurotrophic facial ulcers with 30-minute sessions of TENS therapy TID (sufficient energy to cause vigorous contractions, 120 Hz, 250 \( \mu \text{s} \) pulse width, 0.5 sec pulse train interval). The ulcerations healed after 6 weeks of therapy.

Kaada\textsuperscript{549} treated 10 patients who had ulcers of mixed etiology (traumatic neuropathy, arteriosclerosis, venous stasis ulcers, thrombophlebitis, decubitus ulcers, and scleroderma) to TENS therapy. Patients used a pocket stimulator to apply trains of 5 pulses (15 to 30 mA at 100 Hz internal frequency, 0.1 to 0.2 ms duration) for 30- to 45-minute sessions TID. Seven of the lesions healed after 22 weeks.

Barron et al.\textsuperscript{550} treated 6 patients who had decubitus ulcers with a "percutaneous low-energy nongalvanic stimulator." The stimulation was a modified biphasic square wave of 600 \( \mu \text{A} \), 50 V at 0.5 Hz administered percutaneously by electrodes positioned 2 cm from the edge of the ulcer. Patients underwent sessions TID (of unspecified duration) for 3 weeks. Two patients (22.2\%) completely healed and 3 others nearly healed (remaining surface area <0.1 cm\(^2\)).

In an abstract, Alon et al.\textsuperscript{551} reported treating 15 patients who had diabetic foot ulcers with "high voltage TENS" therapy. Patients underwent stimulation by 200 V, 80 Hz, 5 to 10 \( \mu \text{s} \) pulse durations for 1-hour sessions TID. Twelve patients (80\%) healed in a mean of 11.1 weeks.

Kaada & Emru\textsuperscript{552} treated 32 patients suffering from leprosy with TENS therapy. Patients used a pocket stimulator to apply trains of 5 pulses (25 mA at 100 Hz internal frequency, 0.1 to 0.2 ms duration) for 30-minute sessions, BID, 5 to 6 days per week. Fifty-nine percent of the patients healed after 12 weeks of therapy; all of those who completed therapy healed in a mean of 5.2 weeks. The mean healing index was 1.0 cm\(^3\) per week and was 3 times greater in patients with tuberculous leprosy than those with the lepromatous type.

Frantz\textsuperscript{553} treated 4 patients who had decubitus ulcers with 30 minutes of TENS therapy TID (30 mA at 85 Hz, constant square-wave pulses, 150 \( \mu \text{s} \) pulse width, 1 set of electrodes on hands and other set with anode proximal and cathode distal to lesion). After 4 weeks, 1 lesion had healed.
Karba et al. treated 32 patients who had vascular wounds (diabetes or peripheral vascular disease), 14 patients with decubitus ulcers, and 17 patients with posttraumatic wounds with a biphasic, asymmetrical alternating current of 15 to 25 mA (4 second trains at 40 Hz repetition, 0.25 ms pulse duration) for 1-hour daily sessions. Forty-nine wounds (77.8%) healed in the rehabilitation center and an additional 11 (17.4%) healed 2 to 3 weeks after discharge. All decubitus lesions had healed after 5.5 weeks; 90.6% of all vascular lesions had healed after 10 weeks. The investigators calculated the healing rate based on an exponential model. Healing was described by a normalized healing rate, theta (θ), which is normalized to the initial wound size. [See section 6.] Theta is calculated as follows:

\[ \theta = \frac{\ln\left(\frac{S_0}{S}\right)}{t} \]

where \( S_0 \) is the initial wound size, \( S \) is the size of the wound at a given time \( t \), and \( t \) is the time (usually expressed in weeks). Theta describes the rate of wound healing. Values of \( \theta > 0 \) imply that the wound is healing; greater positive values of \( \theta \) imply faster healing. Values of \( \theta < 0 \) imply that the wound, in fact, is growing larger; greater negative values of \( \theta \) imply increased wound deterioration. At \( \theta = 0 \), the wound is neither healing nor deteriorating. The investigators observed that the healing rates depended on the type of wound. The normalized healing rates were \( \theta = 1.02 \pm 0.26 \) (SE) per week for post-traumatic lesions, \( \theta = 0.83 \pm 0.33 \) per week for decubitus ulcers, and 0.47 ±0.09 per week for vascular lesions.

5.3.2 Controlled Studies

Finsen et al. treated 51 patients who were scheduled to undergo a Syme’s, below-knee, or through-knee amputation for ischemic changes due to diabetes or arteriosclerosis. Patients either underwent TENS stimulation, sham TENS therapy, or sham TENS therapy and chlorpromazine. The investigators reported fewer re-amputations and more rapid stump healing among below-knee amputees who had received active TENS, and that sham therapy decreased pain. However, this study did not directly address wound healing.

In a single-blind randomized trial, Lundeberg et al. treated 24 patients who had recently undergone reconstructive surgery for breast cancer with TENS therapy or sham stimulation. The investigators primarily evaluated blood flow to the postoperative skin flaps and did not specify the rate of wound healing. In a subsequent randomized crossover trial on 20 patients, Kjartansson & Lundeberg observed that local blood flow and capillary refill significantly increased in skin flaps treated by TENS therapy. The study did not directly address wound healing.
Frantz reported preliminary findings in an ongoing RCT employing TENS therapy described in section 5.3.1. However, the report only included 3 patients, which is insufficient for analysis or critique.

In a double-blind RCT, Lundeberg et al. treated 64 patients who had diabetic leg ulcers. Thirty-two patients received TENS therapy (AC constant current square-wave pulses applied outside the ulcer surface at sufficient intensity to evoke paresthesia, 1 ms pulse width at 80 Hz, 20-minute sessions BID) and 32 patients received sham therapy. The polarity was changed after each session. After 4 weeks, 12% of TENS lesions had healed compared to 7% of those treated by sham units. After 8 weeks, 25% of TENS-treated lesions had healed compared to 11% of sham treated. After 12 months, 42% of TENS-treated had healed compared to 15% of sham treated. The only shortcoming of this study was that it did not describe the diabetic population in the study (e.g., insulin-dependent versus non-insulin-dependent), which could affect outcomes.

In an RCT, Stefanovska et al. treated 150 patients who had decubitus ulcers with AC, DC, or conventional therapy. Eighty-two patients received biphasic AC therapy similar to Karba et al.[see section 5.3.1], except that sessions were 2 hours daily; 18 patients received LIDC therapy (600 µA for two hours daily); 50 control patients received conventional therapy. The investigators reported normalized healing rates (expressed in percent per day) of $\gamma = 5.43\% \pm 4.4\%$ (SD) per day for AC-treated ulcers, $\gamma = 3.11\% \pm 3.83\%$ for LIDC-treated ulcers, and $2.21\% \pm 3.27\%$ for controls. They stated that AC current produced a significantly greater rate of normalized wound healing than controls. This study has several shortcomings. First, the investigators did not specify the stage of decubitus ulcers in the study. Without knowing the number or type of ulcer stages in each treatment group, the outcomes may be confounded. For example, if the AC group consisted primarily of stage II lesions and the control group consisted primarily of stage IV lesions, we would expect slow healing rates in the control group. Second, the investigators did not specify the “conventional therapy” used on the control group. Without knowing the regimen, the therapy may not reflect accepted standards of care. Third, they did not specify what type of concomitant therapy was administered to patients in the AC and LIDC groups. This could potentially confound outcomes.
5.4 Pulsed Electromagnetic Induction Studies

Outcomes of pulsed electromagnetic induction (PEMI) studies of wound healing (as reported by study investigators) are presented in Table 5.4. Studies in sections 5.4.1 and 5.4.2 are presented in chronological order.

5.4.1 Uncontrolled Studies

Itoh et al. treated 22 patients who had stages II and III decubitus ulcers of mixed etiology (cerebrovascular accident, multiple sclerosis, spinal cord injury, and diabetes) with pulsed, nonthermal, high-frequency, high peak power electromagnetic energy (27.12 MHz, 80 to 600 pulses/sec, 65 µs pulse width, 293 to 975 W/pulse peak) administered from a device placed on the surface of the wound dressing. Patients underwent 30-minute sessions BID until lesions healed. All 9 stage II patients healed after 6 weeks of therapy; all 13 stage III patients healed after 22 weeks of therapy. However, the patient groups were heterogeneous (e.g., diabetic and nondiabetic). Concomitant therapy variations included cleansing agents (e.g., hydrogen peroxide, normal saline, povidone-iodine) and dressings (e.g., Bacitracin ointment, povidone iodine wet-to-dry, acetic acid wet-to-dry, Vaseline gel, Silvadene, hydrogen peroxide wet-to-dry).

Tung et al. treat 4 four patients who had stage IV decubitus ulcers (including 1 diabetic) with PEE therapy using a regimen similar to Itoh et al. All ulcers healed regardless of size.

5.4.2 Controlled Studies

In a double-blind RCT, Wilson treated 40 patients who had soft tissue injuries around the ankle. Twenty patients received PEE therapy (up to 975 W emission for 65 µs at 27.12 MHz, 1-hour daily sessions for 3 days); 20 patients received sham therapy. The investigators observed significantly reduced swelling, disability, and pain in patients treated by PEE. However, this study did not address healing of lesions.

In a double-blind RCT, Goldin et al. treated the donor sites of 67 patients who underwent medium-thickness split-skin grafting. Twenty-nine donor sites received PEE therapy (25.3 W mean energy output, one 30-minute session preoperatively and one 30-minute session 6 hours postoperatively); 38 patients received sham therapy. The investigators observed that 1 week postoperatively, ≥90% of the lesions had healed in 17 PEE-treated sites (58.6%) compared to 11 (29.0%) sham-treated sites. However, this study did not address chronic wound healing.
In a double-blind RCT, Jeran et al.\textsuperscript{565} treated 21 patients who had venous ulcers. Eleven patients (with 11 ulcers) received PEMF therapy (2.7 mT magnetic field at 75 Hz, 1.3 ms pulse width); 10 patients (with 11 ulcers) received sham therapy. Patients were instructed to use the stimulators at home for 3 to 4 hours a day for 90 days or until complete healing. The investigators reported that 10 ulcers (90.9\%) in the PEMF-treated group had healed in a mean of 71 days whereas 5 (45.5\%) in the sham-treated group had healed in a mean of 78 days. In the follow-up published study 3 years later, Jeran et al.\textsuperscript{566} reported treating 18 patients with PEMF and 19 with sham therapy. After 90 days of therapy, significantly more PEMF-treated patients completely healed (12 patients, 66.6\%) than sham treated (6 patients, 31.5\%). One year after the start of therapy, significantly more PEMF-treated patients had healed (16 patients, 88.8\%) than sham treated (8 patients, 42.1\%). PEMF-treated lesions completely healed in an average of 71 days compared to 76 days for sham-treated lesions. Patient compliance was objectively monitored and did not significantly differ between the groups. This study has several weaknesses. First, the investigators included patients with diabetes (27.8\% of experimental group, 10.5\% of control group), which can confound outcomes. Second, the investigators did not provide a measure of the initial ulcer sizes for all patients in the study. This may affect outcomes, particularly if the differences between initial wound sizes in groups significantly (or nearly significantly) differed. Third, the investigators reported that “. . . oral and local antibiotic therapy was always given concomitantly . . . .” This may be a source of confusion. If the same antibiotics were administered to all patients in a group for prophylaxis, then this is not a source of confounding. If, however, the antibiotics were used to combat ongoing infections, then use of the same agents against different and/or resistant organisms is itself a source of confounding because some patients will benefit from antibiotic therapy whereas others will not.

In a double-blind RCT, Todd et al.\textsuperscript{567} treated 19 patients who had chronic venous ulcers. Ten patients received PEMF therapy (“field strength set at 60” [sic] at 5 Hz intensity, 15-minute sessions twice weekly for 5 weeks); 9 received sham therapy. The investigators found no difference between the healing rates of the 2 groups. There are 3 major shortcomings in this study. First, the number of patients in each group was small (\textless{}10 patients); the study has little statistical power. Second, the investigators provided no measures of variance. Without such measurements, it is not possible to verify whether there was any significant difference between treatment groups. Third, the follow-up period was too brief to adequately determine the number of patients who completely healed.

In a double-blind RCT, Stiller et al.\textsuperscript{568} treated 31 patients who had chronic venous ulcers. Eighteen patients received PEMF therapy (0.06 mV/cm, 22 Gauss, 3.5 ms total width pulse, applied 3 hours per day at home on top of dressing for 8 to 12 weeks); 13 received sham therapy. After 8 weeks, the wound surface area healed was significantly greater in PEMF-treated lesions than sham-treated lesions. PEMF-treated lesions decreased a mean of 47.1\% whereas the
sham-treated lesions increased 48.7%. This study has several flaws. First, both active and placebo groups used 6 different types of dressings and topical agents (Duoderm® dressing, gentamicin ointment and Duoderm dressing, mupirocin ointment and Vigilon®, mupirocin ointment and nonadherent gauze, Elase® debridement ointment and gauze, and Unna boot). Although there appeared to be no significant difference in use of these concomitant therapies between treatment groups, the investigators are combining different types of conventional therapies, which may have different effects on healing. This may introduce confounding. In addition, one is left to wonder what does constitute conventional therapy in such a heterogeneous treatment group. Second, the investigators did not specify how they monitored patient compliance (proper utilization of the devices at home), which can lead to biased outcomes. Third, the investigators did not specify whether variances reported in their study were standard error or standard deviation. This can lead to confusion in interpreting outcomes.

In a double-blind RCT, Salzberg et al. treated 30 patients who had decubitus ulcers (20 stage II and 10 stage III). Patients received PEE therapy (10 stage II, 5 stage III) by the same regimen described in Itoh et al.[see section 5.4-1] or sham therapy (10 stage II, 5 stage III) for 12 weeks or until lesions healed. Nine of ten stage II PEE-treated patients healed within 3 weeks whereas all stage II sham-treated patients required ≥3 weeks. (All sham-treated patients healed in 11.9 weeks.) The median percentage of stage II patients who healed at 1 week was significantly greater for the PEE-treated group than the sham-treated group. PEE-treated patients required a median of 13.0 days for complete healing compared to 31.5 days for sham treated. Among patients with stage III ulcerations, three (60%) of the PEE-treated healed whereas none of the sham treated healed after 12 weeks. This study has 1 main flaw: it described lesion surface area as the product of its length and width. This introduces a systematic error throughout outcome measures.

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9 One patient died of unrelated causes.
5.5 Spinal Cord Stimulation Studies

Outcomes of implanted SCS studies of wound healing (reported by study investigators) are presented in Table 5.5. Studies in sections 5.5.1 are presented in chronological order.

5.5.1 Uncontrolled Studies

Cook et al.\textsuperscript{570} treated a patient who had a foot ulcer due to obliterative arterial disease by epidural spinal cord stimulation. The site healed after 8 weeks of stimulation.

Richardson et al.\textsuperscript{571} reported complete healing of a decubitus ulcer in a patient suffering from paraplegia after therapy with implanted epidural lumbar electrodes (1.0 to 1.5 V, 33 to 50 Hz, 200 µs pulse duration).

Meglio et al.\textsuperscript{572} reported complete healing of a trophic foot ulcer in a patient suffering from arteriosclerosis after 9 months of therapy with an epidural spinal cord stimulator (electrode tips at T-7 and T-8 spinal levels, bipolar stimulation, 60 Hz, 0.5 msec, 1 to 2 hours nightly).

Graber & Lifson\textsuperscript{573} treated 9 patients suffering from limb-threatening ischemia to implanted spinal cord stimulation. None of the patients completely healed and ulcer healing was “erratic.”

Jivegard et al.\textsuperscript{574} treated 32 patients (25 arteriosclerotic disease, 7 diabetic) with spinal cord stimulation (voltage sufficient to induce paresthesia, 100 Hz, 0.2 msec pulse width, treatment duration at patient discretion). Half of the patients had ischemic skin ulcers. (The investigators did not specify which patients.) One year after therapy, 47% of the arteriosclerotic patients with lesions had complete healing, and 1 of the diabetic patients with skin lesions had complete healing.

5.5.2 Controlled Study

In an RCT, Jivegard et al.\textsuperscript{575} studied the effect of SCS on limb salvage in 51 patients (41 arteriosclerotic, 10 diabetic) with inoperable severe leg ischemia. Twenty-five patients received SCS and peroral analgesic therapy; 26 received peroral analgesic therapy alone. After 18 months follow-up, the limb salvage rates did not significantly differ (62% for SCS, 45% for controls). This study did not directly report wound healing outcomes.
5.6 Ongoing Studies

We identified 4 ongoing studies in a search of Federal Research in Progress\textsuperscript{576}: 2 studies of TENS for pressure ulcers, 1 study of PEMF for pressure ulcers in patients with spinal cord injuries, and 1 study of pulsed radio frequency diathermy for pressure ulcers in patients with spinal cord injuries. [See Table 5.6.] All ongoing trial protocols are randomized and controlled.
### 5.7 Tables

#### Table 5.1. Outcomes Reported by Investigators in Direct Current Studies of Wound Healing

<table>
<thead>
<tr>
<th>Study</th>
<th>Electrical Stimulation</th>
<th>Study Type</th>
<th>Number of Patients or Ulcers</th>
<th>% Patients Healed</th>
<th>Other Reported Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katelaris et al.⁵⁷⁷ (1987)</td>
<td>LIDC</td>
<td>Comparative controlled</td>
<td>14 povidone vs. 4 LIDC + povidone; 4 saline; 4 saline + LIDC</td>
<td>Not available</td>
<td>Healing times (mean days ±SE): povidone = 49.2 ±4.3 (SE); povidone + LIDC = 85.3 ±7.2; saline = 46.1 ±7.2; saline + LIDC = 45.9 ±6.4; no significant differences between groups</td>
</tr>
<tr>
<td>Carley &amp; Wainapel⁵⁷⁸ (1985)</td>
<td>LIDC</td>
<td>RCT</td>
<td>15 LIDC ulcers vs. 15 control: TYPE NOT SPECIFIED</td>
<td>Not available</td>
<td>Sizes (mean cm³ ±SD)—Initial: LIDC = 4.74 ±1.39, control = 3.92 ±1.24; 3rd week: LIDC = 1.11 ±0.42, control = 2.62 ±0.98; 4th week: LIDC = 0.69 ±0.26, control = 2.48 ±0.85; 5th week: LIDC = 0.50 ±0.20, control = 2.16 ±0.88; LIDC therapy significantly better than control for weeks 3 to 5 weeks</td>
</tr>
<tr>
<td>Akers &amp; Gabrielson⁵⁷⁹ (1984)</td>
<td>DC</td>
<td>Comparative controlled</td>
<td>14 decubitus ulcers: DC vs. DC + WP vs. WP</td>
<td>Not available</td>
<td>Correlation coefficient (r) for wound healing for patients receiving HVDC = 0.957; r &lt; 0.5 for patients receiving WP alone or WP + HVDC; no significant difference between groups</td>
</tr>
<tr>
<td>Gault &amp; Gatens⁵⁸⁰ (1976)</td>
<td>LIDC</td>
<td>Case series</td>
<td>100 ulcers (mixed)</td>
<td>48%*</td>
<td>Mean healing ratio = 28.4%/week; Mean % of lesion area healed = 80.5%; Mean treatment time = 4.7 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean healing ratio: LIDC = 30.0%, control = 14.7%; Mean % lesion area healing: LIDC = 74.0%, control = 27.3%; Mean treatment time: LIDC = 4 weeks, control = 4 weeks</td>
</tr>
</tbody>
</table>
Table 5.1.  Outcomes Reported by Investigators in Direct Current Studies of Wound Healing (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Electrical Stimulation</th>
<th>Study Type</th>
<th>Number of Patients or Ulcers</th>
<th>% Patients Healed</th>
<th>Other Reported Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolcott et al.581 (1969)</td>
<td>LIDC</td>
<td>Case series</td>
<td>75 ulcers (mixed)</td>
<td>40%*</td>
<td>Paraplegics (N = 53): 9.3% weekly healing rate, 80.5% overall mean % volume decrease; Peripheral arteriosclerotic (N = 15): 14.4% weekly healing rate, 82.2% overall mean volume decrease; Venous stasis (N = 5): 14.4% weekly healing rate; 85.0% overall mean volume decrease; Others (N = 2): 100% weekly and overall healing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>“Embedded” RCT#</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“Embedded”</td>
<td></td>
<td></td>
<td>Weekly healing rates (% volume decrease/week):</td>
</tr>
<tr>
<td></td>
<td>RCT</td>
<td></td>
<td></td>
<td></td>
<td>LIDC ulcers = 27.0%, control = 5.0%</td>
</tr>
<tr>
<td>Assimacopoulos582 (1968)</td>
<td>LIDC</td>
<td>Case report</td>
<td>3 venous ulcer patients</td>
<td>100% @ 6 weeks</td>
<td>—</td>
</tr>
</tbody>
</table>

WP = whirlpool

* Precise duration for healing not specified.

“Embedded” RCT = patients with bilateral lesions (within a case series) treated by ES on one lesion and a control therapy (non-ES) on the contralateral lesion.

Excluded: Fakhri & Amin583 (study of burn patients)
Table 5.2. Outcomes Reported by Investigators in Pulsed Current Studies of Wound Healing

<table>
<thead>
<tr>
<th>Study</th>
<th>Electrical Stimulation</th>
<th>Study Type</th>
<th>Number of Patients or Ulcers</th>
<th>% Patients Healed</th>
<th>Other Reported Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wood et al.584 (1993)</td>
<td>PDC</td>
<td>Double-blind RCT</td>
<td>Stage II/III decubitus ulcers: 43 PDC + 31 sham</td>
<td>@ 8 wks: 56.1% PDC vs. 4.0% sham</td>
<td>73% of PDC ulcers decreased 80% within 8 wks vs. 13% of sham; 0% PDC ulcers increased in size vs. 30% of sham; significant decrease of mean surface area of PDC ulcers compared to controls at 4 to 8 weeks</td>
</tr>
<tr>
<td>Fitzgerald &amp; Newsome585 (1993)</td>
<td>HVPC</td>
<td>Case report</td>
<td>1 quadriplegic with decubitus ulcer</td>
<td>Healed in 10 weeks</td>
<td>—</td>
</tr>
<tr>
<td>Gogia et al.586 (1993)</td>
<td>HVPC</td>
<td>RCT</td>
<td>Mixed ulcer/lesions: 6 HVPC vs. 6 WP</td>
<td>Not available</td>
<td>Rate of surface area healing @ 20 days: 34.7% HVPC vs. 27.2% control; rate of wound depth healing @ 20 days: 30.3% HVPC vs. 56.8% control; observed no increased healing rate of lower leg/foot ulcers</td>
</tr>
<tr>
<td>Gentzkow et al.587 (1991)</td>
<td>PDC</td>
<td>Double-blind RCT</td>
<td>Stage III/IV decubitus ulcers: 21 PDC vs. 19 sham</td>
<td>41% of PDC in average of 11.8 weeks</td>
<td>% of ulceration healed @ 4 wks significantly different: 49.8 ±30.9% SD for PDC, 23.4 ±47.4% SD for sham</td>
</tr>
<tr>
<td>Griffin et al.588 (1991)</td>
<td>HVPC</td>
<td>Single-blind RCT</td>
<td>Grade II-IV decubitus ulcers: 8 HVPC vs. 9 sham</td>
<td>@ 20 days: 37.5% HVPC vs. 22.2% sham</td>
<td>After 20 days—Grade II ulcer healing: 2/2 HVPC vs. 2/2 sham; Grade III ulcer healing: 1/5 HVPC vs. 0/6 sham; Grade IV ulcer healing: none for HVPC or sham</td>
</tr>
<tr>
<td>Feedar et al.589 (1991)</td>
<td>PDC</td>
<td>Double-blind RCT</td>
<td>Mixed etiology ulcers: 26 PDC vs. 24 sham</td>
<td>@ 4 weeks: 0% PDC vs. 0% sham</td>
<td>Significantly greater reduction in % wound size after 4 wks: 43.9% decrease in PDC vs. 67.2% decrease in sham; Average healing rate: 14%/wk PDC vs. 8.25%/wk sham</td>
</tr>
<tr>
<td>Mulder590 (1991)</td>
<td>PDC</td>
<td>Double-blind RCT</td>
<td>Mixed etiology ulcers: 26 PDC vs. 24 sham</td>
<td>Not available</td>
<td>@ 4 wks—Excellent healing (&lt;25% of original size): 38.5% PDC vs. 20.8% sham; Good healing (50% to 75% of original size): 53.8% PDC vs. 33.3% sham; Poor healing (≥75% of original size): 7.7% PDC vs. 45.8% sham</td>
</tr>
</tbody>
</table>
Table 5.2. Outcomes Reported by Investigators in Pulsed Current Studies of Wound Healing (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Electrical Stimulation</th>
<th>Study Type</th>
<th>Number of Patients or Ulcers</th>
<th>% Patients Healed</th>
<th>Other Reported Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unger et al.591 (1991)[Abstract]</td>
<td>HVPC</td>
<td>Double-blind RCT</td>
<td>Decubitus ulcers: 9 HVPC vs. 8 sham</td>
<td>88.9% HVPC vs. 37.5% sham (unspecified time period)</td>
<td>Average time for healing: HVPC = 51.2 days, sham = 77.0 days Average wound area healed: HVPC = 4.60 cm², sham = 1.19 cm²</td>
</tr>
<tr>
<td>Unger592 (1991)[Abstract]</td>
<td>HVPC</td>
<td>Case series</td>
<td>223 (unspecified type) wounds</td>
<td>89.7% healed (mean 10.9 weeks)</td>
<td>—</td>
</tr>
<tr>
<td>Kloth &amp; Feedar593 (1988)</td>
<td>HVPC</td>
<td>Single-blind RCT</td>
<td>Stage IV decubitus ulcers: 9 HVPC vs. 7 sham</td>
<td>100% HVPC @ 16 weeks; 0% sham @ 17 weeks</td>
<td>Healing rate: HVPC = 44.8 ±22.6%/wk (SD), sham = -11.6 ±18.6%/wk</td>
</tr>
<tr>
<td>Feedar &amp; Kloth594 (1985)[Abstract]</td>
<td>HVPC</td>
<td>Single-blind RCT</td>
<td>Stage IV decubitus ulcers: 5 HVPC vs. 3 sham</td>
<td>100% HVPC (mean 7.3 weeks)</td>
<td>Average healing rate: HVPC = 25.3%/wk, sham = -13.8%/wk</td>
</tr>
<tr>
<td>Thurman &amp; Christian595 (1971)</td>
<td>“High frequency” DC</td>
<td>Case report</td>
<td>Diabetic foot ulcer</td>
<td>100% @ 16 weeks</td>
<td>—</td>
</tr>
</tbody>
</table>

Excluded: Ross & Segal596: study evaluating postoperative swelling and edema Weiss et al.597: study evaluating healing at donor sites for skin grafting Mawson et al.598: study evaluating sacral transcutaneous oxygen tension in patients with spinal cord injuries
Table 5.3. Outcomes Reported by Investigators in Alternating Current and TENS Studies of Wound Healing

<table>
<thead>
<tr>
<th>Study</th>
<th>Electrical Stimulation</th>
<th>Study Type</th>
<th>Number of Patients or Ulcers</th>
<th>% Patients Healed</th>
<th>Other Reported Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stefanovska et al.599 (1993)</td>
<td>AC</td>
<td>RCT</td>
<td>Decubitus ulcers: 82 AC vs. 18 LIDC vs. 50 control</td>
<td>Not available</td>
<td>Theta (θ) values in %/day: θ (AC) = 5.43 ±4.4% (SD); θ (LIDC) = 3.11 ±3.83%; θ (control) = 2.21 ±3.27%</td>
</tr>
<tr>
<td>Lundeberg et al.600 (1992)</td>
<td>(T)ENS</td>
<td>Double-blind RCT</td>
<td>Diabetic ulcers: 32 TENS vs. 32 sham</td>
<td>@ 12 weeks: 42% TENS vs. 15% sham</td>
<td>Percentage of ulcers healed at: 2 weeks—0% TENS, 4% sham 4 weeks—12% TENS, 7% sham 8 weeks—25% TENS, 11% sham 12 weeks—42% TENS, 15% sham</td>
</tr>
<tr>
<td>Karba et al.601 (1991)</td>
<td>AC</td>
<td>Case series</td>
<td>Lesions: 82 vascular, 14 decubitus, 17 posttraumatic</td>
<td>95% of all wounds healed (unspecified time)</td>
<td>Complete healing: Vascular lesions = 90.6% healed by 10 weeks, Decubitus lesions = 100% healed by 5.5 weeks Theta (θ) values (per week): θ (vascular) = 0.47 ±0.09 (SE), θ (decubitus) = 0.83 ±0.33, θ (post-traumatic) = 1.02 ±0.26</td>
</tr>
<tr>
<td>Frantz602 (1990)</td>
<td>TENS</td>
<td>Case series (pilot study)</td>
<td>Decubitus ulcers: 4 TENS</td>
<td>25% healed @ 4 weeks</td>
<td>—</td>
</tr>
<tr>
<td>Kaada &amp; Emru603 (1988)</td>
<td>TENS</td>
<td>Case series</td>
<td>Lepromatous lesions: 32 TENS</td>
<td>59% healed @ 12 weeks</td>
<td>Mean healing time = 5.2 weeks Mean healing index = 1.0 cm³/week Mean healing index in tuberculoid type 3 times higher than lepromatous type</td>
</tr>
<tr>
<td>Alon et al.604 (1986)[Abstract]</td>
<td>TENS</td>
<td>Case series</td>
<td>Diabetic foot ulcers: 15 TENS</td>
<td>80% healed (mean 11.1 weeks)</td>
<td>No significant correlation between pre-existing duration of ulcers and healing time; no significant correlation between initial ulcer size and healing time</td>
</tr>
<tr>
<td>Barron et al.605 (1985)</td>
<td>TENS</td>
<td>Case series</td>
<td>Decubitus ulcers: 6 TENS</td>
<td>22.2% healed @ 3 weeks</td>
<td>Significant difference between means of initial lesion size and final reported sizes</td>
</tr>
</tbody>
</table>
### Table 5.3. Outcomes Reported by Investigators in Alternating Current and TENS Studies of Wound Healing (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Electrical Stimulation</th>
<th>Study Type</th>
<th>Number of Patients or Ulcers</th>
<th>% Patients Healed</th>
<th>Other Reported Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaada 606 (1983)</td>
<td>TENS</td>
<td>Case report</td>
<td>Mixed lesions/ulcerations: 10 TENS</td>
<td>70% healed @ 22 weeks</td>
<td>—</td>
</tr>
<tr>
<td>Westerhof &amp; Bos 607 (1983)</td>
<td>TENS</td>
<td>Case report</td>
<td>Neurotrophic facial ulcers: TENS</td>
<td>Healed @ 6 weeks</td>
<td>—</td>
</tr>
</tbody>
</table>

Excluded: Lundeberg et al. 1988; study of circulation in reconstructive skin flaps
Kjartansson & Lundeberg 1990; study of circulation in reconstructive skin flaps
Finsen et al. 1988: study of prevention of repeated lower extremity amputation
### Table 5.4. Outcomes Reported by Investigators in Pulsed Electromagnetic Induction Studies of Wound Healing

<table>
<thead>
<tr>
<th>Study</th>
<th>Electrical Stimulation</th>
<th>Study Type</th>
<th>Number of Patients or Ulcers</th>
<th>% Patients Healed</th>
<th>Other Reported Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salzberg et al.611 (1995)</td>
<td>PEE</td>
<td>Double-blind RCT</td>
<td>Stage II decubitus ulcers: 10 PEE vs. 10 sham</td>
<td>PEE: 90% @ 3 wks; sham: 100% @ 11.9 wks</td>
<td>Median % patients healed at 1 wk significantly greater for PEE than sham; PEE healed in median of 13.0 days vs. 31.5 days for sham</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>@ 12 weeks: 60% PEE; 0% sham</td>
<td>---</td>
</tr>
<tr>
<td>Tung et al.612 (1995)</td>
<td>PEE</td>
<td>Case report</td>
<td>Stage IV decubitus ulcers: 4 PEE</td>
<td>All healed</td>
<td>---</td>
</tr>
<tr>
<td>Stiller et al.613 (1992)</td>
<td>PEMF</td>
<td>Double-blind RCT</td>
<td>Venous ulcers: 18 PEMF vs. 13 sham</td>
<td>Not available</td>
<td>Significant difference in percentage of wound surface healed: PEMF lesions decreased mean of 47.1% vs. 48.7% increase in sham</td>
</tr>
<tr>
<td>Todd et al.614 (1991)</td>
<td>PEMF</td>
<td>Double-blind RCT</td>
<td>Venous ulcers: 10 PEMF vs. 9 sham</td>
<td>Not available</td>
<td>No significant difference in healing rates of groups; 22.0% reduction for PEMF, 9.1% reduction for control</td>
</tr>
<tr>
<td>Itoh et al.615 (1991)</td>
<td>PEE</td>
<td>Case series</td>
<td>Stage II decubitus ulcers: 9 PEE; Stage III decubitus ulcers: 13 PEE</td>
<td>Stage II: 100% @ 6 wks; Stage III: 100% @ 22 wks</td>
<td>---</td>
</tr>
<tr>
<td>Jeran* et al.617 (1987)</td>
<td>PEMF</td>
<td>Double-blind RCT</td>
<td>Venous ulcers: 18 PEMF vs. 19 sham</td>
<td>@ 90 days: 66.6% PEMF; 31.5% sham</td>
<td>Significantly more patients healed after 90 days with PEMF than sham; Significantly more patients healed 1 year posttherapy with PEMF (88.8%) than sham (42.1%); PEMF lesions healed in average of 71 days vs. 76 days for sham</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>---</td>
</tr>
</tbody>
</table>

* Preliminary study of Jeran et al. 1990

Excluded: Goldin et al. 1981⁶¹⁸: study of effect on donor sites for medium-thickness split-skin grafting
Wilson 1972⁶¹⁹: study of soft-tissue (non-wound) healing
Table 5.5. Outcomes Reported by Investigators in Spinal Cord Stimulation Studies of Wound Healing

<table>
<thead>
<tr>
<th>Study</th>
<th>Electrical Stimulation</th>
<th>Study Type</th>
<th>Number of Patients or Ulcers</th>
<th>% Patients Healed</th>
<th>Other Reported Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jivegard et al. 620</td>
<td>SCS</td>
<td>Case series</td>
<td>Half of 25 arteriosclerotic + 7 diabetic patients: 16 SCS</td>
<td>47% of arteriosclerotic patients with lesions*; 1 diabetic patient</td>
<td>—</td>
</tr>
<tr>
<td>Graber et al. 621</td>
<td>SCS</td>
<td>Case series</td>
<td>Limb-threatening ischemia: 9 SCS</td>
<td>None</td>
<td>Wound healing described by investigators as “erratic”</td>
</tr>
<tr>
<td>Meglio et al. 622</td>
<td>SCS</td>
<td>Case report</td>
<td>Trophic ulcer in patient with arteriosclerosis</td>
<td>Completely healed @ 9 months</td>
<td>—</td>
</tr>
<tr>
<td>Richardson et al. 623</td>
<td>SCS</td>
<td>Case report</td>
<td>Decubitus ulcer in paraplegia</td>
<td>Completely healed (duration unspecified)</td>
<td>—</td>
</tr>
<tr>
<td>Cook et al. 624</td>
<td>SCS</td>
<td>Case report</td>
<td>Foot ulcer in patient with obliterative arterial disease</td>
<td>Completely healed @ 8 weeks</td>
<td>—</td>
</tr>
</tbody>
</table>

* Number of patients with lesions and time required for healing unspecified
Excluded: Jivegard et al. 1995: study of limb salvage rate
<table>
<thead>
<tr>
<th>Principal Investigator/ Performing Organization</th>
<th>Description of Ongoing Study</th>
</tr>
</thead>
</table>
| Rita Frantz University of Iowa Iowa City, IA | **Title:** Pressure ulcers in older adults—healing with TENS  
**Purpose:** Determine the effectiveness of TENS on healing of pressure ulcers in older adults. Study will aim to compare the rate of healing of pressure ulcers treated with conventional therapy and compare to patients treated by conventional therapy plus TENS. Study will also compare rate of wound healing and presence of prognostic indicators.  
**Description:** 40 patients randomly assigned to receive TENS therapy (TID for 30 minutes) or sham therapy. All subjects to receive saline-soaked gauze. 8-week follow-up or until healing. |
| Dr. Carl Sutton Dept. Veterans Affairs Milwaukee, WI | **Title:** Pulsed electromagnetic field energy in the treatment of pressure ulcers in spinal cord injured patients  
**Purpose:** Study the effectiveness of PEMF on healing of pressure ulcers in spinal cord injured patients. Study will compare healing rates and percentages of pressure ulcers healed. Study will also evaluate safety and cost-effectiveness of PEMF.  
**Description:** 15 to 25 patients in randomized, double-blind study. One group to receive standard moist wound care 7 days/week for 6 weeks; second group to receive active PEMF therapy for 6 weeks; third group to receive sham (placebo) therapy. 10-week follow-up period. |
| Mary Smerek Dept. Veterans Affairs St. Louis, MO | **Title:** TENS as an alternative to hydrotherapy in treating pressure sores  
**Purpose:** Determine if TENS is an effective alternative to hydrotherapy for healing grade III or IV pressure sores  
**Description:** 20 patients >60 years of age randomly assigned to TENS therapy or hydrotherapy for treatment of grade III or IV decubitus ulcers. |
| Dr. Carl Sutton Dept. Veterans Affairs Milwaukee, WI | **Title:** Pulsed radio frequency diathermy in the treatment of pressure ulcers in spinal cord injured patients  
**Purpose:** Study the effectiveness of pulsed radio frequency diathermy (RFD) on the healing of pressure ulcers in spinal cord injured patients. Study will compare healing rates and percentages of pressure ulcers healed treated by active and inactive therapy. Will also evaluate safety and cost effectiveness.  
**Description:** 15 to 25 patients in randomized, double-blind study. One group to receive standard moist wound care 7 days/week for 6 weeks; second group to receive active RFD therapy for 6 weeks; third group to receive sham (placebo) therapy. 10-week follow-up period. |
6.0 Quantitative Analysis and Meta-Analyses of Outcomes of Electrical Stimulation Studies

Three types of outcome reporting appear throughout published studies of therapies for wound healing:

- subjective assessments describing the healing process,
- objective expressions of the healing rate, and
- objective expressions of complete healing.

[See section 4.2.3.]

Subjective assessments by clinicians (e.g., ratings of granulation tissue formation, exudate, pain) are good qualitative measures of healing, but they are poor quantitative measures.

Objective assessments essentially measure the rate at which wounds heal and/or the number of patients (proportion) who completely heal. We have already discussed flaws associated with outcomes describing the percentage of patients totally healed. [See section 4.2.3.1.]

Unfortunately, wound healing rates in many ES and non-ES studies are reported inconsistently or idiosyncratically. [See section 4.2.3.2.] This makes it difficult to interpret healing-rate outcomes within a study and to generalize or compare such outcomes with other studies. We sought to determine a standardized measure of the wound healing rate that could be applied to all ES and non-ES studies.
6.1 Quantitative Analysis of Normalized Wound Healing Rates: Theta (?) Values

6.1.1 Definition and Description of Theta

Many wound healing studies have either assumed or implied that the rate of wound healing is linear. Some studies subtracted the difference between the initial and final size of a wound and divided by the time interval. This assumes a linear healing rate. Some studies obtained healing rates (percentages of wound healed) empirically at selected time intervals and averaged the results to yield a mean healing rate. If the relationship is indeed linear, then the rate would be constant between any 2 intervals. There is no clear evidence that the wound healing rate is linear. (In fact, Pierard and Pierard-Franchimont\textsuperscript{627} recently concluded that chronic leg ulcers heal at uniform, nonlinear rates, following a “proportional change process”.)

Visual Appearance—To determine whether healing rates appear linear or exponential, or have some other form, we examined curves of the percentages of wound size healed or remaining on the ordinate versus time-for-healing on the abscissa.

In figure 2 of Feedar et al.,\textsuperscript{628} the relationship appears exponential rather than linear. The healing rate after 1 week was 20% ±5% SE. If the healing rate was linear, then one would expect 60% to 100% healing after 4 weeks. The actual healing was 65% ±5%.

In figure 1 of Griffin et al.,\textsuperscript{629} individual patient healing was plotted for stage II through IV ulcers. The curves for patients with grade III ulcers could have been linear or exponential. However, the curves for grade II ulcers (1 patient exhibiting 80% healing after 5 days, but only 90% after 10 days) and grade IV ulcers (1 patient exhibiting 30% healing after 5 days, only 55% after 20 days) appear exponential.

The healing rate curves in figure 1 of Gentzkow et al.\textsuperscript{630} may be linear or exponential. The variance is so large that either might be appropriate.

The healing rate curves in figures 1 and 2 of Gogia et al.\textsuperscript{631} do not appear linear, but there is no measure of variance.

In figure 1 of Wood et al.,\textsuperscript{632} the stimulation therapy curve appears exponential. Approximately 20% of lesion area decreased after 1 week. If healing was linear, we would expect complete healing after 5 weeks instead of 80% healing after 8 weeks.

Healing rate curves in figures 3 and 5 of Karba et al.\textsuperscript{633} are exponential.
In figure 2 of Kaada & Emru, all wound healing curves of individual patients followed a nonlinear, seemingly exponential path.

We examined many conventional therapy RCTs for wound healing and found similar appearances for healing rate curves. Based on our visual inspection, healing rates appear exponential rather than linear.

**Exponential Model**—Karba et al. and Stefanovska et al. have used an exponential model to describe the rate of wound healing. Using an exponential model enables one to express the healing rate as a constant independent of wound size. Karba et al. have described this constant as the normalized healing rate or theta (?), usually expressed as a fraction value per week.

The normalized healing rate (?) is derived from the basic equation for an exponential decay:

\[ S_t = S_0 \times e^{-\theta t} \]

where \( S_t \) is the size of a wound at a time “t” and \( S_0 \) is the initial size of the wound (at time 0; i.e., the size of the wound at the beginning of the study). Solving for theta

\[
\begin{align*}
\frac{S_t}{S_0} &= e^{-\theta t} \\
\ln\left(\frac{S_t}{S_0}\right) &= -\theta t \\
\ln\left(\frac{S_0}{S_t}\right) &= \theta t \\
\theta &= \frac{\ln\left(\frac{S_0}{S_t}\right)}{t}
\end{align*}
\]

Time “t” is usually expressed in weeks. For example, if the initial size of a wound is 4 cm\(^2\) and the size 8 weeks later is 0.25 cm\(^2\), then \( \theta = \frac{\ln(4 \div 0.25)}{8} = 0.3466/\text{week} \).

In an exponential process, the rate constant \( \theta \) should be the same for all time intervals. Wound sizes can be measured by surface area and/or by volume. (The latter is more representative of the healing process.) Assuming healing is exponential, the normalized healing rate can employ either surface area or volume measurements to represent wound size. However, the value of the normalized healing rate depends on whether one measures surface area or volume. For example, if the initial wound size had been 4 cm\(^2\) with 3 mm depth (0.12 cm\(^3\)) and the measured size 8 weeks later had been 0.25 cm\(^2\) with 2 mm depth (.0025 cm\(^3\)), then \( \theta_{\text{vol}} = \frac{\ln(0.12 \div 0.0025)}{8} = 0.4839/\text{week} \). We observe that the numerical value of the exponential-modeled normalized healing rates depend on whether one measures surface area or volume. [Throughout this report, \( \theta \) will represent normalized healing rates for surface area (or in general), and \( \theta_{\text{vol}} \) will represent normalized healing rates measured by volume.]
Validating the Exponential Model—To validate the model, we (1) determined whether ? is independent of initial wound size and (2) determined that the percentage of wound healing fits a negative exponential curve.

To determine whether ? values are independent of wound size, we calculated ? values, when possible, for the placebo (or control) groups used in controlled trials of electrical stimulation for wound healing. (We chose placebo and standard groups to be certain that there was no correlation between initial size and the value of ?.) The correlation between ? and initial wound size (surface area) for control groups from ES studies was not significant (r = 0.0636, p = 0.8419, N = 16 treatment groups). This implies that there is no linear relationship. We plotted ? versus initial wound size and found no other apparent relationships. [See Figure 6.1.] We then calculated ? values for the standard (or placebo) treatment groups taken from RCTs of conventional therapies for venous ulcers and for decubitus ulcers. [See section 7 for description of study inclusion.] The correlation between ? and initial size was not significant for control groups in venous ulcer RCTs (r = -0.3740, p = 0.1696, N = 15) and for control groups in decubitus ulcer RCTs (r = 0.0969, p = 0.8363, N = 7). This implies that there is no linear relationship. We plotted ? versus initial wound size and found no other apparent relationships. [See Figure 6.1.]

If a sufficient number of time points are provided, the model can be validated. The more time points available, the better the validation process. Unfortunately, few published studies provided data on wound size as a function of time. Fewer still provided individual patient data. We used summary data from two studies mentioned previously in this section (Wood et al. 1993 and Feedar et al.) to determine whether data generally fits the negative exponential model. From Wood et al., we plotted summary statistics of percentage of initial surface area of lesions against time; we generated a negative exponential curve to test for goodness of fit. [See Figure 6.2a.] The data appeared to fit the negative exponential model. We repeated this procedure for summary data from Feedar et al. and observed a similar fit. [See Figure 6.2b.] When we used individual patient data, the model did not fit as well. We observed that the normalized exponential healing rate, ?, appears to be a better descriptor of the healing rate for groups of patients than individual patients.

One can think of ? as a “time constant.” When t = 1/?, the area (or volume) of St is approximately 37% of the initial size S0. With each successive time interval, 1/?, lesion size decreased 63%. For example, if ? = 0.1, then at the time interval of 10 weeks (t = 1/0.1 = 10), approximately 63% of lesion size would have healed. In integral multiples of ?, at 20 weeks (2 × (1/0.1)), 86% of the lesion size would be healed; at 30 weeks (3 × (1/0.1)), 95% of the lesion size would be healed; at 40 weeks (4 × (1/0.1)), 98.2% of the lesion size would be healed; and at 50 weeks (5 × (1/0.1)), 99.3% of the lesion size would be healed. On the other hand, if
\( \theta = 0.05 \), then the time interval \( \frac{1}{\theta} \) would be 20 weeks. Therefore, with a \( \theta \) of 0.05, at 40 weeks, 86% of lesion size would be healed compared to 98.2% if \( \theta = 0.1 \).

One difficulty in calculating the value of \( \theta \) is that the exponential approaches but never reaches zero. In actual life, when a wound heals at some given time \( t \), its surface area or volume is 0. By the exponential decay model, \( \theta = \frac{\ln(S_0/S_t)}{t} = \frac{\ln(S_0/0)}{t} = \frac{\ln(\infty)}{t} \)—which has no meaning. Therefore, to calculate for \( \theta \) when given the initial size and time for complete healing, one needs to choose as an endpoint a fraction that is near complete healing. We empirically chose 99% healing as the endpoint of a lesion. For example, if a 4 cm\(^2\) lesion healed in 8 weeks, the 99% endpoint is 0.04 cm\(^2\); \( \theta = \frac{\ln(4/0.04)}{8} = 0.5756 \). A disadvantage of this empirically based endpoint is that small changes in wound size can lead to large changes in \( \theta \) values.

Although the normalized healing rate, \( \theta \), has these shortcomings, it is the best quantitative descriptor of wound healing available.

**Calculating Thetas From Studies**—We calculated the \( \theta \) values for all ES studies (excluding case reports) which presented adequate data (i.e., initial wound size (required), duration of healing, difference in wound size at \( \geq 1 \) time periods). We used the following procedures:

1. Theta values calculated from studies which reported wound size by surface area were not combined with \( \theta \) values from studies reporting wound size by volume.

2. Studies which expressed wound sizes as length and width were converted to surface areas by multiplying length times width. Studies which expressed wound sizes as length, width, and depth were converted to volumes by multiplying length time width times depth. (These can lead to systematic errors.)

3. Some studies reported outcomes only as medians. In these cases, median values were treated as if they were mean values. It was often the only method for handling study data.

4. In studies that reported healing at different time intervals and the time required to complete healing, only one \( \theta \) value was used. This was calculated from an average \( \theta \) value using all reported times except the \( \theta \) value calculated at complete healing (99% of original wound size). These latter values were excluded because calculations of \( \theta \) based on the time to complete healing involves an assumption,
and we sought to avoid empirically based assumptions wherever possible.

(5) For studies providing only the time for complete healing, we calculated \( \theta \) by assuming that the final wound size was 1% of the original (99% healed). This enabled us to calculate \( \theta \) values from studies only providing time-to-complete-healing data.

Confidence intervals (CI) are essential for determining whether the healing rate in one treatment group of a study significantly differs from those reported in other groups in the study. We determined variance (and from them, confidence intervals) using the following procedures:

1. If a study provided the variance at a time “t” during healing but did not provide the variance at the initial time (t = 0), then we assumed that the initial variance was the same at time “t.”

2. If a study provided the variance at the initial time (t = 0), but did not provide it at later or final times, we assumed that the variance at time “t” or final times was the same as the initial time.

3. Standard error (SE) = standard deviation (SD) \( \div n^{0.5} \) (where \( n \) is the number of patients in a group). The 95% confidence interval (CI) = mean \( \pm (1.96 \times SE) \).

4. Groups were considered statistically significantly different when their 95% confidence intervals did not overlap.

6.1.2 Theta Outcomes for Individual Electrical Stimulation Studies

DIRECT CURRENT STUDIES—Theta values for DC studies are presented in Table 6.1. Only 2 studies provided sufficient information for calculating \( \theta \) values: Katelaris et al. (1987)\(^{639}\) and Carley & Wainapel (1985).\(^{640}\)

In the Katelaris et al. trial, the normalized healing rate after ES was not significantly greater than conventional therapies. In fact, LIDC with povidone therapy had a significantly smaller healing rate than povidone therapy alone. However, this is a nonrandomized, controlled study.

In the Carley & Wainapel trial, \( \theta \) is significantly greater for LIDC therapy than saline gauze therapy. However, the study did not specify the types of lesions being treated. These \( \theta \) values are clinically uninterpretable because we do not know whether they apply to diabetic, venous, decubitus, neurotrophic, or some other chronic lesion.
Based on these findings, DC stimulation has not been shown to increase the normalized healing rate of chronic lesions.

**PULSED CURRENT STUDIES**—Theta values for PC studies are presented in Table 6.2. Six studies provided sufficient information for calculating ? values. However, 1 study (Gogia et al. [1993]641) provided no measure of variance.

Three studies had no significant difference in normalized healing rates: the double-blind RCT by Gentzkow et al. (1991)642 comparing PDC to placebo therapy for patients with stage III/IV decubitus ulcers; the single-blind RCT by Griffin et al. (1991)643 comparing HVPC to placebo therapy for patients with “grades II to IV” decubitus ulcers; and the double-blind RCT by Feedar et al. (1991)644 comparing PDC to placebo therapy for patients with different types of lesions.

Two studies demonstrated a significant difference between patients who received ES and those who received sham therapy.

In the Wood et al. double-blind RCT, PDC yielded a significantly greater ? than placebo therapy for patients with stage II or stage III decubitus lesions. The only appreciable flaw of this study was that the investigators did not specify the duration of treatment sessions.

In the Kloth & Feedar single-blind RCT, HVPC had a significantly greater ? than placebo therapy for patients with stage IV decubitus ulcers. However, this study has several major flaws, which makes this outcome suspect: (1) small study size, (2) differences between patients in the 2 groups, and (3) possible confounding concomitant therapy.

Based on these findings, it appears that the type of PDC device used by Wood et al. does improve the normalized rate of wound healing compared to placebo therapy for patients with stage II or III decubitus ulcers. Studies using HVPC have either yielded no significant improvement compared to placebo therapy or highly-suspect outcomes.

**ALTERNATING CURRENT AND TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION STUDIES**—Theta values for AC and TENS studies are presented in Table 6.3. Six studies provided sufficient information for calculating ? values; 4 were uncontrolled case series. (Theta values for uncontrolled trials tended to be much larger than those for controlled trials.) There were 2 controlled studies.

In the RCT by Stefanovska et al. (1993)645 the normalized healing rate for AC therapy was greater than the value for standard therapy for patients with decubitus ulcers. However, this study has several flaws: (1) the investigators did not specify the standard therapy to which AC stimulation was being compared; (2) they did not specify any aspect of concomitant therapy; and
they did not specify the stage of decubitus ulcers.

In the double-blind RCT by Lundeberg et al. (1992), there was no significant difference between TENS and placebo therapy for patients with diabetic ulcers.

Based on these findings, there is no evidence that TENS therapy improves any type of chronic wound healing. There is weak evidence that AC therapy may provide some improvement in the healing rate of patients with decubitus ulcers, but it is not clear for which stage and compared to what type of therapy.

PULSED ELECTROMAGNETIC INDUCTION STIMULATION STUDIES—

Table 6.4. Four studies provided sufficient information for calculating $\theta$ values. One study (Itoh et al. [1991]) is a case series. (The $\theta$ values for this uncontrolled trial are much higher than in controlled trials.) One double-blind RCT (Todd et al. [1991]) provided no measure of variance.

In the double-blind RCT by Salzberg et al. (1995), there was a significant difference between the normalized healing rates of PEE (95% CI for $\theta = 1.3114$ to 1.6370) and placebo therapy for patients with stage II decubitus ulcers (95% CI for $\theta = 0.1488$ to 0.6740).

In the double-blind RCT by Stiller et al. (1992), there was a small, significant difference in the normalized healing rates between PEMF and placebo therapies for patients with venous ulcers. However, the effect of PEMF appears quite small (mean $\theta = +0.0824$, 95% CI = +0.0596 to +0.0975). This study also has 2 flaws: (1) inconsistencies in concomitant therapy and (2) inadequate monitoring of patient compliance.

Based on these findings, there is evidence that PEE therapy improves any type of chronic wound healing. There is weak evidence that PEMF therapy may provide some benefit for patients with venous ulcerations.

SPINAL CORD STIMULATION STUDIES—None of the SCS studies of wound healing was controlled. They consisted of case reports and small case series. In the absence of control groups, normalized healing rates tend to be higher and reflect confounding population characteristics. Therefore, we did not calculate theta values for the case series.

6.1.3 Summary of Normalized Healing Rates for Electrical Stimulation Studies

The statistical significance of normalized healing rate ($\theta$ values) for controlled trials of ES for wound healing are presented in Table 6.5.
Based on these outcomes, we conclude that there is evidence of the following:

- There is evidence that PDC improves the healing rate of stage II or III decubitus ulcers compared to sham (placebo) therapy. There is weak evidence that HVDC improves the healing rate of stage IV decubitus ulcers compared to sham therapy, but these are suspect due to small study size.

- There is evidence that PEE stimulation improves the healing rate of stage II decubitus ulcers.

Based on these outcomes, we conclude that there is weak evidence of the following:

- There is weak evidence that AC stimulation improves the healing of decubitus ulcers compared to “standard” therapy, but these results are suspect because the standard therapy was not specified.

- There is weak evidence that PEMI stimulation improves the healing rate of chronic venous ulcers compared to sham therapy, but these results are suspect because of possible inconsistencies in concomitant therapy.

Based on these outcomes, we conclude that there is no evidence of the following:

- There is no evidence that DC stimulation improves the healing rate of chronic venous, decubitus, or diabetic ulcerations.

- There is no evidence that PC stimulation improves the healing rate of chronic venous or diabetic ulcerations.

- There is no evidence that AC (including transcutaneous electrical nerve stimulation) improves the healing rate of chronic decubitus or diabetic ulcerations.

- There is no evidence that PEMI stimulation improves the healing rate of chronic decubitus or diabetic ulcerations.

- There is no evidence that any other form of ES improves the healing rate of chronic lesions.

Although some ES studies have shown an improved healing rate (effect) compared to placebo therapy, this does not demonstrate whether it is as effective
or more effective than established wound healing therapies—that is, whether it is clinically useful. [See section 8.]
6.2 Meta-Analyses of Outcomes of Electrical Stimulation for Wound Healing

6.2.1 Overview of Meta-Analytic Methods

We performed 2 meta-analyses to determine

- whether ES increases the normalized wound healing rate (\(?\)), and
- whether ES increases the proportion of wounds that completely heal.

These 2 outcome variables are potentially correlated and could be evaluated in a single analysis. We have not done so for 2 reasons: (1) pooling different outcomes is appropriate only when outcome measures are highly correlated, and when these correlations are high, there is only a modest gain the efficiency of the analysis (as noted by Hedges and Olkin\(^{651}\)); and (2) presenting results separately is more informative than are results from a single analysis.

Both of our meta-analyses are designed to answer 2 questions:

- Does ES promote wound healing?
- If ES does promote wound healing, then is there a particular patient or treatment subgroup for whom ES is most effective?

We used the Hedges' \(d\) statistic in our meta-analyses. Hedges' \(d\) is a measure of the effect size of treatment. It is the difference between the experimental and control groups expressed in units of standard deviation and corrected for errors in treatment effect estimations that arise in studies with few patients. [See Appendix II, section 11.1.1.1 for formulae to calculate Hedges' \(d\).] We calculated a \(d\) for each study in the meta-analysis. Values of \(d > 0\) imply that ES therapy promotes wound healing; values of \(d < 0\) imply that ES therapy hinders wound healing. A \(d = 0\) implies that ES therapy has no effect. Because the differences between treatment and control groups (effect sizes) are in standard deviation units, \(d = +0.5\) implies that wound healing in the average patient in the treatment group is >69% of control group patients; \(d = -0.5\) implies that wound healing in the average patient in the treatment group is <31% of control group patients.

The value of \(d\) by itself does not indicate whether the results from a study are statistically significant. That requires constructing 95% confidence intervals (95% CI or CI) intervals around each study's \(d\). These intervals, calculated from the pooled variances of treatment and control groups, provide a range of values in which there is only a 5% probability that the \(d\) for any particular study could fall.
outside of them by chance. As a result, if the 95% CI for a particular study does not contain 0, then there is a statistically significant difference between the outcomes of treatment and control groups. In other words, a treatment effect that promotes healing \((d > 0)\) is statistically significant if its lower confidence limit \((CL_{lower})\) is greater than zero; a treatment effect that hinders healing \((d < 0)\) is statistically significant if its upper confidence limit \((CL_{upper})\) is less than 0.

Once \(d\) values are calculated for individual studies, one must combine them to determine an overall estimate of the effects of treatment (i.e., a \(d\) based on all relevant studies). This is accomplished by weighting each study’s \(d\) value by the inverse of the study’s variance, averaging the weighted \(d\) values, then constructing 95% CI around the overall \(d\) (\(d_o\)) value. These confidence intervals around \(d_o\) determine whether the overall treatment effect is statistically significant.

Another important statistic in this meta-analysis is the \(Q\) statistic, which tests the homogeneity of studies—that is, whether all studies in the meta-analysis share a common effect size.\(^{652}\) [See Appendix II, section 11.1.1.2 for formulae to calculate the \(Q\) statistic.] If the value of \(Q\) is statistically significant, then the studies in the meta-analysis are not homogeneous; some studies may not be measuring the same statistical parameter.\(^{653}\) This implies that one may be observing the effect of something other than treatment. For example, the observed effect may depend on the type of ulcer, patient age, ulcer size, etc. A statistically significant \(Q\) means that it may not be appropriate to conduct the meta-analysis or that the source of the heterogeneity needs to be explained.\(^{654,655}\)

Proper selection of studies is crucial for conducting an appropriate meta-analysis. One of the most common methods of study selection is choosing studies with the best experimental design. Although this may be theoretically sound, in practice, different analysts have different opinions about which studies are “best.” These different opinions reflect potential subjectivity in assessing study quality, and can possibly undermine the analysis. Therefore, in our meta-analysis, we included studies with different experimental quality and then sought to determine whether these differences could have affected outcomes. Our position is justifiable because although some design flaws create the potential for bias, they do not automatically create bias. In such cases, if there is actual bias, it may be determined empirically.

Our analysis also included different types of statistical models. There is controversy in the medical community whether it is better to use a fixed-effects or a random-effects statistical model. [Fleiss and Gross,\(^{656}\) in paraphrasing an argument by Bailey,\(^{657}\) have suggested that when the question concerns whether a treatment has produced an effect in the studies at hand, then the fixed-effects model is the most appropriate one. They continue, however, by noting that when the question involves whether a treatment will have an effect, in other words, if one wishes to generalize to a universe of similar studies and/or to consider the
possibility of future studies being conducted or discovered, then the random-effects model is preferred. On the other hand, Dements\textsuperscript{658} argues against random-effects models, doubting whether there genuinely is a universe of studies to which one can generalize.] Because of this controversy, we elected to perform both fixed- and random-effects analyses.

6.2.2 Meta-Analysis of Normalized Wound Healing Rates

We used all 9 controlled studies obtained from our literature searches [see section 4] in our meta-analysis of normalized wound healing rates (?). These studies and relevant data are shown in Table 6.6.

Because there are insufficient published data from controlled trials for statistical comparisons of devices from different manufacturers, and because we wanted to determine whether different types of devices differentially affected wound healing, we were forced to group devices into broader categories than we used in previous sections of this report. These device categories have limitations but are necessary to construct statistical models to answer our questions and explain observed outcome variations.

6.2.2.1 Overall Study Analysis

**FIXED-EFFECTS MODEL**—We calculated the fixed-effects \( d \) and confidence limits for each study and the overall \( d \) (\( d_o \)) and its confidence limits. The \( d \)'s are listed in Table 6.7 and presented graphically in an effects size plot in Figure 6.3.

ES has an overall statistically significant positive effect on normalized wound healing rates (\( d_o = +1.13, \text{ CI} = +0.91 \text{ to } +1.35 \)). However, the \( Q \) statistic is highly significant (\( p < .0001 \)), indicating that these studies are not homogeneous. [See section 6.2.1 and Appendix II, section 11.1.1.2 for explanation.]

Because these studies are heterogeneous, we first sought to determine whether the apparently positive effects of ES were due to statistical outliers. (An outlier is defined in terms of the \( Q \) statistic, which accounts for both deviation of a study’s \( d \) value from \( d_o \) and a study’s variance.) Whether a study is an outlier is determined by assessing the effect on the \( Q \) statistic when that study is removed from the meta-analysis. Removing the greatest outlier from the meta-analysis has the greatest effect on \( Q \), removal of the second greatest outlier has the second greatest effect on \( Q \), etc. For example, suppose the \( Q \) statistic has a \( p \) value of .0001. If we remove study A and the \( p \) value of \( Q \) becomes nonsignificant (e.g., \( p = 0.23 \)), then study A is the only outlier. If, on the other hand, removing study A leaves us with a \( Q \) statistic that is still significant (e.g., \( p = .009 \)), then we would still need to remove 1 or more additional studies to make the \( Q \) statistic
nonsignificant (i.e., \( p \geq 0.05 \)) and the group homogeneous. If removing study A did not affect the \( Q \) statistic (e.g., \( p = 0.0001 \)), then it would be inappropriate to remove study A from the analysis.

In our outlier analysis, we discarded 3 outlying ES studies: (1) Katelaris et al.,\(^659\) (2) Gentzkow et al.,\(^660\) and (3) Salzberg et al.\(^661\)—leaving us with an apparently homogeneous group of studies. The resulting overall \( d (d_o) \) was +1.32 (CI = +1.07 to +1.57). Because the \( CL_{lower} \) is greater than zero, ES still has a statistically significant, positive effect on the normalized rate of wound healing (?). These results also suggest that the statistically significant effects of ES obtained in all 9 studies (including outliers) are not attributable to a few aberrant trials.

**RANDOM-EFFECTS MODEL**—For illustrative purposes, we analyzed all 9 studies using a random-effects statistical model. Random-effects models do not correct study heterogeneity problems, but they provide a more conservative statistical test and suggest how generalizable results are from a data set.

We obtained a \( d_o \) of +1.11 (CI = +0.56 to +1.65). These results indicate that ES has a statistically significant positive effect on the normalized rate of wound healing.

### 6.2.2.2 Analysis of Study Heterogeneity

The analysis above established that ES has a statistically significant positive effect on the rate of normalized wound healing but as shown by the statistically significant \( Q \) statistic, the studies are not homogeneous. We wanted to determine the source of this heterogeneity. We investigated 2 main sources: (1) study design and (2) patient or wound characteristics and treatment.

#### 6.2.2.2.1 Influence of Study Design

We wanted to determine whether the statistically significant effects of ES on ? was due to study design (e.g., randomization, blinding).

**FIXED-EFFECTS MODEL**—We searched for a relationship between study design and \( d \) using a fixed-effects model. (A fixed-effects model is an appropriate first step because it is less conservative than a random-effects model. If the fixed-effects model demonstrates no statistically significant effects, then the random-effects model must also be nonsignificant.)

Failure to randomize or to blind groups is widely believed to create a potential for bias. In our analysis of study design variations, we looked for potential biases of outcomes caused by (1) not randomizing patients to groups and (2) not blinding physicians to which groups patients belonged.
First, we analyzed studies by blinding. The $d$ statistic for the 5 studies without blinding was $+1.04$ (CI = $+0.76$ to $+1.32$); the $d$ statistic for the 4 studies with blinding was $+1.27$ (CI = $+0.92$ to $+1.61$). These confidence intervals overlap, suggesting that study design by blinding does not affect the measurement or reporting of healing rates. The $Q$ test for differences between these two classes of studies was not significant ($p = .322$). The $Q$ statistics for heterogeneity within these two groups were both significant ($p = .0003$ for nonblind studies, $p = .0007$ for blind studies), indicating that categorizing studies by blinding does not account for the heterogeneity we observed in the original (overall) meta-analysis.

Second, we analyzed studies by randomization. The 2 nonrandomized studies had a $d$ value of $+1.18$ (CI = $+0.82$ to $+1.54$); the 7 randomized studies had a $d$ of $+1.10$ (CI = $+0.82$ to $+1.35$). These confidence intervals overlap, indicating that categorizing study design by randomization does not affect outcomes. The $Q$ statistic for between-group differences was not significant ($p = .74$); the $Q$ statistics for within-group differences were significant ($p = .0007$ for nonrandomized studies, $p = .001$ for randomized studies), indicating that categorizing studies by randomization does not account for the heterogeneity we observed in the original meta-analysis.

Third, we compared results from studies that were (a) not randomized, (b) randomized but not blinded, and (c) randomized and blinded. The $Q$ statistic for this between-groups comparison was not significant ($p = .29$) and the within-group $Q$ statistics for the controlled, nonrandomized and randomized, nonblinded studies were significant ($p = .00007$ for both groups). This indicates that grouping studies in this manner does not account for the heterogeneity we observed in the original analysis.

In conclusion, we found no statistical evidence suggesting that variations in study design influenced the results of our meta-analysis or accounted for the heterogeneity detected by the $Q$ statistic.

### 6.2.2.2 Influence of Patient Characteristics, Wound Characteristics, or Treatment

We wanted to determine whether the statistically significant effects of ES on $?$ were due to patient characteristics (e.g., age), wound characteristics (e.g., initial lesion size), and/or treatment (e.g., DC versus AC).

**Fixed-Effects Model**—This type of analysis requires the use of a multivariate technique that is a meta-analytic version of multiple regression. In such calculations, one attempts to “predict” $d$ from variables that represent relevant patient or treatment characteristics. In a meta-analysis, when $d$ is appropriately predicted by a regression model, the model is said to be...
“correctly specified.” In other words, a correctly specified model explains enough of the variation in \( d \) values so that the amount of unexplained variation is not statistically significant. For multivariate meta-analyses, one uses the \( Q_E \) statistic to assess whether the between-studies variation (heterogeneity) has been adequately accounted for.

In our analysis, we initially considered type of device, type of wound, initial wound size, patient age, and follow-up duration. [See Table 6.6.] However, we only used variables whose relationship with \( d \) were statistically significant and were reported in all studies used in the analysis. (Analyzing variables which were not reported by all studies could not be done using currently available software because it deletes studies with missing data. This would have created data sets different from the one consisting of all studies. In such a situation, if some studies are deleted, one could be explaining only the heterogeneity of the smaller data set but not of the full set consisting of all studies.) We constructed our models using variables whose relationship with \( d \) was statistically significant according to pilot univariate tests. For categorical variables, we performed univariate tests as described above for study design variations. For continuous variables such as age, we searched for linear relationships with \( d \) using Rosenthal’s method of focused contrasts. [See Appendix II, section 11.1.1.3 for formulae to calculate Rosenthal’s method of focused contrasts.]

Because there were a relatively large number of devices and relatively small number of studies, we were forced to analyze device types differently than other variables. We created a variable called “device” \((dv)\) that consisted of the 4 device types shown in Table 6.6 (direct current (DC), pulsed current (PDC), alternating current (AC), and pulsed electromagnetic induction (PEMI)). The device variable \((dv)\) was a composite in which each of the 4 device types was denoted by a “dummy” code. If the relationship between \( d \) and the \( dv \) was not statistically significant, we concluded that the type of device did not affect outcome. If, on the other hand, \( dv \) and outcome were significantly associated, we decomposed this variable into different combinations of device types to discern whether there were more specific relationships between device types and outcomes. (This strategy of decomposing the device variable was necessary because although we could predict a priori that different device types might have different effects, it was not possible to make specific predictions about which device(s) might be superior.) For example, suppose the effect from devices A, B, and C are not different from each other. In such a situation, it is possible that if devices A and B are treated as a single device class (A/B), then A/B could be superior to device C. Searching for such relationships can lead to a very large number of possible relationships between device types and outcomes. If these were combined with other relevant patient or wound variables (e.g., age, lesion size), this could easily lead to “overfitting” of the regression model.

\(^r\) “Overfitting” often occurs when one puts variables into a model simply to explain variance without regard to a hypothesis. This can lead to correctly specified models that make little theoretical sense.
All models we used to explain heterogeneity in the meta-analysis of all 9 studies were unsuccessful; they all yielded statistically significant values of $Q_E$. Therefore, we conducted an analysis excluding one study, Salzberg et al.; this study was the second-most extreme outlier in terms of the $Q$ statistic and the most extreme outlier in terms of outcomes (effect size $d$). Excluding this trial made the analysis more conservative. Overall findings of the remaining 8 studies were similar to the full set (including Salzberg et al.) A fixed-effects meta-analysis on the remaining 8 studies yielded $d_o$ of +1.07 (CI = +0.85 to +1.29), a statistically significant positive effect of ES on the normalized wound healing rate (?). These 8 studies are also heterogeneous ($Q$ statistic p value <.0001). A random-effects meta-analysis of this subset of studies also yielded statistically significant results ($d_o = +0.92$, CI = +0.42 to +1.42).

We constructed our model with criteria previously described using these 8 studies. We found a fixed-effects model in which the composite device variable ($dv$) was statistically significant. We decomposed $dv$ and obtained a correctly specified model which showed (a) a statistically significant positive correlation between ulcer type and $d$, (b) a statistically significant negative correlation between initial ulcer size and $d$, and (c) a statistically significant negative correlation between the combined group of direct current and pulsed direct current devices (DC/PC) and $d$. The equation appears as follows:

$$d = \text{wound type + initial wound size + DC/PC}$$

These results suggest that wounds responding most favorably to ES therapy are initially small, decubitus, and are not treated by DC or PC devices.

**RANDOM EFFECTS MODEL**—We found slightly different results using a random effects analysis. The association between $d$ and initial wound size ($B = -0.06$, CI = -0.11 to -0.10) and type of device ($B = -1.25$, CI = -1.88 to -0.62) remained statistically significant, but wound type ($B = +0.60$, CI = -0.02 to +1.22) was not.

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* We chose to exclude this trial instead of the most extreme outlier, Katelaris et al., because the reporting was less complete in the Salzberg et al. trial. Therefore, the Katelaris et al. study would have been discarded by our computer program in many cases and, hence, have led to an analysis of 7 trials instead of 8.

† Venous ulcers were assigned a “dummy” code, so a positive correlation indicates greater effects in patients with decubitus ulcers. The unstandardized regression coefficient ($B$) for wound type was +0.55 (CI = +0.01 to +1.10).

‡ Unstandardized regression coefficient ($B$) = -0.06, CI = -0.10 to -0.02.

§ Unstandardized regression coefficient ($B$) = -1.20, CI = -1.74 to -0.66.
6.2.3 Meta-Analysis of Complete Wound Healing

We used all 9 controlled studies obtained from our literature search in our meta-analysis of complete wound healing. These studies and relevant data are shown in Table 6.8. Details of this table are similar to those described for Table 6.6. Our strategy for the meta-analysis of complete healing was similar to that described for the normalized healing rate.

6.2.3.1 Overall Study Analysis

**FIXED-EFFECTS MODEL**—We calculated the fixed-effects \( d \) statistic and confidence limits for each study and the overall \( d \) statistic (\( d_o \)) and its confidence limits. The \( d \) statistics are listed in Table 6.9 and presented graphically in an effects size plot in Figure 6.4.

ES has an overall statistically significant positive effect on complete wound healing (\( d_o = +0.85 \), CI = +0.59 to +1.12). However, the \( Q \) statistic is highly significant (\( p < .0001 \)), indicating that these studies are not homogeneous.

Because these studies are heterogeneous, we first sought to determine whether the apparently positive effects of ES were due to statistical outliers. (See section 6.2.2.1.)

In our outlier analysis, we discarded 2 outlying ES studies to yield a nonsignificant \( Q \) statistic (\( p = .31 \)): Kloth & Feedar\(^{664}\) and Wood et al.,\(^{665}\) leaving us with an apparently homogeneous group. The resulting overall \( d \) (\( d_o \)) was +0.57 (CI = +0.26 to +0.87). Because the CI\(_{lower}\) is greater than zero, ES still demonstrates a statistically significant, positive effect on complete wound healing. These results also suggest that the statistically significant effects obtained in all 9 studies (including outliers) are not attributable to a few aberrant trials.

**RANDOM EFFECTS MODEL**—For illustrative purposes, we analyzed the 8 studies using a random effects statistical model. We obtained a \( d_o \) of +0.95 (CI = +0.39 to +1.52). These results indicate that ES has a statistically significant positive effect on complete wound healing.

6.2.3.2 Analysis of Study Heterogeneity

We established that ES has a statistically significant positive effect on complete wound healing but that these studies are not homogeneous. We wanted to determine the source of this heterogeneity. We investigated 2 main sources (1) study design and (2) patient or wound characteristics and treatment.
6.2.3.2.1  Influence of Study Design

**FIXED-EFFECTS MODEL**—We searched for a relationship between study design and $d$ using a fixed-effects model.

First, we analyzed studies by blinding. The $d$ values from studies in which clinicians were not blind ($d = +0.62$, CI = +0.21 to +1.03) were not significantly different than the $d$ values from studies employing blinding ($d = +1.01$, CI = +0.67 to +1.35). Similarly, the $Q$ statistic p value for the between-groups comparison was 0.15. As in the meta-analysis on normalized wound healing rates, the within-group $Q$ statistic for nonblind studies was statistically significant ($p = .0003$), indicating that categorizing studies in this manner does not adequately account for heterogeneity.

Second, we evaluated differences among studies that were (a) controlled but not randomized, (b) randomized but not blinded, and (c) randomized and blinded. The $Q$ statistic for the between-group comparison was not significant ($p = .08$). Similarly, the $d$ value for the 1 controlled, nonrandomized study was 0.00 (CI = -0.83 to +0.83); the $d$ value for the 3 randomized, unblinded studies was +0.82 (CI = +0.35 to +1.30); the $d$ value for the 5 randomized, blinded studies was +1.01 (CI = +0.67 to +1.35). The within-group $Q$ for the randomized, unblinded studies was statistically significant ($p = .0003$), indicating that grouping studies in this manner does not adequately account for the heterogeneity of the studies.\[^w\]

Third, we analyzed studies by randomization.\[^x\] The 1 nonrandomized study had a $d$ value of 0.00 (CI = -0.83 to +0.83); the 8 randomized studies had a $d$ value of +0.95 (CI = +0.59 to +1.12). The $Q$ statistic for the within-group heterogeneity of the randomized studies was statistically significant ($p = .0007$), indicating that this categorization of studies does not explain the heterogeneity among all 9 studies.

Although these analyses of the influence of report quality are flawed, they are suggestive. It is generally thought that failure to blind physicians or failure to randomly assign patients to different groups creates the potential for investigators to bias their results. This putative bias could lead to investigators finding larger effects by ES in unblinded or nonrandomized studies. These studies show the converse—larger effects in blinded and/or randomized trials. Because these data run counter to prevailing hypotheses, it seems likely that randomization and blinding quality are not altering results in the expected direction.

\[^w\] An additional caveat to this analysis is that there was only 1 controlled, nonrandomized study. This artificially sets the variance within this group to 0 and artificially reduces the p value of the between-groups comparison.

\[^x\] Same caveat as previous footnote.
6.2.3.2.2 Influence of Patient Characteristics, Wound Characteristics, or Treatment

We wanted to determine whether the statistically significant effects of ES on complete healing were due to patient characteristics (e.g., age), wound characteristics (e.g., initial lesion size), and/or treatment (e.g., DC versus AC).

**FIXED-EFFECTS MODEL**—We used the same type of multivariate technique as the meta-analysis for normalized healing rates. [See section 6.2.2.2.2.]

As with the previous analysis, all models we used to explain the heterogeneity in the meta-analysis that included the 9 studies were unsuccessful; they all yielded statistically significant values of $Q_E$. Therefore, we conducted an analysis excluding one study, Kloth & Feedar, because it was the most extreme outlier in the complete wound healing data set, both in terms of the $Q$ statistic and in terms of the deviation of its $d$ from $d_o$. A fixed-effects meta-analysis on the remaining 8 studies yielded $d_o$ of +0.78 (CI = +0.52 to +1.05), a statistically significant positive effect of ES on complete wound healing. These 8 studies were also heterogeneous ($Q$ statistic p = .048). A random-effects meta-analysis of this subset also yielded statistically significant results ($d_o$ = +0.73, CI = +0.33 to +1.13).

Fixed-effects univariate analyses of relevant variables (e.g., wound type, device type) suggested that the only variable that could explain the heterogeneity of $d$ values was wound type. Studies of patients with decubitus ulcers had a $d_o$ of +1.22 (CI = +0.82 to +1.62); studies of patients with venous ulcers had a $d_o$ of +0.45 (CI = +0.09 to +0.80.) The $Q$ statistic for the between-group differences was statistically significant, and the $Q$ statistic for within-group differences was not significant for decubitus ulcers (p = 0.56) or for venous ulcers (p = 0.53).

We conducted multiple regression analyses to confirm these results and to determine whether any other variable could modify the effects of ES on complete wound healing. We used the same strategy as for the meta-analysis of normalized healing rates. A fixed-effects regression analysis showed that the effects of type of wound were statistically significant (the unstandardized regression coefficient $B = +0.77$, CI = +0.24 to +1.30). The $Q_E$ statistic showed that the model was correctly specified (p = 0.41). No other variable showed a statistically significant relationship with $d$ when entered into the model.

**RANDOM-EFFECTS MODEL**—The random-effects variance was zero. Therefore, the random-effects model is identical to the fixed-effects model.
6.2.4 Publication Bias

Publication bias occurs when the meta-analysis tends to contain studies that show statistically significant results but does not contain studies that tend to show non-significant results. Publication bias presents major problems for a meta-analysis because the analysis itself becomes predicated on a biased sample of studies.

Funnel plots are an important means for detecting publication bias. In theory, results of smaller studies will be more variable than those from larger studies. If there is no publication bias, a scatter plot (funnel plot) of the $d$ value for each study (plotted on the x-axis) versus the number of patients in that study (plotted on the y-axis) should be shaped like a funnel with the spout pointing up. Points nearest the x-axis ($d$ values) should be spread apart and those farthest from this axis should be close together. On the other hand, if there is publication bias, small or negative effects of smaller studies will be absent from the plot. The resulting plot will not look like a funnel.

Funnel plots for the analyses of $\alpha$ and complete wound healing are shown in Figure 6.5 and Figure 6.6. Neither funnel plot shows the expected pattern of publication bias. These plots also show that the trials excluded from the multiple regression analyses (Salzberg et al. from normalized healing rates, Kloth & Feedar from complete healing) were among the smallest trials we analyzed.

There are several reasons why these plots do not conclusively rule out bias. First, each plot is based on only 9 studies. The addition of only 2 or 3 studies with “aberrant” results could easily change the perception of possible publication bias. Second, the plots depict results obtained from both patients with decubitus ulcers and from patients with venous ulcers. It is not clear that data from different ulcer types can be unambiguously contained within the same funnel plot, especially when evaluating complete wound healing. Third, funnel plots can be difficult to interpret. For example, if studies reporting positive results have an 80% chance of being published and studies obtaining nonsignificant results have a 10% chance of being published, then interpreting a funnel plot becomes more difficult because it partly depends on one’s ability to discern differences in the density and distribution of points, and not merely detecting the absence of points in the lower left hand corner of the plot.

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1. For the purposes of this report, publication bias will be defined in a broad sense, and includes the bias that occurs when studies finding statistically significant results are accepted for publication and studies failing to find such results are not, and the failure of investigators to submit non-significant results for publication. This latter form of bias has also been called reporting bias.

2. As noted above, the results of small trials tend to be highly variable, so omitting such trials from the meta-analyses may not appreciably hinder interpretation of results.
Another way of accounting for publication bias is determining the number of studies with an average effect size of 0 that would be needed to overturn the results of the meta-analysis. Rosenthal’s method\(^ {667}\) involves converting each study’s effect size into a \(z\) score and then computing the number of studies needed to bring this score below a specified level of significance—in this case, \(p = 0.05\) level. [See Appendix II, section 11.3.] If only a few such studies are required, then even a small amount of publication bias would alter the conclusions of the meta-analysis. If, however, a large number of studies are needed to overturn the results, then the conclusions of the analysis are robust. Using Rosenthal’s method, 95 studies with nonsignificant results are required to overturn the significance of the meta-analysis of normalized healing rates (for all 9 studies), 51 when the Salzberg et al. trial is excluded. Sixty-seven studies are required to overturn the meta-analysis of complete wound healing (for all 9 studies), 31 when the Kloth & Feedar trial is excluded. It seems unlikely that this number of unpublished RCTs exists.

Another method by Orwin\(^ {668}\) is based on determining how many studies would be required to drop \(d_0\) to a negligible level. [See Appendix II, section 11.3 for determining negligible levels of \(d_0\).] According to the Orwin method, 20 studies would be required to overturn the results of the meta-analysis on \(\ldots\) (for all 9 studies), 16 when the Salzberg et al. trial is excluded. Thirty-three studies would be required to overturn the meta-analysis of complete wound healing (for all 9 studies), 31 when the Kloth & Feedar trial is excluded. It seems unlikely that this number of unpublished trials exists.

These methods are open to criticism. These criticisms are discussed in Appendix II, section 11.3.

Although these methods of assessing publication bias are experimental, they provide no evidence that publication affected the results of our meta-analysis.

### 6.2.5 Conclusions of Meta-Analyses of Electrical Stimulation for Wound Healing

Our meta-analyses are not conclusive, having been hampered by a number of limitations in the literature. First, we could only meta-analyze the data by excluding 1 or 2 outliers from each analysis. Second, many of the studies are relatively small. Although this does not appreciably affect values of \(d\), it does affect the \(Q\) statistic. The heterogeneity statistic works reasonably well when the treatment and control groups each contain \(\geq 10\) patients.\(^ {669}\) However, 2 studies in our analyses of \(\ldots\) and 3 studies in our analyses of complete wound healing...
contained less than 20 patients. The $Q$ statistic is less reliable under such circumstances. Third, it is not clear whether our random-effects models contained enough studies to accurately estimate the true random-effects variance. For example, a random-effects meta-analysis on wound healing rates conducted prior to 1995 would not have “anticipated” the Salzberg trial, which was a statistical outlier that prevented combining all trials into the analysis. This failure to “anticipate” is probably due to the relatively small number of studies in our meta-analyses. Fourth, our conclusions are limited by weaknesses in the literature. We were unable to account for ulcer stage in both meta-analyses. Only 1 study in each meta-analysis specified using a homogeneous-staged group. The remainder used an unspecified mixture of ulcer stages or completely failed to specify ulcer stage at all. This means that our meta-analytic conclusions may not be generalizable beyond stage II decubitus ulcerations. Another weakness in the literature is that some studies either failed to specify the control treatment or primarily used saline-soaked gauze as the control treatment. (These treatments were employed in 5 of 8 studies included in the multiple regressions of complete wound healing and 4 of 8 multiple regressions of normalized healing rates.) Therefore, it is not possible for us to meta-analytically determine whether ES is superior to treatments that do not rely primarily on untreated or saline-soaked gauze.

In spite of these weaknesses, our meta-analyses suggest that ES increases the normalized healing rate and the complete healing of chronic ulcers. However, the relationship between these outcomes and ES is not always direct. The effects of ES on wound healing rates appear to decrease in patients with larger wounds and is affected by the type of stimulator. There is also weaker evidence suggesting that decubitus ulcers have greater healing rates than venous ulcers. Finally, ES appears more likely to enhance complete healing of decubitus ulcers.

There were 2 studies with less than 20 patients in the analysis of all 9 studies of healing rates and the analysis wherein the Salzberg et al. trial was excluded, 4 such studies in our analysis of complete healing based on all 9 trials, and 3 such studies in our analysis of complete healing from which the Kloth and Feedar trial was excluded. The Kloth and Feedar trial was 1 of these small trials.
6.3 Figures and Tables

Figure 6.1. Plots of Initial Wound Size versus Normalized Healing Rates

A

Initial Size vs. Theta:
Control Groups from All ES Studies

B

Initial Size vs. Theta:
Control Groups from Conventional Venous Studies

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Figure 6.1. Plots of Initial Wound Size vs. Normalized Healing Rates (?) (continued)

Plots of normalized healing rates (?) versus initial wound size of control groups for (A) all controlled ES studies, (B) conventional therapies for venous ulcers, and (C) all controlled ES studies and conventional therapies for venous and decubitus ulcers.
Figure 6.2. Computer-Generated Negative Exponential Model Plots of Wound Healing

A

Wound Healing: Negative Exponential Fit (Computer-Generated)
Wood et al. 1993

B

Wound Healing: Negative Exponential Fit (Computer-Generated)
Feedar et al. 1991

Computer-generated fit for exponential decay model using data from (A) Wood et al.\textsuperscript{670} and (B) Feedar et al.\textsuperscript{671}
Table 6.1. Normalized Healing Rates for Direct Current Stimulation Studies of Wound Healing

<table>
<thead>
<tr>
<th>Study</th>
<th>Stimulation</th>
<th>Study Type</th>
<th>Lesions</th>
<th>Treatment Group</th>
<th>Number Patients or Lesions</th>
<th>Initial Wound Size</th>
<th>Mean Normalized Healing Rate (θ)</th>
<th>95% CI around Mean θ</th>
<th>Statistical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katelaris et al. (1987)</td>
<td>LIDC</td>
<td>Comparative Controlled</td>
<td>Venous</td>
<td>LIDC + povidone</td>
<td>4</td>
<td>12.0 cm²</td>
<td>0.3779a</td>
<td>0.3243 to 0.4315</td>
<td>Significant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LIDC + saline</td>
<td>11</td>
<td>12.4 cm²</td>
<td>0.6552</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Saline (Gauze)</td>
<td>5</td>
<td>13.7 cm²</td>
<td>0.7023</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>5.1 cm²</td>
<td>0.6993</td>
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<tr>
<td>Carley &amp; Wainapel (1985)</td>
<td>LIDC</td>
<td>RCT</td>
<td>—</td>
<td>LIDC Saline Gauze</td>
<td>15</td>
<td>4.74 cm³ (vol)</td>
<td>0.4720b</td>
<td>0.4620 to 0.4820</td>
<td>Significant</td>
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<td></td>
<td>15</td>
<td>3.92 cm³ (vol)</td>
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<td>0.1163 to 0.1291</td>
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<td>Akers &amp; Gabrielson (1984)</td>
<td>DC</td>
<td>Comparative Controlled</td>
<td>Decubitus</td>
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<td>—</td>
<td>—</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DC + Whirlpool</td>
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<td>Whirlpool</td>
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<td>—</td>
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<td>—</td>
</tr>
<tr>
<td>Gault &amp; Gatens (1976)</td>
<td>LIDC</td>
<td>Case series</td>
<td>Mixed</td>
<td>LIDC</td>
<td>100</td>
<td>—</td>
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<tr>
<td>Wolcott et al. (1969)</td>
<td>LIDC</td>
<td>Case series</td>
<td>Mixed</td>
<td>LIDC</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&quot;Embedded&quot; RCT</td>
<td>6</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<td></td>
<td></td>
<td></td>
<td>Conventional</td>
<td>6</td>
<td>—</td>
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</tr>
</tbody>
</table>

Case reports excluded

- Contralateral lesions on same patient
- θ calculations for study based on complete healing time
- θ calculations for study based on wound sizes at different time intervals
- NS = nonsignificant
- — = not specified or not applicable

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286961.WGE
### Table 6.2. Normalized Healing Rates for Pulsed Current Stimulation Studies of Wound Healing

<table>
<thead>
<tr>
<th>Study</th>
<th>Stimulation</th>
<th>Study Type</th>
<th>Lesions</th>
<th>Treatment Group</th>
<th>Number Patients or Lesions</th>
<th>Initial Wound Size</th>
<th>Mean Normalized Healing Rate ((\theta))</th>
<th>95% CI around Mean ((\theta))</th>
<th>Statistical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wood et al.1993</td>
<td>PDC</td>
<td>Double-blind RCT</td>
<td>Decubitus (stage II/III)</td>
<td>PDC Sham (placebo)</td>
<td>43</td>
<td>2.61 cm(^2) 1.91 cm(^2)</td>
<td>0.4199(^b) 0.0859</td>
<td>0.3571 to .4827 -0.0098 to +.0859</td>
<td>Significant</td>
</tr>
<tr>
<td>Gogia et al.1993</td>
<td>HVPC</td>
<td>RCT</td>
<td>Mixed</td>
<td>HVPC Whirlpool</td>
<td>6</td>
<td>11.5 cm(^2) 10.0 cm(^2)</td>
<td>0.0762(^a) 0.0892</td>
<td>No variance provided in study</td>
<td>—</td>
</tr>
<tr>
<td>Gentzkow et al.1991</td>
<td>PDC</td>
<td>Double-blind RCT</td>
<td>Decubitus (stage III/IV)</td>
<td>PDC Sham (placebo)</td>
<td>21</td>
<td>19.2 cm(^2) 12.5 cm(^2)</td>
<td>0.1582(^b) 0.0771</td>
<td>.0297 to .2867 .0634 to .0908</td>
<td>NS</td>
</tr>
<tr>
<td>Griffin et al.1991</td>
<td>HVPC</td>
<td>Single-blind RCT</td>
<td>Decubitus (grades II-IV)</td>
<td>HVPC Sham (placebo)</td>
<td>8</td>
<td>2.34 cm(^2) 2.72 cm(^2)</td>
<td>0.4783(^a) 0.2750</td>
<td>.3390 to .9568 .1924 to .5060</td>
<td>NS</td>
</tr>
<tr>
<td>Feedar et al.1991</td>
<td>PDC</td>
<td>Double-blind RCT</td>
<td>Mixed</td>
<td>PDC Sham (placebo)</td>
<td>26</td>
<td>14.7 cm(^2) 16.9 cm(^2)</td>
<td>0.3375(^a) 0.2111</td>
<td>.1964 to .4785 .0792 to .2111</td>
<td>NS</td>
</tr>
<tr>
<td>Unger et al.1991</td>
<td>HVPC</td>
<td>Double-blind RCT</td>
<td>Decubitus (stage IV)</td>
<td>HVPC Sham (placebo)</td>
<td>9</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Ungerootnote{Abstract}1991</td>
<td>HVPC</td>
<td>Case series</td>
<td>—</td>
<td>HVPC</td>
<td>223</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Kloth &amp; Feedar1988</td>
<td>HVPC</td>
<td>Single-blind RCT</td>
<td>Decubitus (stage IV)</td>
<td>HVPC Sham (placebo)</td>
<td>9</td>
<td>4.08 cm(^2) 5.20 cm(^2)</td>
<td>0.8835(^b) -0.0143</td>
<td>.4201 to 1.3469 -.0893 to +.0607</td>
<td>Significant</td>
</tr>
<tr>
<td>Feedar &amp; Kloth1985</td>
<td>HVPC</td>
<td>Single-blind RCT</td>
<td>Decubitus (stage IV)</td>
<td>HVPC Sham (placebo)</td>
<td>5</td>
<td>—</td>
<td>—</td>
<td>—</td>
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</tr>
</tbody>
</table>

Case reports excluded

\footnotetext{a}{Theta calculations for study based on complete healing time (or single point)}

\footnotetext{b}{Theta calculations for study based on wound sizes at different time intervals}

NS = nonsignificant;
— = not specified or not available

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Table 6.3. Normalized Healing Rates for Alternating Current and TENS Stimulation Studies of Wound Healing

<table>
<thead>
<tr>
<th>Study</th>
<th>Stimulation</th>
<th>Study Type</th>
<th>Lesions</th>
<th>Treatment Group</th>
<th>Number Patients or Lesions</th>
<th>Initial Wound Size</th>
<th>Mean Normalized Healing Rate (?)</th>
<th>95% CI around Mean (?)</th>
<th>Statistical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stefanovska et al.687 (1993)</td>
<td>AC</td>
<td>RCT</td>
<td>Decubitus</td>
<td>AC</td>
<td>82</td>
<td>12.0 cm²</td>
<td>0.3801c</td>
<td>.3461 to .4141</td>
<td>Significant*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DC</td>
<td>18</td>
<td>12.4 cm²</td>
<td>0.2177</td>
<td>.1547</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Standard</td>
<td>50</td>
<td>16.6 cm²</td>
<td>0.1547</td>
<td>.1223 to .1871</td>
<td></td>
</tr>
<tr>
<td>Lundeborg et al.688 (1992)</td>
<td>TENS</td>
<td>Double-blind RCT</td>
<td>Diabetic</td>
<td>TENS</td>
<td>32</td>
<td>24.2 cm²</td>
<td>0.0846h</td>
<td>.0473</td>
<td>NS*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sham (placebo)</td>
<td>32</td>
<td>22.0 cm²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karba et al.689 (1991)</td>
<td>AC</td>
<td>Case series</td>
<td>Decubitus</td>
<td>AC</td>
<td>14</td>
<td>1.03 cm²</td>
<td>0.8300a</td>
<td>0.1862 to 1.4768</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vascular</td>
<td>32</td>
<td>1.77 cm²</td>
<td>0.4700a</td>
<td>.2936 to .6464</td>
<td>—</td>
</tr>
<tr>
<td>Frantz690 (1990) [Pilot study]**</td>
<td>TENS</td>
<td>Case series</td>
<td>Decubitus</td>
<td>TENS</td>
<td>4</td>
<td>11.3 cm²</td>
<td>0.1603a</td>
<td>-.4801 to +.8009</td>
<td>—</td>
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<tr>
<td>Kaada &amp; Emru691 (1988)</td>
<td>TENS</td>
<td>Case series</td>
<td>Leperomatous</td>
<td>TENS</td>
<td>32</td>
<td>5.2 cm³</td>
<td>0.8350b ? vol</td>
<td>0.6696 to 1.0003</td>
<td>—</td>
</tr>
<tr>
<td>Barron et al.693 (1985)</td>
<td>TENS</td>
<td>Case series</td>
<td>Decubitus</td>
<td>TENS</td>
<td>6</td>
<td>5.09 cm²</td>
<td>1.4827a</td>
<td>0.7468 to 2.2185</td>
<td>—</td>
</tr>
</tbody>
</table>

Case studies excluded

* Compared to standard therapy; ** Insufficient data in preliminary RCT for analysis
a Theta calculations for study based on complete healing time (or single point)
b Theta calculations for study based on wound sizes at different time intervals
c Theta values specified by investigators
NS = non-significant; — = not specified or not applicable

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<table>
<thead>
<tr>
<th>Study</th>
<th>Stimulation</th>
<th>Study Type</th>
<th>Lesions</th>
<th>Treatment Group</th>
<th>Number Patients or Lesions</th>
<th>Initial Wound Size</th>
<th>Mean Normalized Healing Rate (?</th>
<th>95% CI around Mean (?)</th>
<th>Statistical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salzberg et al.694 (1995)</td>
<td>PEE</td>
<td>Double-blind RCT</td>
<td>Decubitus</td>
<td>PEE</td>
<td>10</td>
<td>15 cm² (median) 33 cm² (median)</td>
<td>1.4740</td>
<td>0.5209</td>
<td>1.3114 to 1.6370</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(stage II)</td>
<td>Sham (placebo)</td>
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<td></td>
<td></td>
<td>0.1488 to 0.6740</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Decubitus</td>
<td>PEE</td>
<td>5</td>
<td>—</td>
<td></td>
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<td>—</td>
</tr>
<tr>
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<td>(stage III)</td>
<td>Sham (placebo)</td>
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</tr>
<tr>
<td>Stiller et al.695 (1992)</td>
<td>PEMF</td>
<td>Double-blind RCT</td>
<td>Venous</td>
<td>PEMF</td>
<td>18</td>
<td>7.25 cm² 7.66 cm²</td>
<td>+0.0824a</td>
<td>-0.0754</td>
<td>.0596 to .0975 -.0984 to +0.0082</td>
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<td>Sham (placebo)</td>
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<tr>
<td>Todd et al.696 (1991)</td>
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<td>Double-blind RCT</td>
<td>Venous</td>
<td>PEMF</td>
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<td>83.5 cm² 53.8 cm²</td>
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<tr>
<td>Itoh et al.697 (1991)</td>
<td>PEE</td>
<td>Case series</td>
<td>Decubitus</td>
<td>PEE</td>
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<td>1.7377 to 4.4627</td>
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<td>(stage II)</td>
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<tr>
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<td></td>
<td></td>
<td>Decubitus</td>
<td>PEE</td>
<td>13</td>
<td>8.78 cm²</td>
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<td>0.2683 to 1.6546</td>
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<td>(stage III)</td>
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<td></td>
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<td>—</td>
</tr>
<tr>
<td>Jeran et al.698 (1990)</td>
<td>PEMF</td>
<td>Double-blind RCT</td>
<td>Venous</td>
<td>PEMF</td>
<td>18</td>
<td>—</td>
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<td>—</td>
<td>—</td>
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<td>Sham (placebo)</td>
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<td>—</td>
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<tr>
<td>Jeran* et al.699</td>
<td>PEMF</td>
<td>Double-blind RCT</td>
<td>Venous</td>
<td>PEMF</td>
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<td></td>
<td></td>
<td></td>
<td>Sham (placebo)</td>
<td>11</td>
<td>—</td>
<td></td>
<td>—</td>
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</table>

Case studies excluded
* Preliminary early study of Jeran et al. (1990)
+ Theta calculations for study based on complete healing time (or single point)
— = not specified or not available
Table 6.5. Summary of Normalized Healing Rates in Controlled Trials of Electrical Stimulation for Chronic Wound Healing

<table>
<thead>
<tr>
<th>Type of Lesion</th>
<th>Direct Current (DC)</th>
<th>Pulsed Current (PC)</th>
<th>Alternating Current (AC)/TENS</th>
<th>Pulsed Electromagnetic Induction (PEMI)</th>
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<tbody>
<tr>
<td></td>
<td>Study</td>
<td>Significance</td>
<td>Study</td>
<td>Significance</td>
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<td></td>
<td></td>
<td>Griffin709 (1991)</td>
<td>NS</td>
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<td></td>
<td></td>
<td>Unger710 (1991)</td>
<td>Significant</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Kloth711 (1988)</td>
<td>—</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Feedar712 (1985)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gentzkow708 (1991)</td>
<td>—</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Griffin709 (1991)</td>
<td>—</td>
</tr>
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<td></td>
<td></td>
<td>Unger710 (1991)</td>
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<td>Kloth711 (1988)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Feedar712 (1985)</td>
<td>—</td>
</tr>
<tr>
<td>Groups of Mixed Lesions or Unspecified Lesions</td>
<td>Carley714 (1985)</td>
<td>Significant</td>
<td>—</td>
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<td></td>
<td>Gaul717,718** (1978)</td>
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<td>—</td>
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</tr>
<tr>
<td></td>
<td>Wolcott719*** (1969)</td>
<td></td>
<td>—</td>
<td>—</td>
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<td></td>
<td></td>
<td></td>
<td>Gogia714 (1993)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Feedar716 (1991)</td>
<td></td>
</tr>
</tbody>
</table>

* Nonrandomized comparative controlled study
** In one comparison, ? for LIDC + povidone < ? for povidone alone
*** Randomized therapy ("embedded" RCT) on same patient
# Abstract
NS = nonsignificant;
— = not specified or not available

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### Table 6.6. Studies and Relevant Data for Meta-Analysis of Normalized Wound Healing Rates

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Randomization</th>
<th>Blinding</th>
<th>Device Type</th>
<th>Wound Type</th>
<th>Initial Wound Size (cm²)</th>
<th>Patient Age</th>
<th>Study Length (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katelaris et al.⁷²¹</td>
<td>1987</td>
<td>No</td>
<td>No</td>
<td>DC</td>
<td>Venous</td>
<td>12.00</td>
<td>72.6</td>
<td>104.0</td>
</tr>
<tr>
<td>Kloth &amp; Feeder⁷²²</td>
<td>1988</td>
<td>Yes</td>
<td>No</td>
<td>PC</td>
<td>Decubitus</td>
<td>4.57</td>
<td>68.1</td>
<td>7.4</td>
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<tr>
<td>Gentzkow et al.⁷²³</td>
<td>1991</td>
<td>Yes</td>
<td>Yes</td>
<td>PC</td>
<td>Decubitus</td>
<td>16.01</td>
<td>62.7</td>
<td>4.0</td>
</tr>
<tr>
<td>Griffin et al.⁷²⁴</td>
<td>1991</td>
<td>Yes</td>
<td>No</td>
<td>PC</td>
<td>Decubitus</td>
<td>2.55</td>
<td>28.8</td>
<td>2.9</td>
</tr>
<tr>
<td>Lundberg et al.⁷²⁵</td>
<td>1992</td>
<td>No</td>
<td>Yes</td>
<td>AC</td>
<td>Venous</td>
<td>23.16</td>
<td>66.7</td>
<td>12.0</td>
</tr>
<tr>
<td>Stiller et al.⁷²⁶</td>
<td>1992</td>
<td>Yes</td>
<td>Yes</td>
<td>PEMI</td>
<td>Venous</td>
<td>7.42</td>
<td>63.5</td>
<td>8.0</td>
</tr>
<tr>
<td>Stefanovska et al.⁷²⁷</td>
<td>1993</td>
<td>No</td>
<td>No</td>
<td>AC</td>
<td>Decubitus</td>
<td>13.74</td>
<td>36.9</td>
<td>2.1</td>
</tr>
<tr>
<td>Wood et al.⁷²⁸</td>
<td>1993</td>
<td>Yes</td>
<td>Yes</td>
<td>PC</td>
<td>Decubitus</td>
<td>2.32</td>
<td>75.3</td>
<td>8.0</td>
</tr>
<tr>
<td>Salzberg et al.⁷²⁹</td>
<td>1995</td>
<td>Yes</td>
<td>Yes</td>
<td>PEMI</td>
<td>Decubitus</td>
<td>24.00</td>
<td>54.0</td>
<td>12.0</td>
</tr>
</tbody>
</table>

AC = alternating current; DC = direct current; PDC = pulsed direct current; PEM = pulsed electromagnetic

---

⁷²¹ This study contained 4 groups, providone-iodine, providone-iodine with ES, normal saline, and normal saline with ES. For the purposes of analysis, outcomes from the 2 groups without ES were combined, and outcomes from the 2 groups with ES were combined.

⁷²² This study included 82 patients treated with AC devices and 18 patients given treatment with DC devices and who showed a lower normalized rate of healing. These latter data were not used in the meta-analysis because these results may not be independent and may, therefore, create errors in tests of statistical significance. In excluding this set of results we follow Rosenthal’s recommendation "to have each study contribute only a single effect size estimate and a single significance level to the overall analysis."⁷³⁰

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### Table 6.7. Meta-Analysis (Fixed Effects) of Normalized Wound Healing Rates: $d$ Statistic with Confidence Limits

<table>
<thead>
<tr>
<th>Study</th>
<th>$d$</th>
<th>$CL_{lower}$</th>
<th>$CL_{upper}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katelaris et al.</td>
<td>-0.51</td>
<td>-1.25</td>
<td>0.33</td>
</tr>
<tr>
<td>Kloth and Feedar</td>
<td>1.57</td>
<td>0.44</td>
<td>2.70</td>
</tr>
<tr>
<td>Gentzkow et al.</td>
<td>0.36</td>
<td>-0.26</td>
<td>0.99</td>
</tr>
<tr>
<td>Griffin et al.</td>
<td>0.36</td>
<td>-0.60</td>
<td>1.32</td>
</tr>
<tr>
<td>Lundberg et al.</td>
<td>0.80</td>
<td>0.23</td>
<td>1.37</td>
</tr>
<tr>
<td>Stiller et al.</td>
<td>1.55</td>
<td>0.74</td>
<td>2.36</td>
</tr>
<tr>
<td>Stefanoska et al.</td>
<td>1.56</td>
<td>1.17</td>
<td>1.96</td>
</tr>
<tr>
<td>Wood et al.</td>
<td>1.46</td>
<td>0.95</td>
<td>1.98</td>
</tr>
<tr>
<td>Salzberg et al.</td>
<td>3.57</td>
<td>2.16</td>
<td>4.99</td>
</tr>
<tr>
<td><strong>OVERALL</strong></td>
<td>1.13</td>
<td>0.91</td>
<td>1.35</td>
</tr>
</tbody>
</table>

$CL_{lower} = $ lower 95% confidence limit

$CL_{upper} = $ upper 95% confidence limit
Effect sizes (expressed in terms of Hedges’ $d$) with confidence intervals for $\theta$ in all 9 studies and overall $d$ ($d_o$). Studies with $CL_{lower} > 0$ exhibit a positive effect on normalized wound healing rate. (6 studies exhibit a positive effect; 3 studies exhibit no effect.) There is a positive overall effect.
### Table 6.8. Studies and Relevant Data for Meta-Analysis of Complete Wound Healing

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Randomization(^a)</th>
<th>Blinding(^b)</th>
<th>Device Type</th>
<th>Wound Type</th>
<th>Initial Wound Size (cm(^2))(^c,d)</th>
<th>Patient Age(^d)</th>
<th>Study Length (wks)(^d,e)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katelaris et al(^f)</td>
<td>111987</td>
<td>No</td>
<td>No</td>
<td>DC</td>
<td>Venous</td>
<td>12.00</td>
<td>72.6</td>
<td>104.0</td>
</tr>
<tr>
<td>Kloth and Feedar(^g)</td>
<td>1988</td>
<td>Yes</td>
<td>No</td>
<td>PC</td>
<td>Decubitus</td>
<td>4.57</td>
<td>68.1</td>
<td>7.4</td>
</tr>
<tr>
<td>Ieran et al(^h)</td>
<td>1990</td>
<td>Yes</td>
<td>Yes</td>
<td>PEMI</td>
<td>Venous</td>
<td>Not available</td>
<td>65.5</td>
<td>12.8</td>
</tr>
<tr>
<td>Griffin et al(^i)</td>
<td>1991</td>
<td>Yes</td>
<td>No</td>
<td>PC</td>
<td>Decubitus</td>
<td>2.55</td>
<td>32.5</td>
<td>2.9</td>
</tr>
<tr>
<td>Todd et al(^j)</td>
<td>1991</td>
<td>Yes</td>
<td>Yes</td>
<td>PEMI</td>
<td>Venous</td>
<td>52.27</td>
<td>74.4</td>
<td>6.0</td>
</tr>
<tr>
<td>Unger et al(^k)</td>
<td>1992</td>
<td>Yes</td>
<td>Yes</td>
<td>AC</td>
<td>Decubitus</td>
<td>Not available</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td>Lundberg et al(^l)</td>
<td>1993</td>
<td>Yes</td>
<td>No</td>
<td>PC</td>
<td>Decubitus</td>
<td>2.32</td>
<td>75.3</td>
<td>8</td>
</tr>
<tr>
<td>Wood et al(^m)</td>
<td>1995</td>
<td>Yes</td>
<td>Yes</td>
<td>PEMI</td>
<td>Decubitus</td>
<td>Not available</td>
<td>Not available</td>
<td>Not available</td>
</tr>
</tbody>
</table>

\(AC =\) alternating current; \(DC =\) direct current; \(PDC =\) pulsed direct current; \(PEM =\) pulsed electromagnetic device

\(^a\) “Random” refers to whether patients were randomly assigned to treatment and control groups.

\(^b\) “Blinding” refers to whether physicians were blinded.

\(^c\) Initial wound size refers to the size of the wound at the beginning of the study.

\(^d\) Initial wound sizes patient ages, and, occasionally study length were reported separately for experimental and control groups. When this occurred, an average weighted by the number of patients in each group was computed.

\(^e\) Study length includes follow-up. It does not necessarily refer to the length or time treatment was given.

\(^f\) This study contained 4 groups: providone-iodine, providone-iodine with ES, normal saline, and normal saline with ES. For the purposes of analysis, outcomes from the 2 groups without ES were combined, and outcomes from the 2 groups with ES were combined.

\(^g\) In this study, 0 of 7 controls, and 9 of 9 treated subjects healed. This led to incalculable variances. To allow for computation of a variance, we arbitrarily assumed that 0.5 wounds in the control group healed.

\(^h\) Authors presented results gathered after 90 days and 1 year of follow-up. In this analysis, only the results gathered at 90 days were used because this is more similar to the follow-up time of other studies. We also excluded the 1 year data from the meta-analysis because the results from both sets are not likely to be independent. Nonindependence of results can create errors in tests of statistical significance. In excluding 1 set of results we follow Rosenthal’s recommendation “to have each study contribute only a single effect size estimate and a single significance level to the overall analysis”\(^i\).

\(^i\) That no healing occurred was inferred from the data. This inference is reasonable because the authors did not explicitly state that any wounds healed, because the maximum percentage of the area of healing is low (17.5%), and because the authors not that they failed to “show a statistically significant improvement in the ulcers treated with active coils.” Because this created a study for which variance was incalculable, we arbitrarily assumed that 0.5 patients in the experimental group healed.

\(^j\) Thirty-two patients in each of the treatment and control groups began the study, but 5 control and 8 experimental subjects did not complete it. Authors state that there was no statistically significant difference between groups in failure to complete the study. Patient characteristics in this table are based on the patients who entered the study because article does not separately provide information on only those patients who completed the study.

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Table 6.8.  Studies & Relevant Data for Meta-Analysis of Complete Wound Healing (continued)

This study reported data on patients with stage II and III ulcers. Because stage III ulcers may be of more clinical interest than those with stage II ulcers (because stage III ulcers are presumably more difficult to heal than stage II ulcers), and because patient characteristics shown to be relevant to outcomes by pilot analyses were reported for patients with stage III ulcers, data from patients with stage II ulcers were excluded from this analysis. This contrasts with the data used in the meta-analysis of wound healing rates. An additional reason for excluding 1 set of data is that the data from both types of ulcers may be nonindependent. Nonindependence of results can create errors in tests of statistical significance. In excluding one set of results we follow Rosenthal's recommendation "to have each study contribute only a single effect size estimate and a single significance level to the overall analysis." 741
Table 6.9. Meta-Analysis (Fixed Effects) of Complete Wound Healing: 
d Statistic with Confidence Limits

<table>
<thead>
<tr>
<th>Study</th>
<th>d</th>
<th>CL_lower</th>
<th>CL_upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katelaris et al.</td>
<td>0.00</td>
<td>-0.83</td>
<td>0.83</td>
</tr>
<tr>
<td>Kloth and Feedar</td>
<td>5.21</td>
<td>3.15</td>
<td>7.26</td>
</tr>
<tr>
<td>Ieran et al.</td>
<td>0.73</td>
<td>0.07</td>
<td>1.40</td>
</tr>
<tr>
<td>Griffin et al.</td>
<td>0.43</td>
<td>-0.57</td>
<td>1.43</td>
</tr>
<tr>
<td>Todd et al.</td>
<td>0.00</td>
<td>-0.90</td>
<td>0.90</td>
</tr>
<tr>
<td>Unger et al.</td>
<td>1.21</td>
<td>0.18</td>
<td>2.25</td>
</tr>
<tr>
<td>Lundberg et al.</td>
<td>0.62</td>
<td>0.06</td>
<td>1.18</td>
</tr>
<tr>
<td>Wood et al.</td>
<td>1.38</td>
<td>0.87</td>
<td>1.89</td>
</tr>
<tr>
<td>Salzberg et al.</td>
<td>1.56</td>
<td>0.15</td>
<td>2.98</td>
</tr>
<tr>
<td>OVERALL</td>
<td>0.85</td>
<td>0.59</td>
<td>1.12</td>
</tr>
</tbody>
</table>

\( CL_{\text{lower}} = \text{lower 95}\% \text{ confidence limit.} \\
\( CL_{\text{upper}} = \text{upper 95}\% \text{ confidence limit.} \)
Figure 6.4. Effect Size Plot (d Values) for Complete Wound Healing

Effect sizes (expressed in terms of Hedges' $d$) with confidence intervals for complete healing in all 9 studies and overall $d$ ($d_o$). Studies with $C_{lower} > 0$ exhibit a positive effect on complete healing. (6 studies exhibit a positive effect; 3 studies exhibit no effect.) There is a positive overall effect.
Figure 6.5. Funnel Plot for Detecting Publication Bias in Normalized Healing Rates

Plot depicts effect size (d) on the x-axis and number of patients (N) in each study on the y-axis. Study authors names are shown above each point, and denoted in parentheses next to these names is whether the study was on venous (V) or decubitus (D) ulcers.
Figure 6.6. Funnel Plot for Detecting Publication Bias in Complete Healing

Plot depicts effect size (d) on the x-axis and number of patients (N) in each study on the y-axis. Study authors names are shown above each point, and denoted in parentheses next to these names is whether the study was on venous (V) or decubitus (D) ulcers.
7.0 Quality of Study Comparison: Electrical Stimulation versus Conventional and Alternative Therapies for Wound Healing

The RCTs of ES therapy for wound healing have many design and reporting weaknesses. [See sections 4 and 5.] We wanted to determine whether these flaws are unique to ES studies or are common shortcomings throughout published studies of wound healing.

In the fourth part of our analysis, we compare the quality of ES studies to that reported in non-ES therapies for venous and for decubitus ulcers. [We excluded RCTs of diabetic ulcerations because only one ES study (Lundeberg et al. (1992)) evaluated them.]
7.1 Quality Comparison for Venous Ulcers

7.1.1 Comparison with Conventional Therapies

We used the search strategy specified in section 4.1 to identify RCTs of venous ulcers treated by different conventional therapies (e.g., dressings, topical agents). We excluded studies

- that did not appear to be randomized controlled,
- that did not define the type of ulceration,
- in which <80% of the patients (in any treatment group) had venous ulcers,
- that were published before 1970,
- that did not directly address the healing of wounds (e.g., studies of bacterial counts in lesions),
- that did not specify the number of patients in each treatment group, or
- in which most (specified) wounds were <30 days duration.

Our definition of conventional RCT was any therapeutic study of venous ulcers that evaluated debridement, cleaning agents, topical agents, dressings, bandages, antibiotics (systemic or local), compression therapies, systemic medications, or nutritional supplements.\textsuperscript{bb}

Our search identified 40 conventional RCTs for the treatment of venous ulcers that met our exclusion criteria. [See Table 7.1.]

We compared the quality of these 40 conventional RCTs to the ES RCTs (Stiller et al.\textsuperscript{742} 1992, Todd et al.\textsuperscript{743} 1991, and Ieran et al.\textsuperscript{744} 1990). [The study by Jeran et al.\textsuperscript{745} 1987 was not analyzed because it was a preliminary version of the study by Ieran et al.] We evaluated study homogeneity; study size; whether the study specified the randomization technique; blinding of groups; patient age; gender; location of lesions; duration of lesions; stage of lesions; specifications of lesion size; the use of pre-therapy vascular perfusion, inclusion criteria; possible confounding by patient selection (e.g., infection, peripheral arterial disease;

\textsuperscript{bb} The term “conventional” is not meant to imply that the (experimental group) therapy or therapies in the RCT are accepted treatment regimens.
diabetes; rheumatoid arthritis; steroid usage; nutritional status); specification of concomitant therapy; and possible confounding by inconsistencies in concomitant therapy (e.g., debridement, use of topical and/or cleansing agents, dressings, and oral or systemic antibiotics). [See Table 7.2.] These are the same study characteristics that we used to evaluate the quality of ES studies.

The study quality of the 40 conventional RCTs for venous ulcers appears similar to the individual RCTs for ES, with the following exceptions:

(1) Stiller et al. 1992: PEMF therapy

- Possibly confounded by concomitant therapy: debridement (reported in none of conventional RCTs), dressings (12.5% of conventional), and antibiotic therapy (7.5% of conventional)

(2) Todd et al. 1991: PEMF therapy

- Smaller study size than most conventional (smaller than 25th percentile of 40 RCTs)
- Did not specify inclusion or exclusion of patients with peripheral arterial disease (reported in 62.5% of conventional RCTs) or diabetes (40% of conventional)

(3) Ieran et al. 1990: PEMF therapy

- Possibly confounded by inclusion of diabetic patients (reported in 7.5% of conventional RCTs)
- Possibly confounded by antibiotic therapy (7.5% of conventional)

In general, the design and reporting shortcomings presented in the RCT studies of ES for venous ulcers are common throughout published studies of conventional therapies for venous ulcers. However, because the Stiller et al. study showed several different types of potential confounding by concomitant therapy and because this type of confounding appeared only infrequently in conventional RCTs, the Stiller et al. study appears inferior in quality to conventional RCTs for venous ulcers.
7.1.2 Comparison with Alternative Therapies

We used the databases specified in section 4.1 to identify RCTs of venous ulcers treated by alternative therapies, which we defined as (1) hyperbaric oxygen (HBO), (2) growth factors, (3) ultrasound, (4) lasers, and (5) ultraviolet light. (Our definition of “alternative” was based on the definition of “active therapy” described in section 2.3.)

Our search strategies for identifying alternative therapies used the following keywords:

- Debridement; bandages, dressings; hydrotherapy; whirlpool; hyperbaric oxygenation; drug therapy; antibiotics; electrococagulation; dermatologic agents; ultrasonic therapy; lasers; growth substances; pressure surfaces; ultraviolet light; physical therapy devices.

Our exclusion criteria was the same used for conventional therapies in section 7.1.1.

We identified 10 alternative therapy RCTs for the treatment of venous ulcers that met our exclusion criteria. [See Table 7.3.] These included 4 growth factor studies (2 human growth factor {hGF}, 1 human epidermal growth factor {hEGF}, and 1 placental growth factor {PGF}); 4 ultrasound (US) studies; and 2 laser studies (1 gallium-arsenide {GaAs} and 1 helium-neon {HeNe}).

We compared the quality of these 10 alternative RCTs to the same ES studies listed in section 7.1.1 (Stiller et al.\textsuperscript{746} 1992, Todd et al.\textsuperscript{747} 1991, and Ieran et al.\textsuperscript{748} 1990) and evaluated the same study features. [See Table 7.4.]

We observed the following differences between study quality of the 10 alternative RCTs for venous ulcers and individual RCTs for ES:

(1) Stiller et al. 1992: PEMF therapy

- Reported lesion duration by group with variance (compared to 80% of alternatives which did not report lesion durations)
- Did not specify inclusion or exclusion or patients with rheumatoid arthritis (60% of alternatives)
- Does not appear to be confounded by infections of lesions (compared to 20% of alternatives)
- Possibly confounded by concomitant therapy: debridement (reported in none of conventional RCTs), dressings (12.5% of conventionals), and antibiotic therapy (7.5% of conventionals)
(2) Todd et al. 1991: PEMF therapy

- Smaller study size than most alternatives (smaller than 25th percentile of 10 RCTs)

- Did not describe randomization process (reported in 50% of alternative RCTs)

- Did not specify inclusion or exclusion or patients with peripheral arterial disease (reported in 90% of alternatives), diabetes (80% of alternatives) or rheumatoid arthritis (60% of alternatives)

- Does not appear to be confounded by infections of lesions (compared to 20% of alternatives)

(3) Ieran et al. 1990: PEMF therapy

- Did not specify inclusion or exclusion or patients with rheumatoid arthritis (60% of alternatives)

- Does not appear to be confounded by infections of lesions (compared to 20% of alternatives)

- Possibly confounded by inclusion of diabetic patients (reported in 7.5% of conventional RCTs)

- Possibly confounded by antibiotic therapy (7.5% of conventionals)

In general, the design and reporting shortcomings presented in the RCTs of ES for venous ulcers are common throughout published studies of alternative therapies for venous ulcers. However, 2 of the 3 ES studies may have been confounded by inconsistencies in concomitant therapy whereas none of the 10 alternative studies was confounded. Therefore, ES study quality may be slightly inferior to that in other alternative-therapy studies of venous lesions.
7.2 Quality Comparison for Decubitus Ulcers

7.2.1 Comparison with Conventional Therapies

We used the search strategy specified in section 4.1 to identify RCTs of decubitus ulcers (pressure sores) treated by different conventional therapies (e.g., dressings, topical agents). Using similar criteria to section 7.1.1, we excluded studies

- that did not appear to be randomized controlled,
- that did not define the type of ulceration,
- in which <80% of the patients (in any treatment group) had decubitus ulcers,
- that were published before 1970,
- that did not directly address the healing of wounds (e.g., studies of bacterial counts in lesions),
- that did not specify the number of patients in each treatment group, or
- in which most (specified) wounds were <30 days duration.

Our definition of conventional RCT was any therapeutic study of decubitus ulcers that evaluated debridement, cleaning agents, topical agents, dressings, bandages, antibiotics (systemic or local), pressure relief, systemic medications, or nutritional supplements. cc

We identified 16 conventional RCTs for the treatment of decubitus ulcers which also met our exclusion criteria. [See Table 7.5.]

We compared the quality of these 16 conventional RCTs to the following ES RCTs for decubitus ulcers (Wood et al. 1993, Stefanovska et al. 1993, Gentzkow et al. 1991, Griffin et al. 1991, Kloth & Feedar 1988, and Salzberg et al. 1995). [We did not include abstracts by Unger et al. and Feedar et al. because it would be inappropriate to compare the quality of an abstract with journal articles.] We evaluated these studies for the same quality criteria specified in section 7.1. [See Table 7.6.]

cc The term “conventional” does not imply that the (experimental group) therapy or therapies in the RCT are accepted treatment regimens for decubitus ulcers.
We observed the following differences between study quality of the 16 conventional RCTs for decubitus ulcers and individual RCTs for ES:

(1) **Wood et al. 1993: PDC therapy**

- Used double blinding (compared to only 6.3% of conventional RCTs)
- Reported patient age and duration of lesions by subject (compared to 0% for conventional RCTs)
- Did not specify inclusion or exclusion of patients with infected lesions (43.8% of conventional RCTs), peripheral arterial disease (37.5% of conventional RCTs), diabetes (56.3% of conventional RCTs), or patient nutritional status (56.3% of conventional RCTs)
- Outcomes not confounded by patients with diabetes (25% of conventional RCTs)
- Outcomes not confounded by concomitant therapy including debridement (18.8% of conventional RCTs), topical and/or cleansing agents (31.3% of conventional RCTs), and dressings (25% of conventional RCTs)

(2) **Stefanovska et al. 1993: AC therapy**

- Larger study size than most conventional studies (greater than 75th percentile)
- Reported duration of lesions by group with variance (compared to 18.8% of conventional RCTs)
- Did not specify stage of lesions (compared to 81.3% of conventional RCTs)
- Did not specify inclusion or exclusion of patients with infected lesions (43.8% of conventional RCTs), diabetes (56.3% of conventional RCTs), or patient nutritional status (56.3% of conventional RCTs)
- Did not specify use of debridement agents (18.8% of conventional RCTs), topical or cleansing agents (56.3% of conventional RCTs), dressings (87.5% of conventional RCTs), or use of pressure-relieving devices (43.8% of conventional RCTs).
(3) Gentzkow et al. 1991: PDC therapy

- Used double blinding (compared to only 6.3% of conventional RCTs)
- Did not specify inclusion or exclusion of patients with infected lesions (43.8% of conventionals), peripheral arterial disease (37.5% of conventionals), diabetes (56.3% of conventionals), or patient nutritional status (56.3% of conventionals)
- Outcomes not confounded by patients with diabetes (25% of conventionals)
- Outcomes not confounded by dressings (25% of conventionals)

(4) Griffin et al. 1991: HVPC therapy

- Smaller study size than most conventionals (smaller than 25th percentile of 16 RCTs)
- Did not specify inclusion or exclusion of patients with infected lesions (43.8% of conventionals), peripheral arterial disease (37.5% of conventionals), diabetes (56.3% of conventionals), or patient nutritional status (56.3% of conventionals)
- Outcomes not confounded by patients with diabetes (25% of conventionals)
- Outcomes not confounded by concomitant therapy including debridement (18.8% of conventionals), topical and/or cleansing agents (31.3% of conventionals), and dressings (25% of conventionals)

(5) Kloth & Feedar 1988: HVPC therapy

- Smaller study size than most conventionals (smaller than 25th percentile of 16 RCTs)
- Reported patient age by subject (compared to 0% for conventionals)
- Did not specify location of lesions (75% of conventionals)
- Did not specify inclusion or exclusion of patients with infected lesions (43.8% of conventionals) or patient nutritional status (56.3% of conventionals)
- Outcomes possibly confounded by inclusion of patients with peripheral arterial disease
- Outcomes not confounded by topical and/or cleansing agents (31.3% of conventionals) and dressings (25% of conventionals)

(6) Salzberg et al. 1995: PEE therapy

- Smaller study size than most conventionals (smaller than 25th percentile of 16 RCTs)
- Used double blinding (compared to only 6.3% of conventional RCTs)
- Did not specify location of lesions (75% of conventionals)
- Did not specify inclusion or exclusion of patients with peripheral arterial disease (37.5% of conventionals) or diabetes (56.3% of conventionals)
- Outcomes not confounded by patients with diabetes (25% of conventionals)
- Outcomes not confounded by concomitant therapy including debridement (18.8% of conventionals), topical and/or cleansing agents (31.3% of conventionals), and dressings (25% of conventionals)

In general, the design and reporting shortcomings presented in the RCT studies of ES for decubitus ulcers are common throughout published studies of conventional therapies for decubitus ulcers. However, because ES studies were usually blinded and were usually not confounded by the inclusion of diabetic patients or concomitant therapy, particularly topical/cleansing agents and dressings, it appears that their quality may be slightly superior to RCTs of conventional therapies for decubitus ulcers—with the possible exception of the study by Stefanovska et al.

7.2.2 Comparison with Alternative Therapies

We searched the databases specified in section 4.1 to identify RCTs of decubitus ulcers treated by alternative therapies, which we defined as (1) HBO, (2) growth factors, (3) ultrasound, (4) lasers, and (5) ultraviolet light.

We identified 7 alternative therapy RCTs for the treatment of decubitus ulcers that met our exclusion criteria. [See Table 7.7.] These included 3 growth factor studies (2 platelet-derived growth factor-BB [PDGF-BB] and 1 recombinant basic
fibroblast growth factor (bFGF); 3 ultrasound (US) therapy studies; and 1 ultraviolet (UV) study.

We compared the quality of these 7 alternative RCTs to the same ES studies listed in section 7.2.1 (Wood et al.\textsuperscript{757} 1993, Stefanovska et al.\textsuperscript{758} 1993, Gentzkow et al.\textsuperscript{759} 1991, Griffin et al.\textsuperscript{760} 1991, Kloth & Feedar\textsuperscript{761} 1988, and Salzberg et al.\textsuperscript{762} 1995) and evaluated the same study features. [See Table 7.8.]

We observed the following differences between study quality of the 7 alternative RCTs for decubitus ulcers and individual RCTs for ES:

(1) Wood et al. 1993: PDC therapy

- Larger study size than most alternative studies (greater than 75\textsuperscript{th} percentile of 7 RCTs)
- Did not specify inclusion or exclusion of patients with infected lesions (28.6\% of alternatives), peripheral arterial disease (42.9\% of alternatives), diabetes (57.1\% of alternatives), or patient nutritional status (42.9\% of alternatives)
- Specified duration of lesions (compared to 71.4\% not specified by alternatives)
- Outcomes not confounded by concomitant therapy of pressure-relieving devices (28.6\% of alternatives)

(2) Stefanovska et al. 1993: AC therapy

- Larger study size than most alternative studies (greater than 75\textsuperscript{th} percentile of 7 alternative RCTs)
- Not blind (compared to 71.4\% of alternatives double-blind and 14.3\% single-blind)
- Reported duration of lesions by group with variance (compared to none of alternatives)
- Did not specify stage of lesions (compared to 57.1\% of alternatives)
- Did not specify inclusion or exclusion of patients with infected lesions (28.6\% of alternatives), with diabetes (57.1\% of alternatives), who used steroids (57.1\% of alternatives), or patient nutritional status (42.9\% of alternatives)
• Did not specify use of debridement agents (57.1% of alternatives), topical or cleansing agents (85.7% of alternatives), dressings (71.4% of alternatives), or pressure-relieving devices (57.1% of alternatives)

(3) Gentzkow et al. 1991: PDC therapy

• Did not specify inclusion or exclusion of patients with infected lesions (28.6% of alternatives), peripheral arterial disease (42.9% of alternatives), diabetes (57.1% of alternatives), or patient nutritional status (42.9% of alternatives)

• Specified duration of lesions (compared to 71.4% not specified by alternatives)

• Outcomes possibly confounded by concomitant therapy using debridement and topical or cleansing agents

• Outcomes not confounded by concomitant therapy of pressure-relieving devices (28.6% of alternatives)

(4) Griffin et al. 1991: HVPC therapy

• Did not specify inclusion or exclusion of patients with infected lesions (28.6% of alternatives), peripheral arterial disease (42.9% of alternatives), diabetes (57.1% of alternatives), or patient nutritional status (42.9% of alternatives)

• Specified duration of lesions (compared to 71.4% not specified by alternatives)

• Outcomes not confounded by concomitant therapy of pressure-relieving devices (28.6% of alternatives)

(5) Kloth & Feedar 1988: HVPC therapy

• Smaller study size than most alternative studies (smaller than 25th percentile of 7 RCTs)

• Did not specify location of lesions (57.1% of alternatives)

• Did not specify inclusion or exclusion of patients with infected lesions (28.6% of alternatives) or patient nutritional status (42.9% of alternatives)

• Outcomes possibly confounded by patient heterogeneity: inclusion of patients with peripheral arterial/venous disease or diabetes
• Outcomes possibly confounded by concomitant therapy of debridement

• Outcomes not confounded by concomitant therapy of pressure-relieving devices (28.6% of alternatives)

(6) Salzberg et al. 1995: PEE therapy

• Did not specify location of lesions (57.1% of alternatives),

• Did not specify inclusion or exclusion of patients with peripheral arterial disease (42.9% of alternatives) or diabetes (57.1% of alternatives)

• Outcomes not confounded by concomitant therapy of pressure-relieving devices (28.6% of alternatives)

In general, the design and reporting shortcomings presented in the RCT studies of ES for decubitus ulcers are common throughout published studies of alternative therapies for decubitus ulcers. Two of the 6 ES studies were possibly confounded by patient heterogeneity (peripheral arterial/venous disease and diabetes) and/or concomitant therapy (inconsistencies in debridement and use of topical/cleansing agents). Two of the 7 alternative studies were possibly confounded by inconsistencies in concomitant therapy (use of pressure-relieving devices). Therefore, the quality of ES randomized controlled studies of decubitus ulcers appears to be similar to the quality of alternative therapy RCTs.
### 7.3 Tables

**Table 7.1. Randomized Controlled Studies of Conventional Therapies for Venous Ulcers Used in Qualitative Comparative Analysis**

<table>
<thead>
<tr>
<th>Venous Ulcer Study</th>
<th>Year</th>
<th>Number of Patients/Ulcers</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowszyc et al.763</td>
<td>1995</td>
<td>82</td>
<td>RCT: Hydrocolloid dressing vs. polyurethane foam dressing</td>
</tr>
<tr>
<td>Ohlsson* et al.764</td>
<td>1994</td>
<td>28</td>
<td>RCT: Hydrocolloid dressing vs. saline gauze dressing</td>
</tr>
<tr>
<td>Werner-Schlenzka’ &amp; Kuhlmann765</td>
<td>1994</td>
<td>128</td>
<td>Double-blind RCT: Topical iloprost vs. placebo</td>
</tr>
<tr>
<td>Greguric et al.766</td>
<td>1994</td>
<td>110</td>
<td>RCT: Hydrocolloid dressing vs. magnesium sulfate paste dressing</td>
</tr>
<tr>
<td>Smith*767</td>
<td>1994</td>
<td>28</td>
<td>RCT: Hydrocolloid dressing vs. alginate dressing</td>
</tr>
<tr>
<td>Arnold et al.768</td>
<td>1994</td>
<td>30</td>
<td>RCT: Hydrocolloid + zinc paste dressing vs. standard + zinc paste dressing</td>
</tr>
<tr>
<td>McCullough et al.769</td>
<td>1994</td>
<td>22</td>
<td>RCT: Pneumatic compression + Unna boot vs. Unna boot alone</td>
</tr>
<tr>
<td>Layton* et al.770</td>
<td>1994</td>
<td>20</td>
<td>Double-blind RCT: Aspirin + compression vs. placebo + compression</td>
</tr>
<tr>
<td>Huovinen* et al.771</td>
<td>1994</td>
<td>31</td>
<td>Double-blind RCT: Ciprofloxacin (antibiotic) vs. trimethoprim vs. placebo</td>
</tr>
<tr>
<td>Nikolova772</td>
<td>1994</td>
<td>42</td>
<td>Single-blind RCT: Flunarizine (Ca-channel blocker) vs. placebo</td>
</tr>
<tr>
<td>Teepe* et al.773</td>
<td>1993</td>
<td>43</td>
<td>RCT: Hydrocolloid dressing vs. cryopreserved cultured allograft</td>
</tr>
<tr>
<td>Cordts’ et al.774</td>
<td>1992</td>
<td>30</td>
<td>RCT: Hydrocolloid dressing vs. Unna boot dressing</td>
</tr>
<tr>
<td>Barbarino775</td>
<td>1992</td>
<td>12</td>
<td>Double-blind RCT: Pentoxifylline (intravenous) vs. placebo</td>
</tr>
<tr>
<td>Davis et al.776</td>
<td>1992</td>
<td>12</td>
<td>RCT: Semi-permeable polyurethane + Unna boot dressing vs. Unna boot alone</td>
</tr>
<tr>
<td>Bishop’ et al.777</td>
<td>1992</td>
<td>86</td>
<td>Double-blind RCT: 1% silver sulfadiazine cream vs. 0.4% tripeptide copper complex vs. placebo</td>
</tr>
<tr>
<td>Brandrup’ et al.778</td>
<td>1990</td>
<td>31</td>
<td>RCT: Hydrocolloid dressing vs. zinc oxide paste dressing</td>
</tr>
<tr>
<td>Colgan et al.779</td>
<td>1990</td>
<td>80</td>
<td>Double-blind RCT: Oxpentifylline vs. placebo</td>
</tr>
<tr>
<td>Rubin et al.780</td>
<td>1990</td>
<td>36</td>
<td>Single-blind RCT: Polyurethane foam dressing vs. Unna boot dressing</td>
</tr>
<tr>
<td>Queral et al.781</td>
<td>1990</td>
<td>25</td>
<td>RCT: Sclerotherapy + Unna boot vs. Unna boot alone</td>
</tr>
<tr>
<td>Smith* et al.782</td>
<td>1990</td>
<td>45</td>
<td>RCT: Intermittent pneumatic pressure + compression stockings vs. compression stockings alone</td>
</tr>
</tbody>
</table>
Table 7.1. Randomized Controlled Studies of Conventional-Type Therapies for Venous Ulcers Used in Qualitative Comparative Analysis (continued)

<table>
<thead>
<tr>
<th>Venous Ulcer Study</th>
<th>Year</th>
<th>Number of Patients/Ulcers</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valtonen et al.</td>
<td>1989</td>
<td>26</td>
<td>RCT: Ciprofloxacin antibiotic + standard therapy vs. standard therapy alone</td>
</tr>
<tr>
<td>Roelens</td>
<td>1989</td>
<td>23</td>
<td>Double-blind RCT: Ketanserin ointment vs. placebo</td>
</tr>
<tr>
<td>Rudofsky</td>
<td>1989</td>
<td>42</td>
<td>Double-blind RCT: Intravenous prostaglandin E1 vs. placebo</td>
</tr>
<tr>
<td>Holloway et al.</td>
<td>1989</td>
<td>75</td>
<td>RCT: Cadexomer iodine vs. standard dressing</td>
</tr>
<tr>
<td>Hillstrom</td>
<td>1988</td>
<td>74</td>
<td>RCT: Cadexomer iodine vs. standard dressing in infected ulcers</td>
</tr>
<tr>
<td>Kikta et al.</td>
<td>1988</td>
<td>69</td>
<td>RCT: Hydrocolloid dressing vs. Unna boot dressing</td>
</tr>
<tr>
<td>Handfield-Jones et al.</td>
<td>1988</td>
<td>88</td>
<td>RCT: Hydrocolloid dressing vs. paraffin wax dressing</td>
</tr>
<tr>
<td>Blair et al.</td>
<td>1988</td>
<td>40</td>
<td>RCT: 4-layer bandage vs. adhesive plaster dressing</td>
</tr>
<tr>
<td>Laudanska &amp; Gustavson</td>
<td>1988</td>
<td>60</td>
<td>RCT: Cadexomer iodine vs. standard dressing</td>
</tr>
<tr>
<td>Poskitt et al.</td>
<td>1987</td>
<td>103</td>
<td>RCT: Pinch skin grafts vs. porcine dermis</td>
</tr>
<tr>
<td>Backhouse et al.</td>
<td>1987</td>
<td>56</td>
<td>RCT: Hydrocolloid dressing vs. nonocclusive (nonadherent) dressing</td>
</tr>
<tr>
<td>Eriksson</td>
<td>1986</td>
<td>34</td>
<td>RCT: Hydrocolloid dressing vs. double-layer bandage</td>
</tr>
<tr>
<td>Alinovi et al.</td>
<td>1986</td>
<td>47</td>
<td>RCT: Systemic antibiotics + standard therapy vs. standard therapy alone</td>
</tr>
<tr>
<td>Harvey et al.</td>
<td>1985</td>
<td>21</td>
<td>Double-blind RCT: 3 amino acids (l-cysteine, glycine, dl-threonine) vs. placebo</td>
</tr>
<tr>
<td>Biland et al.</td>
<td>1985</td>
<td>197</td>
<td>Double-blind RCT: (a) Intravenous solcoseryl + solcoseryl ointment vs. (b) intravenous solcoseryl + placebo ointment vs. (c) placebo IV + solcoseryl ointment vs. (d) placebo IV + placebo ointment</td>
</tr>
<tr>
<td>Ormiston et al.</td>
<td>1985</td>
<td>60</td>
<td>RCT: Cadexomer iodine vs. standard dressing</td>
</tr>
<tr>
<td>Mann et al.</td>
<td>1981</td>
<td>26</td>
<td>Double-blind RCT: Oral rutoside vs. placebo</td>
</tr>
<tr>
<td>Phillips et al.</td>
<td>1977</td>
<td>42</td>
<td>Double-blind RCT: Oral zinc vs. placebo</td>
</tr>
<tr>
<td>Hallbook &amp; Lanner</td>
<td>1972</td>
<td>26</td>
<td>Double-blind RCT: Oral zinc vs. placebo</td>
</tr>
<tr>
<td>Greaves &amp; Ivo</td>
<td>1972</td>
<td>36</td>
<td>Double-blind RCT: Oral zinc vs. placebo</td>
</tr>
</tbody>
</table>

* Theta value(s) calculated
Table 7.2. Comparison of Quality of Conventional RCTs and Electrical Stimulation RCTs for the Treatment of Venous Ulcers

<table>
<thead>
<tr>
<th>Study or Studies Specified...</th>
<th>Number (Percentage) of 40 RCTs of Conventional Therapies for Venous Ulcers Specifying...</th>
<th>Electrical Stimulation Studies for Venous Ulcers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Homogeneity</td>
<td>Yes = 32 (80%)</td>
<td>Yes</td>
</tr>
<tr>
<td>N (Patients or Lesions)</td>
<td>49 ±5.8 (SE); Q1 = 26, median = 38, Q3 = 64.5</td>
<td>31</td>
</tr>
<tr>
<td>Randomization technique</td>
<td>Yes = 6 (15%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Blinding</td>
<td>Single = 13 (32.5%)</td>
<td>Double-blind</td>
</tr>
<tr>
<td></td>
<td>Double = 15 (37.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not blinded = 12 (30%)</td>
<td></td>
</tr>
<tr>
<td>Patient Age</td>
<td>By subject = 0</td>
<td>By group alone</td>
</tr>
<tr>
<td></td>
<td>By group (no variance) = 13 (32.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>By group + variance = 16 (40%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not specified = 11 (27.5%)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Yes = 24 (60%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Location of Lesions</td>
<td>Yes = 39 (97.5%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Duration of Lesions</td>
<td>By subject = 0</td>
<td>By group + variance</td>
</tr>
<tr>
<td></td>
<td>By group (no variance) = 10 (25%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>By group + variance = 14 (35%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not specified = 16 (40%)</td>
<td></td>
</tr>
</tbody>
</table>
Table 7.2.  Comparison of Quality of Conventional-Type RCTs and Electrical Stimulation RCTs for the Treatment of Venous Ulcers (continued)

<table>
<thead>
<tr>
<th>Study or Studies Specified...</th>
<th>Number (Percentage) of 40 RCTs of Conventional Therapies for Venous Ulcers Specifying...</th>
<th>Electrical Stimulation Studies for Venous Ulcers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage of Lesions</td>
<td>Yes = 7 (17.5%)</td>
<td>No</td>
</tr>
<tr>
<td>Size of Lesions</td>
<td>By surface area = 33 (82.5%)</td>
<td>Surface area</td>
</tr>
<tr>
<td></td>
<td>By volume = 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not specified = 7 (17.5%)</td>
<td></td>
</tr>
<tr>
<td>Initial Size of Lesions</td>
<td>By subject = 3 (7.5%)</td>
<td>By group + variance</td>
</tr>
<tr>
<td></td>
<td>By group (no variance) = 14 (35%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>By group + variance = 15 (37.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not specified = 8 (20%)</td>
<td></td>
</tr>
<tr>
<td>Pre-tx Vascular Perfusion Performed</td>
<td>Yes = 23 (57.5%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Inclusion criteria considered:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>Yes = 10 (25%)</td>
<td>No</td>
</tr>
<tr>
<td>PAD/PVD</td>
<td>Yes = 25 (62.5%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes = 16 (40%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Yes = 7 (17.5%)</td>
<td>No</td>
</tr>
<tr>
<td>Steroids</td>
<td>Yes = 9 (22.5%)</td>
<td>No</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Yes = 0</td>
<td>Yes</td>
</tr>
<tr>
<td>Possibly confounded by:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>Yes = 3 (7.5%)</td>
<td>No</td>
</tr>
<tr>
<td>PAD/PVD</td>
<td>Yes = 4 (10%)</td>
<td>No</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes = 3 (7.5%)</td>
<td>No</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Yes = 0</td>
<td>No</td>
</tr>
<tr>
<td>Steroids</td>
<td>Yes = 0</td>
<td>No</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Yes = 0</td>
<td>No</td>
</tr>
</tbody>
</table>
### Table 7.2. Comparison of Quality of Conventional-Type RCTs and Electrical Stimulation RCTs for the Treatment of Venous Ulcers (continued)

<table>
<thead>
<tr>
<th>Study or Studies Specified...</th>
<th>Number (Percentage) of 40 RCTs of Conventional Therapies for Venous Ulcers Specifying...</th>
<th>Electrical Stimulation Studies for Venous Ulcers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Debridement</td>
<td>Yes = 8 (20%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Topical/Cleansing Agents</td>
<td>Yes = 25 (62.5%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Dressings</td>
<td>Yes = 36 (90%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Yes = 5 (12.5%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Possibly confounded by:</td>
<td>Yes = 0</td>
<td>Yes</td>
</tr>
<tr>
<td>Debridement</td>
<td>Yes = 2 (5%)</td>
<td>No</td>
</tr>
<tr>
<td>Topical/Cleansing Agents</td>
<td>Yes = 5 (12.5%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Dressings</td>
<td>Yes = 3 (7.5%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Q\textsubscript{1} = 1\textsuperscript{st} quartile (25\textsuperscript{th} percentile)
Q\textsubscript{3} = 3\textsuperscript{rd} quartile (75\textsuperscript{th} percentile)
### Table 7.3. Randomized Controlled Studies of Alternative Therapies for Venous Ulcers Used in Qualitative Comparative Analysis

<table>
<thead>
<tr>
<th>Venous Ulcer Study</th>
<th>Year</th>
<th>Type of Therapy</th>
<th>Number of Patients/Ulcers</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rasmussen et al.</td>
<td>1994</td>
<td>(Human) growth hormone</td>
<td>92</td>
<td>Double-blind RCT: intravenous injections of low-dose hGH vs. intermediate-dose hGH vs. high-dose hGH vs. placebo</td>
</tr>
<tr>
<td>Falanga* et al.</td>
<td>1992</td>
<td>(Human) epidermal growth factor</td>
<td>35</td>
<td>Double-blind RCT: topical hEGF vs. placebo</td>
</tr>
<tr>
<td>Rasmussen et al.</td>
<td>1991</td>
<td>(Human) growth hormone</td>
<td>29</td>
<td>Double-blind RCT: intravenous injections of hGH vs. placebo</td>
</tr>
<tr>
<td>Burgos et al.</td>
<td>1989</td>
<td>Placental growth factor</td>
<td>18</td>
<td>Double-blind RCT: topical PGF vs. placebo</td>
</tr>
<tr>
<td>Eriksson et al.</td>
<td>1991</td>
<td>Ultrasound</td>
<td>38</td>
<td>Single-blind RCT: ultrasound + standard therapy vs. sham (placebo) + standard therapy</td>
</tr>
<tr>
<td>Lundeberg* et al.</td>
<td>1990</td>
<td>Pulsed ultrasound</td>
<td>44</td>
<td>Single-blind RCT: ultrasound + standard therapy vs. sham (placebo) + standard therapy</td>
</tr>
<tr>
<td>Callam* et al.</td>
<td>1987</td>
<td>Ultrasound</td>
<td>108</td>
<td>RCT: ultrasound + standard therapy vs. standard therapy alone</td>
</tr>
<tr>
<td>Dyson et al.</td>
<td>1976</td>
<td>Ultrasound</td>
<td>18</td>
<td>Single-blind RCT: ultrasound vs. sham (placebo) therapy</td>
</tr>
<tr>
<td>Malm et al.</td>
<td>1991</td>
<td>Gallium-Arsenide laser</td>
<td>42</td>
<td>Double-blind RCT: GaAs laser + standard therapy vs. sham (placebo) + standard therapy</td>
</tr>
<tr>
<td>Lundeberg &amp; Malm</td>
<td>1991</td>
<td>Helium-Neon laser</td>
<td>46</td>
<td>Single-blind RCT: HeNe laser + standard therapy vs. sham (placebo) + standard therapy</td>
</tr>
</tbody>
</table>

* Theta value(s) calculated
Table 7.4. Comparison of Quality of Alternative RCTs and Electrical Stimulation RCTs for the Treatment of Venous Ulcers

<table>
<thead>
<tr>
<th>Study or Studies Specified...</th>
<th>Number (Percentage) of 10 RCTs of Alternative Therapies for Venous Ulcers Specifying...</th>
<th>Electrical Stimulation Studies for Venous Ulcers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Homogeneity</td>
<td>Yes = 7 (70%)</td>
<td>Yes</td>
</tr>
<tr>
<td>N (Patients or Lesions)</td>
<td>48.0 ±9.3 (SE); Q1 = 18, median = 43, Q3 = 45.5</td>
<td>31</td>
</tr>
<tr>
<td>Randomization technique</td>
<td>Yes = 5 (50%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Blinding</td>
<td>Single = 4 (40%)</td>
<td>Double-blind</td>
</tr>
<tr>
<td></td>
<td>Double = 5 (50%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not blinded = 1 (10%)</td>
<td></td>
</tr>
<tr>
<td>Patient Age</td>
<td>By subject = 0</td>
<td>By group alone</td>
</tr>
<tr>
<td></td>
<td>By group (no variance) = 2 (20%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>By group + variance = 6 (60%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not specified = 2 (20%)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Yes = 8 (80%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Location of Lesions</td>
<td>Yes = 10 (100%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Duration of Lesions</td>
<td>By subject = 0</td>
<td>By group + variance</td>
</tr>
<tr>
<td></td>
<td>By group (no variance) = 20 (20%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>By group + variance = 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not specified = 80 (80%)</td>
<td></td>
</tr>
</tbody>
</table>
Table 7.4.  Comparison of Quality of Alternative-Type RCTs and Electrical Stimulation RCTs for the Treatment of Venous Ulcers (continued)

<table>
<thead>
<tr>
<th>Study or Studies Specified...</th>
<th>Number (Percentage) of 10 RCTs of Alternative Therapies for Venous Ulcers Specifying...</th>
<th>Electrical Stimulation Studies for Venous Ulcers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage of Lesions</td>
<td>Yes = 3 (30%)</td>
<td>No</td>
</tr>
<tr>
<td>Size of Lesions</td>
<td>By surface area = 9 (90%)</td>
<td>Surface area</td>
</tr>
<tr>
<td></td>
<td>By volume = 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not specified = 1 (10%)</td>
<td></td>
</tr>
<tr>
<td>Initial Size of Lesions</td>
<td>By subject = 0</td>
<td>By group + variance</td>
</tr>
<tr>
<td></td>
<td>By group (no variance) = 3 (30%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>By group + variance = 4 (40%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not specified = 3 (30%)</td>
<td></td>
</tr>
<tr>
<td>Pre-tx Vascular Perfusion Performed</td>
<td>Yes = 4 (40%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Inclusion criteria considered:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>Yes = 2 (20%)</td>
<td>No</td>
</tr>
<tr>
<td>PAD/PVD</td>
<td>Yes = 9 (90%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes = 8 (80%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Yes = 6 (60%)</td>
<td>No</td>
</tr>
<tr>
<td>Steroids</td>
<td>Yes = 2 (20%)</td>
<td>No</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Yes = 0</td>
<td>Yes</td>
</tr>
<tr>
<td>Possibly confounded by:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>Yes = 2 (20%)</td>
<td>No</td>
</tr>
<tr>
<td>PAD/PVD</td>
<td>Yes = 0</td>
<td>No</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes = 0</td>
<td>No</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Yes = 0</td>
<td>No</td>
</tr>
<tr>
<td>Steroids</td>
<td>Yes = 0</td>
<td>No</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Yes = 0</td>
<td>No</td>
</tr>
</tbody>
</table>
Table 7.4. Comparison of Quality of Alternative-Type RCTs and Electrical Stimulation RCTs for the Treatment of Venous Ulcers (continued)

<table>
<thead>
<tr>
<th>Study or Studies Specified...</th>
<th>Number (Percentage) of 10 RCTs of Alternative Therapies for Venous Ulcers Specifying...</th>
<th>Electrical Stimulation Studies for Venous Ulcers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Specified use of:</td>
<td>Stiller\textsuperscript{816} (1992): PEMF</td>
</tr>
<tr>
<td></td>
<td>Debridement</td>
<td>Yes = 3 (30%)</td>
</tr>
<tr>
<td></td>
<td>Topical/Cleansing Agents</td>
<td>Yes = 8 (80%)</td>
</tr>
<tr>
<td></td>
<td>Dressings</td>
<td>Yes = 9 (90%)</td>
</tr>
<tr>
<td></td>
<td>Antibiotics</td>
<td>Yes = 0</td>
</tr>
<tr>
<td></td>
<td>Possibly confounded by:</td>
<td>Yes = 0</td>
</tr>
<tr>
<td></td>
<td>Debridement</td>
<td>Yes = 0</td>
</tr>
<tr>
<td></td>
<td>Topical/Cleansing Agents</td>
<td>Yes = 0</td>
</tr>
<tr>
<td></td>
<td>Dressings</td>
<td>Yes = 0</td>
</tr>
<tr>
<td></td>
<td>Antibiotics</td>
<td>Yes = 0</td>
</tr>
</tbody>
</table>

Q₁ = 1\textsuperscript{st} quartile (25\textsuperscript{th} percentile)  
Q₃ = 3\textsuperscript{rd} quartile (75\textsuperscript{th} percentile)
Table 7.5. Randomized Controlled Studies of Conventional Therapies for Decubitus Ulcers Used in Qualitative Comparative Analysis

<table>
<thead>
<tr>
<th>Decubitus Ulcer Study</th>
<th>Year</th>
<th>Number of Patients/Ulcers</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day et al.819</td>
<td>1995</td>
<td>96</td>
<td>RCT: Triangular vs. oval shaped hydrocolloidal dressing in stage II/III sacral pressure ulcers</td>
</tr>
<tr>
<td>Honde et al.820</td>
<td>1994</td>
<td>168</td>
<td>RCT: Copolymer dressing vs. hydrocolloid dressing in grade II-IV pressure ulcers</td>
</tr>
<tr>
<td>Colwell et al.821</td>
<td>1993</td>
<td>70</td>
<td>RCT: Hydrocolloid dressing vs. moist gauze dressing in stage II/III pressure ulcers</td>
</tr>
<tr>
<td>Kraft et al.822</td>
<td>1993</td>
<td>17</td>
<td>RCT: Polyurethane foam dressing vs. saline-soaked gauze dressing in stage II/III pressure ulcers</td>
</tr>
<tr>
<td>Xakellis &amp; Chrischilles823</td>
<td>1992</td>
<td>39</td>
<td>RCT: Hydrocolloid dressing vs. saline-soaked wet-to-dry dressing in grade II/III pressure ulcers</td>
</tr>
<tr>
<td>LaVasseur* &amp; Helme824</td>
<td>1991</td>
<td>21</td>
<td>Double-blind RCT: Topical F14001 cream vs. placebo in grade II/III pressure ulcers</td>
</tr>
<tr>
<td>Darkovich* et al.825</td>
<td>1990</td>
<td>90</td>
<td>RCT: Hydrogel dressing vs. hydrocolloid dressing in stage II/III pressure sores</td>
</tr>
<tr>
<td>Alm* et al.826</td>
<td>1989</td>
<td>56</td>
<td>Single-blind RCT: Hydrocolloid dressing vs. saline-soaked gauze dressing</td>
</tr>
<tr>
<td>Neill* et al.827</td>
<td>1989</td>
<td>87</td>
<td>RCT: Hydrocolloid dressing vs. saline-soaked gauze dressing in grade II/III pressure sores</td>
</tr>
<tr>
<td>Gorse &amp; Messner828</td>
<td>1987</td>
<td>128</td>
<td>RCT: Hydrocolloid dressing vs. Dakin's solution in wet-to-dry dressings in grades II-IV pressure sores</td>
</tr>
<tr>
<td>Allman et al.829</td>
<td>1987</td>
<td>65</td>
<td>RCT: Air-fluidized beds vs. air-mattress beds with standard therapy</td>
</tr>
<tr>
<td>Oleske* et al.830</td>
<td>1986</td>
<td>15</td>
<td>RCT: Polyurethane dressing vs. saline-soaked gauze dressing in grade II pressure ulcers</td>
</tr>
<tr>
<td>Sebern831</td>
<td>1986</td>
<td>77</td>
<td>RCT: Transparent moist vapor permeable dressing vs. gauze dressing in grade II/III pressure ulcers</td>
</tr>
<tr>
<td>Agren &amp; Stromberg832</td>
<td>1985</td>
<td>25</td>
<td>Single-blind RCT: Varidase (streptokinase-streptodornase) enzymatic debridement vs. zinc oxide in necrotic pressure ulcers</td>
</tr>
<tr>
<td>Moberg* et al.833</td>
<td>1983</td>
<td>34</td>
<td>Single-blind RCT: Cadexomer iodine vs. standard therapy used in each participating institution in study</td>
</tr>
<tr>
<td>Taylor et al.834</td>
<td>1974</td>
<td>20</td>
<td>Single-blind RCT: Oral ascorbic acid vs. placebo</td>
</tr>
</tbody>
</table>

* Theta value(s) calculated
### Table 7.6. Comparison of Quality of Conventional RCTs and Electrical Stimulation RCTs for the Treatment of Decubitus Ulcers

<table>
<thead>
<tr>
<th>Study or Studies Specified...</th>
<th>Number (Percentage) of 16 RCTs of Conventional Therapies for Decubitus Ulcers Specifying...</th>
<th>Electrical Stimulation Studies for Decubitus Ulcers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Homogeneity</td>
<td>Yes = 10 (62.5%)</td>
<td>Yes</td>
</tr>
<tr>
<td>N (Patients or Lesions)</td>
<td>64.5 ±10.6 (SE); Q₁ = 31, median = 60.5, Q₃ = 85.5</td>
<td>74</td>
</tr>
<tr>
<td>Randomization technique</td>
<td>Yes = 5 (31.3%)</td>
<td>No</td>
</tr>
<tr>
<td>Blinding</td>
<td>Single = 4 (25%); Double = 1 (6.3%); Not blinded = 11 (68.7%)</td>
<td>Double-blind</td>
</tr>
<tr>
<td>Patient Age</td>
<td>By subject = 0; By group alone = 3 (18.8%); By group + variance = 8 (50%); Not specified = 5 (31.2%)</td>
<td>By subject</td>
</tr>
<tr>
<td>Gender</td>
<td>Yes = 10 (62.5%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Location of Lesions</td>
<td>Yes = 12 (75%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Duration of Lesions</td>
<td>By subject = 0; By group alone = 3 (18.8%); By group + variance = 3 (18.8%); Not specified = 10 (62.4%)</td>
<td>By subject</td>
</tr>
</tbody>
</table>

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286961.WGE
Table 7.6.  Comparison of Quality of Conventional-Type RCTs and Electrical Stimulation RCTs for the Treatment of Decubitus Ulcers (continued)

<table>
<thead>
<tr>
<th>Study or Studies Specified...</th>
<th>Number (Percentage) of 16 RCTs of Conventional Therapies for Decubitus Ulcers Specifying...</th>
<th>Electrical Stimulation Studies for Decubitus Ulcers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage of Lesions</td>
<td>Yes = 13 (81.3%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Size of Lesions</td>
<td>By surface area = 14 (87.5%)</td>
<td>Surface area + volume</td>
</tr>
<tr>
<td></td>
<td>By volume = 0</td>
<td>Surface area</td>
</tr>
<tr>
<td></td>
<td>Not specified = 2 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>Initial Size of Lesions</td>
<td>By subject = 2 (12.5%)</td>
<td>By group + variance</td>
</tr>
<tr>
<td></td>
<td>By group alone = 8 (50%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>By group + variance = 4 (25%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not specified = 2 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>Pre-tx Vascular Perfusion Performed</td>
<td>Yes = 0</td>
<td>No</td>
</tr>
<tr>
<td>Inclusion criteria considered:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>Yes = 7 (43.8%)</td>
<td>No</td>
</tr>
<tr>
<td>PAD/PVD</td>
<td>Yes = 6 (37.5%)</td>
<td>No</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes = 9 (56.3%)</td>
<td>No</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Yes = 0</td>
<td>No</td>
</tr>
<tr>
<td>Steroids</td>
<td>Yes = 0</td>
<td>Yes</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Yes = 9 (56.3%)</td>
<td>No</td>
</tr>
<tr>
<td>Possible confounding by:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>Yes = 0</td>
<td>No</td>
</tr>
<tr>
<td>PAD/PVD</td>
<td>Yes = 0</td>
<td>No</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes = 4 (25%)</td>
<td>No</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Yes = 0</td>
<td>No</td>
</tr>
<tr>
<td>Steroids</td>
<td>Yes = 0</td>
<td>No</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Yes = 0</td>
<td>No</td>
</tr>
</tbody>
</table>
Table 7.6.  Comparison of Quality of Conventional-Type RCTs and Electrical Stimulation RCTs for the Treatment of Decubitus Ulcers (continued)

<table>
<thead>
<tr>
<th>Study or Studies Specified...</th>
<th>Number (Percentage) of 16 RCTs of Conventional Therapies for Decubitus Ulcers Specifying...</th>
<th>Electrical Stimulation Studies for Decubitus Ulcers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Wood$^{835}$ (1993): PDC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stefanovska$^{836}$ (1993): AC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gentzkow$^{837}$ (1991): PDC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Griffin$^{838}$ (1991): HVPC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kloth$^{839}$ (1988): HVPC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Salzberg$^{840}$ (1995): PEE</td>
</tr>
<tr>
<td>Specified use of:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Debridement</td>
<td>Yes = 3 (18.8%)</td>
<td>No</td>
</tr>
<tr>
<td>Topical/Cleansing Agents</td>
<td>Yes = 9 (56.3%)</td>
<td>No</td>
</tr>
<tr>
<td>Dressings</td>
<td>Yes = 14 (87.5%)</td>
<td>No</td>
</tr>
<tr>
<td>Pressure-relieving Devices</td>
<td>Yes = 7 (43.8%)</td>
<td>No</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Yes = 0</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Possible confounding by:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Debridement</td>
<td>Yes = 3 (18.8%)</td>
<td>No</td>
</tr>
<tr>
<td>Topical/Cleansing Agents</td>
<td>Yes = 5 (31.3%)</td>
<td>No</td>
</tr>
<tr>
<td>Dressings</td>
<td>Yes = 4 (25%)</td>
<td>No</td>
</tr>
<tr>
<td>Pressure-relieving Devices</td>
<td>Yes = 0</td>
<td>Yes</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Yes = 0</td>
<td>No</td>
</tr>
</tbody>
</table>

Excluded electrical stimulation RCTs reported as abstracts
Table 7.7. Randomized Controlled Studies of Alternative Therapies for Decubitus Ulcers Used in Qualitative Comparative Analysis

<table>
<thead>
<tr>
<th>Decubitus Ulcer Study</th>
<th>Year</th>
<th>Type of Therapy</th>
<th>Number of Patients/Ulcers</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mustoe* et al.841</td>
<td>1994</td>
<td>Platelet-derived growth factor-BB</td>
<td>31</td>
<td>Double-blind RCT: Topical low-dose PDGF-BB vs. topical high-dose PDGF-BB vs. placebo for stage III/IV pressure ulcers</td>
</tr>
<tr>
<td>Robson* et al.842</td>
<td>1992</td>
<td>Platelet-derived growth factor-BB</td>
<td>20</td>
<td>Double-blind RCT: Topical low-dose PDGF-BB vs. topical intermediate-dose PDGF-BB vs. topical high-dose PDGF-BB vs. placebo for grades III/IV pressure ulcers</td>
</tr>
<tr>
<td>Robson et al.843</td>
<td>1992</td>
<td>Recombinant basic fibroblast growth factor</td>
<td>49</td>
<td>Single-blind RCT: Topical bFGF vs. placebo for grade III/IV pressure sores</td>
</tr>
<tr>
<td>ter Riet et al.844</td>
<td>1995</td>
<td>Ultrasound</td>
<td>88</td>
<td>Double-blind RCT: US therapy vs. sham (placebo) for stage II or worse pressure ulcers</td>
</tr>
<tr>
<td>Nussbaum* et al.845</td>
<td>1994</td>
<td>Pulsed ultrasound, ultraviolet-C, and laser</td>
<td>17</td>
<td>RCT: US + UV-C therapy vs. laser therapy vs. standard care therapy for pressure ulcers</td>
</tr>
<tr>
<td>McDiarmid et al.846</td>
<td>1985</td>
<td>Ultrasound</td>
<td>40</td>
<td>Double-blind RCT: US therapy vs. sham (placebo) for pressure sores</td>
</tr>
<tr>
<td>Wills* et al.847</td>
<td>1983</td>
<td>Ultraviolet</td>
<td>16</td>
<td>Double-blind RCT: UV therapy vs. sham (placebo) for superficial pressure sores</td>
</tr>
</tbody>
</table>

* Theta value(s) calculated
Table 7.8. Comparison of Quality of Alternative RCTs and Electrical Stimulation RCTs for the Treatment of Decubitus Ulcers

<table>
<thead>
<tr>
<th>Study or Studies Specified...</th>
<th>Number (Percentage) of 7 RCTs of Alternative Therapies for Decubitus Ulcers Specifying...</th>
<th>Electrical Stimulation Studies for Decubitus Ulcers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Wood$^{88}$ (1993): PDC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stefanovska$^{89}$ (1993): AC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gentzkow$^{80}$ (1991): PDC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Griffin$^{81}$ (1991): HVPC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kloth$^{82}$ (1988): HVPC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Salzberg$^{83}$ (1995): PEE</td>
</tr>
<tr>
<td>Study Homogeneity</td>
<td>Yes = 6 (85.7%)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
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<td>Yes</td>
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<td></td>
<td>Yes</td>
</tr>
<tr>
<td>N (Patients or Lesions)</td>
<td>37.3 ±9.7 (SE); Q₁ = 17, median = 31, Q₂ = 49</td>
<td>74</td>
</tr>
<tr>
<td></td>
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<td>150</td>
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<td>16</td>
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<td>20</td>
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<tr>
<td>Randomization technique</td>
<td>Yes = 0</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Blinding</td>
<td>Single = 1 (14.3%)</td>
<td>Double-blind</td>
</tr>
<tr>
<td></td>
<td>Double = 5 (71.4%)</td>
<td>Not blind</td>
</tr>
<tr>
<td></td>
<td>Not blinded = 1 (14.3%)</td>
<td>Double-blind</td>
</tr>
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<td></td>
<td></td>
<td>Single-blind</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Single-blind</td>
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<tr>
<td></td>
<td></td>
<td>Double-blind</td>
</tr>
<tr>
<td>Patient Age</td>
<td>By subject = 0</td>
<td>By subject</td>
</tr>
<tr>
<td></td>
<td>By group alone = 2 (28.6%)</td>
<td>By group + variance</td>
</tr>
<tr>
<td></td>
<td>By group + variance = 3 (42.9%)</td>
<td>By group only</td>
</tr>
<tr>
<td></td>
<td>Not specified = 2 (28.5%)</td>
<td>By subject</td>
</tr>
<tr>
<td></td>
<td></td>
<td>By group only</td>
</tr>
<tr>
<td>Gender</td>
<td>Yes = 4 (57.1%)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
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<tr>
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<tr>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Location of Lesions</td>
<td>Yes = 4 (57.1%)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Duration of Lesions</td>
<td>By subject = 0</td>
<td>By subject</td>
</tr>
<tr>
<td></td>
<td>By group alone = 2 (28.6%)</td>
<td>By group + variance</td>
</tr>
<tr>
<td></td>
<td>By group + variance = 0</td>
<td>By group only</td>
</tr>
<tr>
<td></td>
<td>Not specified = 5 (71.4%)</td>
<td>By group only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>By group only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Stage of Lesions</td>
<td>Yes = 4 (57.1%)</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes</td>
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<td>Yes</td>
</tr>
<tr>
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<td>Yes</td>
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</tbody>
</table>
Table 7.8. Comparison of Quality of Alternative-Type RCTs and Electrical Stimulation RCTs for the Treatment of Decubitus Ulcers (continued)

<table>
<thead>
<tr>
<th>Study or Studies Specified...</th>
<th>Number (Percentage) of 7 RCTs of Alternative Therapies for Decubitus Ulcers Specifying...</th>
<th>Electrical Stimulation Studies for Decubitus Ulcers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size of Lesions</td>
<td>By surface area = 2 (28.6%) By volume = 3 (42.9%) Not specified = 2 (28.5%)</td>
<td>Surface area + volume</td>
</tr>
<tr>
<td>Initial Size of Lesions</td>
<td>By subject = 2 (28.6%) By group alone = 1 (14.3%) By group + variance = 2 (28.6%) Not specified = 2 (28.5%)</td>
<td>By subject</td>
</tr>
<tr>
<td>Pre-tx Vascular Perfusion Performed</td>
<td>Yes = 0</td>
<td>No</td>
</tr>
<tr>
<td>Inclusion criteria considered:</td>
<td>Infection</td>
<td>Yes = 2 (28.6%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes = 3 (42.9%)</td>
<td>No</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Yes = 4 (57.1%)</td>
<td>No</td>
</tr>
<tr>
<td>Steroids</td>
<td>Yes = 0</td>
<td>No</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Yes = 4 (57.1%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Possible confounding by:</td>
<td>Infection</td>
<td>Yes = 0</td>
</tr>
<tr>
<td>PAD/PVD</td>
<td>Yes = 0</td>
<td>No</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes = 0</td>
<td>No</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Yes = 0</td>
<td>No</td>
</tr>
<tr>
<td>Steroids</td>
<td>Yes = 0</td>
<td>No</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Yes = 0</td>
<td>No</td>
</tr>
<tr>
<td>Specified use of:</td>
<td>Debridement</td>
<td>Yes = 4 (57.1%)</td>
</tr>
<tr>
<td>Topical/Cleansing Agents</td>
<td>Yes = 6 (85.7%)</td>
<td>No</td>
</tr>
<tr>
<td>Dressings</td>
<td>Yes = 5 (71.4%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Pressure-relieving Devices</td>
<td>Yes = 4 (57.1%)</td>
<td>No</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Yes = 0</td>
<td>No</td>
</tr>
</tbody>
</table>
Table 7.8. Comparison of Quality of Alternative-Type RCTs and Electrical Stimulation RCTs for the Treatment of Decubitus Ulcers (continued)

<table>
<thead>
<tr>
<th>Study or Studies Specified...</th>
<th>Number (Percentage) of 7 RCTs of Alternative Therapies for Decubitus Ulcers Specifying...</th>
<th>Electrical Stimulation Studies for Decubitus Ulcers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possible confounding by:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Debridement</td>
<td>Yes = 0</td>
<td>No</td>
</tr>
<tr>
<td>Topical/Cleansing Agents</td>
<td>Yes = 0</td>
<td>No</td>
</tr>
<tr>
<td>Dressings</td>
<td>Yes = 0</td>
<td>No</td>
</tr>
<tr>
<td>Pressure-relieving Devices</td>
<td>Yes = 2 (28.6%)</td>
<td>No</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Yes = 0</td>
<td>No</td>
</tr>
</tbody>
</table>

Excluded electrical stimulation RCTs reported as abstracts

127-002
8.0 Comparison of Normalized Healing Rates: Electrical Stimulation versus Conventional and Alternative Therapies for Wound Healing

In section 6.1, we calculated the normalized healing rates (\(?\) values) for ES RCTs. There was a significant difference in the normalized healing rates between some types of ES (\(?_{tx}\)) and control (\(?_{con}\)) groups. In section 6.2.2, we determined that the effect sizes (Hedges’ \(d\)) for \(?\) for some studies were significant.

However, these studies only demonstrate that patients treated by ES may heal faster than those undergoing no therapy at all. These outcomes, by themselves, are not clinically useful because they do not compare ES to wound healing therapies patients are likely to receive. The best way to determine whether ES therapy is effective is to conduct RCTs that compare ES therapy to common therapies for chronic wound healing. In the absence of such RCTs, we can only compare ES outcomes with outcomes from RCTs of other therapies.

A good outcome for comparing ES with non-ES therapies is the normalized healing rate (\(\mathcal{H}\)). This value allows us to assess whether one therapy appears to accelerate wound healing compared to another. Currently, it is the only way to determine whether healing rates of patients treated by ES are less, roughly equivalent to, or greater than other therapies. For example, from the Wood et al. RCT, we know that the mean \(\mathcal{H}\) is +0.4199 (95% CI = +0.3571 to +0.4827). If we were treating a 10 cm\(^2\) lesion, we would expect it to heal (99%) in approximately 10.9 weeks (\(t = [\ln (10 \text{ cm}^2 / .1 \text{ cm}^2)] / \mathcal{H} = 10.9\)). Without the context of \(\mathcal{H}\) values from other therapies, one wonders if this is a poor or excellent healing time. If another therapy, such as hydrocolloidal dressing, typically has \(\mathcal{H}\) values between +0.1 and +0.2, then the identical lesion would require 23 to 46 weeks to heal. If, on the other hand, it typically has values between +0.6 and +0.7, then the same lesion would require 6.6 to 7.7 weeks.

Unfortunately, we cannot directly compare normalized healing rates from different studies because of heterogeneity, numerous variables, confounding factors—and too few studies. These weaknesses and the poor quality of published studies of wound healing circumvent any analysis that would account for different patient and wound characteristics. We can only conduct crude comparisons to assess whether \(\mathcal{H}\) values from ES studies appear greater than, smaller than, or similar to those for other therapies.

Therefore, we compared ES RCTs to non-ES RCTs that used (a) patients with similar types of lesions (i.e., venous, decubitus) and (b) control groups with similar healing rates. We performed the latter by comparing \(\mathcal{H}\) values for ES control groups with \(\mathcal{H}\) values for non-ES control groups. If the 95% confidence intervals for the control groups of ES and non-ES studies overlapped, then we compared the experimental groups of the studies. [Sacks et al.\(^{854}\) noted that bigger effect sizes are found in historically controlled trials than in RCTs because

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the control groups in these types of designs are different—not because of
differences between treatment groups. By matching control-group values from
different RCTs, we eliminate this problem.] This provides a crude comparison of
ES therapy and non-ES therapy for venous and for decubitus ulcers.
8.1 Comparison of Normalized Healing Rates for Venous Ulcers

8.1.1 Comparison with Conventional Therapies

Twenty-one of the 40 conventional RCTs (in section 7.1.1) for the treatment of venous ulcers provided sufficient data to calculate normalized healing rates. Theta values for these studies are presented in Table 8.1.

Stiller et al.\(^{855}\) (1992), using PEMF therapy, was the only ES RCT study of venous ulcers that provided sufficient data for calculating \(\theta\) values. It also demonstrated a positive significant difference from its control group. [See Table 6.5.] Seven of the 21 conventional RCTs (8 treatment arms) had control groups with 95% CI \(\theta\) values that overlapped the Stiller trial \((\theta_{\text{con}} = -0.0984 \text{ to } +0.0082)\). A study-by-study comparison is presented in Table 8.2.

In our crude comparison, which did not consider possible patient and wound differences, normalized healing rates of PEMF therapy appeared greater than 1 conventional therapy (12.5% of conventional treatment groups), less than 2 (25%), and showed no discernible difference from 5 others (62.5%). PEMF healing rates appeared greater than trimethoprim therapy but were substantially less than rates for hydrocolloidal dressing and for pentoxifylline therapy.

Based on these findings, it appears that PEMF produces a normalized healing rate appearing roughly similar to most conventional RCTs.\(^{dd}\) (From the Stiller et al. 95% CI \(\theta\) value interval, we would expect a 10 cm\(^2\) lesion to be 99% healed in 47.2 to 77.3 weeks.) However, this is substantially less than found in hydrocolloid dressing, a common therapy. (From the Cordts et al.\(^{856}\) 95% CI \(\theta\) value interval, we would expect a 10 cm\(^2\) lesion to be 99% healed in 23.0 to 29.1 weeks.)

8.1.2 Comparison with Alternative Therapies

Three of the 10 alternative RCTs (in section 7.1.2) for the treatment of venous ulcers provided sufficient data to calculate normalized healing rates. Theta values for these studies are presented in Table 8.3. Only 2 studies had control groups with 95% CI \(\theta\) values that overlapped the Stiller trial \((\theta_{\text{con}} = -0.0984 \text{ to } +0.0082)\). A study by study comparison is presented in Table 8.4.

In our crude comparison, which did not consider possible patient and wound heterogeneity, normalized healing rates of PEMF therapy appeared less than

---

\(^{dd}\) For which \(\theta\) values can be calculated.
1 study of ultrasound therapy; there was no discernible difference from another US therapy. From the Callam et al. study, which had a 95% CI value interval, we would expect a 10 cm² lesion to be 99% healed in 17.3 to 41.3 weeks.

Based on these findings, the clinical value of PEMF therapy for accelerating the healing of venous ulcerations is minimal.
8.2 Comparison of Normalized Healing Rates for Decubitus Ulcers

8.2.1 Comparison with Conventional Therapies

Seven of the 16 conventional RCTs (in section 7.2.1) for the treatment of decubitus ulcers provided sufficient data to calculate normalized healing rates. Theta values for these studies are presented in Table 8.5.

Eight RCTs evaluated the effect of ES on decubitus ulcers. Two provided insufficient data for calculating ? (Unger et al. and Feedar & Kloth) and 3 studies (3 treatment arms) showed no significant difference between ES and control groups (Gentzkow et al., Griffin et al., and Stefanovska et al. [DC therapy alone]). We analyzed the 4 ES studies that demonstrated significant differences between ?tx and ?con:

- Salzberg et al. (1995): PEE therapy
- Wood et al. (1993): PDC therapy
- Stefanovska et al. (1993): AC therapy
- Kloth & Feedar (1988): HVPC therapy

We compared conventional RCTs that had control groups with normalized healing rates that overlapped the 95% CI ? values of the ES studies:

- Salzberg et al. (95% CI ?con = +0.1488 to +0.6740),
- Wood et al. (95% CI ?con = -0.0008 to +0.0859),
- Stefanovska et al. (95% CI ?con = +0.1223 to +0.1871), and
- Kloth & Feedar (95% CI ?con = -0.0893 to +0.0607).

[See Table 8.6.]

In our crude comparison, which did not consider possible patient and wound differences (including lesion stage), PEE therapy (Salzberg et al.) normalized healing rates for stage II decubitus ulcers appeared greater than those in 1 conventional therapy (cadexomer iodine) but showed no discernible difference from 3 others (including hydrocolloid and polyurethane dressings for grade I/II lesions). PDC therapy (Wood et al.) ? values for stage II/III ulcers appeared greater than those in 2 conventional therapies (hydrocolloid for grade III ulcerations and cadexomer iodine) but showed no discernible difference from 2 others (hydrocolloid for grade II and polyurethane dressing for grade I/II).
AC therapy (Stefanovska et al.) \( \Rightarrow \) values (for unstaged lesions) appeared greater than cadexomer iodine (for unstaged lesions), but there was no detectable difference when compared with polyurethane dressings (for grade I/II lesions). HVPC therapy (Kloth & Feedar) \( \Rightarrow \) values for stage IV lesions yielded similar comparative outcomes to PDC (Wood et al.).

The following are based on these crude comparisons:

- PEE therapy for stage II decubitus ulcers yields normalized healing rates that are indistinguishable from established therapies.
- PDC therapy for stage II or III decubitus ulcers yield normalized healing rates that are indistinguishable from established therapies.
- There is insufficient data to compare HVPC therapy for stage IV decubitus ulcers to conventional therapies.
- There is insufficient information to compare AC therapy to conventional therapies for decubitus ulcers.

However, even this crude comparison may not be valid because most of the conventional RCTs used grade I through III ulcers or stage I or II lesions, whereas all patients in HVPC were stage IV.

### 8.2.2 Comparison with Alternative Therapies

Four of the 7 alternative RCTs (in section 7.2.2) for the treatment of decubitus ulcers provided sufficient data to calculate the exponential decay normalized healing rates. Theta values for these studies are presented in Table 8.7. We compared them with the 4 ES studies showing significant effect sizes. [See Table 8.8.]

In our crude comparison, which did not consider possible patient and wound differences (including lesion stage), PEE therapy (Salzberg et al.) normalized healing rates for stage II decubitus ulcers appeared greater than those for laser therapy but showed no discernible difference from 3 others (including US and UV, and bFGF in different grade lesions). PDC therapy (Wood et al.) \( \Rightarrow \) values for stage II/III lesions appeared greater than those for stage III or IV decubitus ulcers treated by high-dose PDGF-BB but were not discernible from low-dose PDGF-BB. There were no alternative RCTs for decubitus ulcers with \( \Rightarrow \) control values suitable for comparison with AC therapy (Stefanovska et al.). HVPC therapy (Kloth & Feedar) \( \Rightarrow \) values for stage IV decubitus ulcers appeared greater than those for stage III/IV lesions treated by high-dose PDGF-BB but were not discernible from low-dose PDGF-BB.
The following are based on these crude comparisons:

- PEE therapy for stage II decubitus ulcers yields normalized healing rates that are indistinguishable from established and alternative therapies.

- PDC therapy for stage II or III decubitus ulcers yield normalized healing rates that are indistinguishable from established or alternative therapies.

- There is insufficient data to compare HVPC therapy for stage IV decubitus ulcers to conventional therapies. Normalized rates for HVPC may, however, be indistinguishable from PDGF-BB therapy.

- There is insufficient information to compare AC therapy with non-ES therapies for decubitus ulcers.
### 8.3 Tables

#### Table 8.1. Normalized Healing Rates for RCTs of Conventional Therapies for Venous Ulcers

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Number of Patients/Ulcers</th>
<th>Normalized Healing Rates for Experimental Group ($\bar{r}_x$)</th>
<th>Normalized Healing Rates for Control Group ($\bar{r}_{con}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean $\bar{r}_x$ Value</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td>Ohlsson et al.[867]</td>
<td>1994</td>
<td>28</td>
<td>.1193</td>
<td>Not available</td>
</tr>
<tr>
<td>Werner-Schlenzka &amp; Kuhlmann[868]</td>
<td>1994</td>
<td>128</td>
<td>.0364</td>
<td>Not available</td>
</tr>
<tr>
<td>Smith[869]</td>
<td>1994</td>
<td>28</td>
<td>.1407</td>
<td>Not available</td>
</tr>
<tr>
<td>Layton et al.[870]</td>
<td>1994</td>
<td>28</td>
<td>.1193</td>
<td>Not available</td>
</tr>
<tr>
<td>Huovinen et al.[871]</td>
<td>1994</td>
<td>31</td>
<td>.0630</td>
<td>.0568 to .0765</td>
</tr>
<tr>
<td>Nikolova[872]</td>
<td>1994</td>
<td>42</td>
<td>.0786</td>
<td>.0415 to .2568</td>
</tr>
<tr>
<td>Teepe et al.[873]</td>
<td>1993</td>
<td>43</td>
<td>.1487</td>
<td>.1317 to .1657</td>
</tr>
<tr>
<td>Cordts et al.[874]</td>
<td>1992</td>
<td>30</td>
<td>.1790</td>
<td>.1582 to .1998</td>
</tr>
<tr>
<td>Barbarino[875]</td>
<td>1992</td>
<td>12</td>
<td>.4230</td>
<td>.2371 to .6090</td>
</tr>
<tr>
<td>Bishop et al.[876]</td>
<td>1992</td>
<td>86</td>
<td>.0517</td>
<td>.0198 to .0836</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>.1450</td>
<td>.1225 to .1566</td>
</tr>
<tr>
<td>Brandrup et al.[877]</td>
<td>1990</td>
<td>31</td>
<td>.0874</td>
<td>.0571 to .1177</td>
</tr>
<tr>
<td>Smith et al.[878]</td>
<td>1990</td>
<td>45</td>
<td>.2343</td>
<td>.1366 to .3319</td>
</tr>
<tr>
<td>Holloway et al.[879]</td>
<td>1989</td>
<td>75</td>
<td>.0701</td>
<td>.0575 to .0827</td>
</tr>
</tbody>
</table>
Table 8.1. Normalized Healing Rates for RCTs of Conventional-Type Therapies for Venous Ulcers (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Number of Patients/Ulcers</th>
<th>Normalized Healing Rates for Experimental Group ((\bar{r}_\text{tx}))</th>
<th>Normalized Healing Rates for Control Group ((\bar{r}_\text{con}))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean (\bar{r}_\text{tx}) Value 95% Confidence Interval</td>
<td>Mean (\bar{r}_\text{con}) Value 95% Confidence Interval</td>
</tr>
<tr>
<td>Hillstrom(^{880})</td>
<td>1988</td>
<td>74</td>
<td>0.0805 95% CI: -0.0038 to +0.1648</td>
<td>-0.0128 95% CI: -0.0143 to -0.0113</td>
</tr>
<tr>
<td>Laudanska &amp; Gustavson(^{881})</td>
<td>1988</td>
<td>60</td>
<td>0.2007 95% CI: 0.1980 to 0.2088</td>
<td>0.1233 95% CI: 0.1033 to 0.1433</td>
</tr>
<tr>
<td>Backhouse et al.(^{882})</td>
<td>1987</td>
<td>56</td>
<td>0.1063 95% CI: 0.0783 to 0.1343</td>
<td>0.1140 95% CI: 0.0813 to 0.1467</td>
</tr>
<tr>
<td>Alinovi et al.(^{883})</td>
<td>1986</td>
<td>47</td>
<td>0.2163 95% CI: 0.1842 to 0.2484</td>
<td>0.1073 95% CI: 0.0724 to 0.1422</td>
</tr>
<tr>
<td>Harvey et al.(^{884})</td>
<td>1985</td>
<td>21</td>
<td>Mean not available</td>
<td>0.0010 95% CI: Not available</td>
</tr>
<tr>
<td>Ormiston et al.(^{885})</td>
<td>1985</td>
<td>60</td>
<td>0.785 95% CI: 0.729 to 0.831</td>
<td>0.0649 95% CI: 0.0532 to 0.0766</td>
</tr>
<tr>
<td>Mann et al.(^{886})</td>
<td>1981</td>
<td>26</td>
<td>0.0876 95% CI: -0.0423 to +0.2172</td>
<td>0.0538 95% CI: -0.0922 to 0.198</td>
</tr>
<tr>
<td>Hallbrook &amp; Lanner(^{887})</td>
<td>1972</td>
<td>26</td>
<td>0.1418 95% CI: Not available</td>
<td>0.1393 95% CI: Not available</td>
</tr>
</tbody>
</table>

\(^{a}\) Treatment group received oral ciprofloxacin.  
\(^{b}\) Treatment group received oral trimethoprim.  
\(^{c}\) Treatment group received topical copper mixture.  
\(^{d}\) Treatment group received topical silvadene.
<table>
<thead>
<tr>
<th>Electrical Stimulation RCT</th>
<th>Control-matched Conventional Venous RCT*</th>
<th>Crude Comparison of Normalized Healing Rates** by $\gamma_{tx}$ 95% Confidence Interval Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>Treatment: $\gamma_{tx}$ 95% CI</td>
<td>Study</td>
</tr>
<tr>
<td>Stiller et al.$^888$: PEMF</td>
<td>.0596 to .0975</td>
<td>Layton et al.$^{889}$; oral aspirin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Huovinen et al.$^{890}$; ciprofloxacin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nikolova$^{891}$; flunarizine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hillstrom$^{892}$; cadexomer iodine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cordts et al.$^{893}$; hydrocolloid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Barbarino$^{894}$; pentoxifylline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Marinetti et al.$^{895}$; oral rutoside</td>
</tr>
<tr>
<td></td>
<td>.0079 (mean)</td>
<td>.0536 to .0765</td>
</tr>
<tr>
<td></td>
<td>.0277 to .0588</td>
<td>.0415 to .2568</td>
</tr>
<tr>
<td></td>
<td>.0415 to .2568</td>
<td>-.0038 to +.1648</td>
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<td>-.0038 to +.1648</td>
<td>.1582 to .1998</td>
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<td>.1582 to .1998</td>
<td>.15 to .21</td>
</tr>
<tr>
<td></td>
<td>.15 to .21</td>
<td>-.04 to +.21</td>
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</tbody>
</table>

* $\gamma_{con}$ 95% CI of ES study overlaps $\gamma_{con}$ 95% CI of non-ES study

** Note: This comparison does not consider patient and wound differences and therefore is not a statistical comparison.

Excluded: Todd et al.$^{896}$: Comparison not possible because no variance available.

Ieran et al.$^{897}$: Comparison not possible because cannot calculate theta values.
Table 8.3. Normalized Healing Rates for RCTs of Alternative Therapies for Venous Ulcers

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Type of Therapy</th>
<th>Number of Patients/Ulcers</th>
<th>Normalized Healing Rates for Experimental Group ((\bar{x}_n))</th>
<th>Normalized Healing Rates for Control Group ((\bar{x}_c))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean (\bar{x}_n) Value</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td>Falanga et al.</td>
<td>1992</td>
<td>(Human) Epidermal Growth Factor</td>
<td>35</td>
<td>.0654</td>
<td>Not available</td>
</tr>
<tr>
<td>Lundeberg et al.</td>
<td>1990</td>
<td>Pulsed Ultrasound</td>
<td>44</td>
<td>.0805</td>
<td>-.0401 to +.1260</td>
</tr>
<tr>
<td>Callam et al.</td>
<td>1987</td>
<td>Ultrasound</td>
<td>108</td>
<td>.1888</td>
<td>.1114 to .2662</td>
</tr>
</tbody>
</table>
Table 8.4. Comparison of Individual Electrical Stimulation RCTs with Normalized Healing Rate Control Group-Matched (\( ?_{con} \)) Alternative RCTs for Venous Ulcers

<table>
<thead>
<tr>
<th>Electrical Stimulation RCT</th>
<th>Control-matched Alternative Venous RCT*</th>
<th>Crude Comparison of Normalized Healing Rates** by ( ?_{tx} ) 95% Confidence Interval Values:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>Treatment: ( ? ) 95% CI</td>
<td>Study</td>
</tr>
<tr>
<td>Stiller et al.901: PEMF</td>
<td>.0596 to .0975</td>
<td>Lundeberg et al.902: ultrasound</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Callam et al.903: ultrasound</td>
</tr>
</tbody>
</table>

* \( ?_{con} \) 95% CI of ES study overlaps \( ?_{con} \) 95% CI of non-ES study

** Note: This comparison does not consider patient and wound differences and therefore is not a statistical comparison.

Excluded: Todd et al.904: Comparison not possible because no variance available.
Ieran et al.905: Comparison not possible because cannot calculate theta values.
Table 8.5. Normalized Healing Rates for RCTs of Conventional Therapies for Decubitus Ulcers

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Number of Patients/Ulcers</th>
<th>Normalized Healing Rates for Experimental Group ((\tau_\text{ex})) Mean (\tau_\text{ex}) Value 95% Confidence Interval</th>
<th>Normalized Healing Rates for Control Group ((\tau_\text{con})) Mean (\tau_\text{con}) Value 95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>LaVasseur &amp; Helme(^6)</td>
<td>1991</td>
<td>21 (grade I/II)</td>
<td>.5157 .1488 to .8827</td>
<td>.4350 .1962 to .6739</td>
</tr>
<tr>
<td>Darkovich et al.(^7)</td>
<td>1990</td>
<td>90 (grade I/II)</td>
<td>.1336 Not available</td>
<td>.0600 Not available</td>
</tr>
<tr>
<td>Alm et al.(^8)</td>
<td>1989</td>
<td>56*</td>
<td>.7675 Not available</td>
<td>.2388 Not available</td>
</tr>
<tr>
<td>Neill et al.(^9)</td>
<td>1989</td>
<td>87</td>
<td>.3010 (grade II) .1162 to .4862 .0003 to .0005</td>
<td>.0817 .0521 to .1113 .0446 .0289 to .0603</td>
</tr>
<tr>
<td>Oleske et al.(^10)</td>
<td>1986</td>
<td>15 (grade III)</td>
<td>.5965 0.0194 to 1.1738</td>
<td>.6274 -0.3552 to 1.6064</td>
</tr>
<tr>
<td>Sebern(^11)</td>
<td>1986</td>
<td>77</td>
<td>.5756 (stage II) Not available</td>
<td>.0817 Not available</td>
</tr>
<tr>
<td>Moberg et al.(^12)</td>
<td>1983</td>
<td>34*</td>
<td>.1513 .1045 to .1927</td>
<td>.0897 .0242 to .1558</td>
</tr>
</tbody>
</table>

* Stage or grade of ulcerations not specified
Table 8.6. Comparison of Individual Electrical Stimulation RCTs with Normalized Healing Rate Control Group-Matched (\( ?_{\text{con}} \)) RCTs for Decubitus Ulcers

<table>
<thead>
<tr>
<th>Electrical Stimulation RCT</th>
<th>Control-matched Conventional Decubitus RCT*</th>
<th>Crude Comparison of Normalized Healing Rates** by ( ?_{\alpha} 95% ) Confidence Interval Values:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>Treatment: ( ?_{\alpha} 95% ) CI</td>
<td>Study</td>
</tr>
<tr>
<td>Salzberg et al.(^{913}); PEE</td>
<td>.3114 to 1.6370</td>
<td>LaVasseur et al.(^{914}); F14001 cream (grade I/II)</td>
</tr>
<tr>
<td>stage II</td>
<td></td>
<td>Alm et al.(^{915}); hydrocolloid (unstaged)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oleske et al.(^{916}); polyurethane dress (grade I/II)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moberg et al.(^{917}); cadexomer iodine (unstaged)</td>
</tr>
<tr>
<td>Wood et al.(^{918}); PDC</td>
<td>.3571 to .4827</td>
<td>Darkovich et al.(^{919}); hydrogel (stage III)</td>
</tr>
<tr>
<td>stage II/III</td>
<td></td>
<td>Neill et al.(^{920}); hydrocolloid (grade II)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oleske et al.(^{921}); polyurethane dress (grade I/II)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sebern(^{922}); MVP dressing (stage II)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moberg et al.(^{923}); cadexomer iodine (unstaged)</td>
</tr>
<tr>
<td>Stefanovska et al.(^{924}); AC</td>
<td>.3461 to .4141</td>
<td>Oleske et al.(^{925}); polyurethane dress (grade I/II)</td>
</tr>
<tr>
<td>unspecified stage</td>
<td></td>
<td>Moberg et al.(^{926}); cadexomer iodine (unstaged)</td>
</tr>
<tr>
<td>Kloth &amp; Feedar(^{927}); HVPC</td>
<td>.4201 to 1.3469</td>
<td>Darkovich et al.(^{928}); hydrogel (stage VII)</td>
</tr>
<tr>
<td>stage IV</td>
<td></td>
<td>Neill et al.(^{929}); hydrocolloid (grade II)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oleske et al.(^{930}); polyurethane dress (grade I/II)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moberg et al.(^{931}); cadexomer iodine (unstaged)</td>
</tr>
</tbody>
</table>

* \( ?_{\text{con}} 95\% \) CI of ES study overlaps \( ?_{\text{con}} 95\% \) CI of non-ES study

** Note: This comparison does not consider patient and wound differences and therefore is not a statistical comparison.

Excluded: Unger et al.\(^{932}\)
Feedar & Kloth\(^{933}\); Comparison not possible because cannot calculate theta values.
Stefanovska et al. (DC therapy), Gentzkow et al.\(^{934}\)
Griffin et al.\(^{935}\)
Salzberg et al.\(^{936}\); No significant difference between ES & control group within study

MVP = moisture vapor permeable

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Table 8.7. Normalized Healing Rates for RCTs of Alternative Therapies for Decubitus Ulcers

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Type of Therapy</th>
<th>Number of Patients/Ulcers</th>
<th>Normalized Healing Rates for Experimental Group ((?_{tx}))</th>
<th>Normalized Healing Rates for Control Group ((?_{con}))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean (?_{tx}) Value</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td>Mustoe et al.937</td>
<td>1994</td>
<td>Platelet-derived growth factor-BB</td>
<td>31</td>
<td>(0.2906^*) (stages III/IV)</td>
<td>0.1436 to 0.4376</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.1927^{**}) (stages III/IV)</td>
<td>0.0900 to 0.2954</td>
</tr>
<tr>
<td>Nussbaum et al.938</td>
<td>1994</td>
<td>Pulsed ultrasound, ultraviolet-C, and laser</td>
<td>17</td>
<td>(0.5565^#) (unstaged)</td>
<td>0.5000 to 0.6130</td>
</tr>
<tr>
<td>Robson et al.939</td>
<td>1992</td>
<td>Recombinant basic fibroblast growth factor</td>
<td>49</td>
<td>(0.6636^*) (stages III/IV)</td>
<td>0.6291 to 0.6981</td>
</tr>
<tr>
<td>Wills et al.940</td>
<td>1983</td>
<td>Ultraviolet</td>
<td>16</td>
<td>(0.8101) (superficial)</td>
<td>0.5398 to 1.0803</td>
</tr>
</tbody>
</table>

* Low-dose regimen; ** High-dose regimen
# Ultrasound + ultraviolet-C therapy;
* Ultrasound + ultraviolet-C therapy;
** Laser therapy
Table 8.8.  Comparison of Individual Electrical Stimulation RCTs with Normalized Healing Rate Control Group-Matched (\(\equiv_{\text{con}}\)) Alternative RCTs for Decubitus Ulcers

<table>
<thead>
<tr>
<th>Electrical Stimulation RCT Study</th>
<th>Treatment: (?_{\alpha} \ 95%) CI</th>
<th>Control-matched Conventional Decubitus RCT* Study</th>
<th>Treatment: (?_{\alpha} \ 95%) CI</th>
<th>Crude Comparison of Normalized Healing Rates** by (?_{\alpha}) 95% Confidence Interval Values:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salzberg et al.941: PEE stage II</td>
<td>.3144 to 1.6370</td>
<td>Nussbaum et al.942: US/UV-C (unstaged) Laser (unstaged)</td>
<td>.5000 to .6130</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Robson et al.943: bFGF (grades III/IV) Wills et al.944: UV (superficial)</td>
<td>.1532 to .3036</td>
<td>PEE therapy &gt; laser</td>
</tr>
<tr>
<td>Wood et al.945: PDC stage II/III</td>
<td>.3571 to .4827</td>
<td>Mustoe et al.946: PDGF-BB+ (stages III/IV) PDGF-BB++ (stages III/IV)</td>
<td>.1436 to .4376 .0900 to .2954</td>
<td>No difference</td>
</tr>
<tr>
<td>Stefanovska et al.947: AC unspecified stage</td>
<td>.3461 to .4141</td>
<td>No studies for comparison</td>
<td></td>
<td>PDC therapy &gt; high-dose PDGF-BB</td>
</tr>
<tr>
<td>Kloth &amp; Feedar948: HVPC stage IV</td>
<td>.4201 to 1.3469</td>
<td>Mustoe et al.946: PDGF-BB+ (stages III/IV) PDGF-BB++ (stages III/IV)</td>
<td>.1436 to .4376 .0900 to .2954</td>
<td>No difference HVPC therapy &gt; high-dose PDGF-BB</td>
</tr>
</tbody>
</table>

* Low-dose regimen; ** High-dose regimen

\(?_{\text{con}}\) 95% CI of ES study overlaps \(?_{\text{con}}\) 95% CI of non-ES study

** Note: This comparison does not consider patient and wound differences and therefore is not a statistical comparison.

Excluded: Unger et al.950
Feedar & Kloth951: Comparison not possible because cannot calculate theta values.
Stefanovska et al. (DC therapy), Gentzkow et al.,952
Griffin et al.,953
Salzberg et al.954: No significant difference between ES and control group within study

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9.0 General Summary

9.1 Basic Description of Electrical Stimulators

Because human skin may act like a battery that can drive electrical currents into a wound, electrical stimulation (ES) has been studied as a possible therapy for accelerating wound healing. Preclinical studies have shown that externally applied ES can increase ATP (adenosine triphosphate) concentrations in tissues, increase DNA synthesis, promote healing of soft tissue or ulcers, cause epithelial and fibroblasts to migrate into wound sites, accelerate the recovery of damage neural tissue, reduce edema, and inhibit the growth of some pathogens.

ES has been used or studied for many different therapeutic applications. It has been used for stimulating the healing of fractures in the lower leg, spine, and wrist and for relieving chronic intractable pain in the spine. Studies have also tested the effectiveness of ES to heal jaw fractures, reduce pain and swelling in soft tissue injuries, alleviate spinal cord lesions, eliminate intermittent claudication, improve healing from assorted hand injuries, reduce cerebral edema in cases of head trauma, reduce swelling in grades I and II ankle sprains, and accelerate healing after foot, dental, or oral surgery.

We identified several types of ES for wound healing:

- direct current (DC),
- pulsed current (PC),
- alternating current (AC),
- pulsed electromagnetic induction (PEMI), and
- spinal cord stimulation (SCS).

**Direct Current (DC)**—Most published studies of DC stimulation for the treatment of wound healing used low-intensity direct current (LIDC). Clinicians applied 20 to 100 microamps (µA) of current at low voltage (< 8 volts). The cathode was usually wrapped in saturated (saline) gauze and placed directly over the wound site; the anode was placed on the skin surface near the wound. Patients underwent 2-hour sessions 2 or 3 times daily. After several days or if the wound apparently stopped healing, clinicians reversed (switched) the polarity of the electrode by placing the anode directly over the wound and the cathode at a nearby site. They reversed polarity one or more times (depending on the regimen) to stimulate healing if the wound had not improved or reached a “growth plateau.”
Pulsed Current (PC)—We classified published studies of PC stimulation for the treatment of wound healing into 2 subcategories: (a) PDC and (b) HVPC. PDC studies generally used 30 to 40 mA (generated by a 6 to 12 V battery) at 128 pulses per second (Hz), although 1 study (Wood et al.955) used 300 to 600 µA at only 0.8 Hz. HVPC studies generally used 100 to 250 V at 80 to 100 pulses per second (Hz).

Alternating Current (AC) and TENS—We classified published studies of AC stimulation for the treatment of wound healing into 2 subcategories: (a) TENS devices and (b) biphasic pulsed. Studies of TENS generally used small, portable devices capable of generating square-wave pulses at 80 to 90 Hz with 0.1 to 0.2 ms pulse widths. Biphasic AC studies used 15 to 25 mA with 0.25 ms pulses at 40 Hz frequency.

Pulsed Electromagnetic Induction (PEMI)—We classified published studies of pulsed electromagnetic stimulation for the treatment of wound healing into 2 subcategories: (a) those using PEMF devices containing electromagnetic coils capable of generating a magnetic field and (b) those using PEE devices capable of generating a high peak wattage. Both types of devices are nonthermal and are applied externally on top of dressings. Neither uses electrodes wrapped in wet gauze. PEMF studies generally used a low-level magnetic field that induced a low-level nonthermal electrical field. PEE studies used Diapulse devices exclusively, which employed a pulsed, nonthermal high-frequency, high peak power electromagnetic energy delivered at 27.12 MHz, with a pulse repetition rate of 80 to 600 pulses/second, 65 µs pulse width, peak pulse power of 273 to 975 W, and 0.5% to 4.0% duty cycle. As with PEMF devices, the device is applied externally over existing dressings.

Spinal Cord Stimulation (SCS)—Spinal cord stimulators are primarily designed to reduce intractable pain in patients with failed back syndrome and other chronically painful disorders. These devices significantly differ from the types of electrical stimulators previously mentioned for wound healing because spinal cord stimulators (a) are invasive and (b) are not primarily intended to increase the rate of wound healing.

SAFETY OF ELECTRICAL STIMULATORS FOR WOUND HEALING—General contraindications include use in the presence of metallic implants, in the presence of neoplasms, in the presence of osteomyelitis, or on patients with demand-type cardiac pacemakers. We searched the ECRI Health Devices Alerts database and found no reported patient injuries associated with ES devices for wound healing as of December 14, 1995.

** Also known as “pulsed radio frequency energy.”
9.2 Analyses of Electrical Stimulation Studies

9.2.1 Quality of Electrical Stimulation Studies

We searched 17 databases and identified 41 studies of ES for the treatment of chronic wounds. They included:

- 6 studies using direct current stimulation (2 randomized controlled trials [RCTs], 1 comparative, 2 case series [with embedded RCTs], and 1 case report);  
- 14 studies using pulsed current stimulation (9 RCTs, 2 case series, and 3 case reports);  
- 9 studies using AC or TENS stimulation (2 RCTs, 6 case series [1 with a very preliminary RCT], and 1 case report);  
- 7 studies using pulsed electromagnetic induction devices (5 RCTs, 1 case series, and 1 case report); and  
- 5 studies using implanted spinal cord stimulation (2 case series, 3 case reports) + 1 background article (on SCS for amputations).

These studies formed the basis of our qualitative and quantitative analyses.

Our only selection criteria was that these studies did not explicitly state that they primarily included patients with lesions <30 day duration. Our definition of chronic wounds was a duration of ≥30 days.

Outcomes of wound healing studies may be biased (compromised) by several types of confounding factors: (1) lack of homogeneity of study groups, (2) failure to account for systemic or local medical conditions that can interrupt or alter wound healing, (3) inconsistencies in regimen of primary wound therapy, and (4) inconsistencies in concomitant wound therapy.

In addition, study outcomes were often expressed with flawed measurements. For example, many wound healing studies report the number (and/or percentage) of patients healed at given time intervals. One might assume that this is a straightforward, simple measurement of a therapy to promote healing. Unfortunately, the number (percentage) of patients healed is a flawed outcome measure because it depends on study follow-up duration and initial wound size.

Throughout our analysis, we used the terms “lesion,” “wound,” and “ulcer” interchangeably.
Most wound healing studies express healing as a rate, usually the percentage of ulcer healed per week. Unfortunately, nearly all wound healing studies expressed healing rates by surface area, which may substantially differ from volumetric healing rates that more accurately represent true healing. Whenever possible, we used an exponential decay model, also known as the normalized healing rate (\( ? \)), to express healing rates for wound healing.

We evaluated the quality of each electrical stimulation study for wound healing by

- study design (e.g., type of study, randomization, blinding, size);
- differences between study groups (e.g., patient age, patient gender, wound type, duration of wound, stage, anatomical location of wound, infective status of wound);
- medical conditions affecting wound healing (e.g., presence of peripheral arterial or peripheral vascular disease, rheumatoid arthritis, exogenous use of steroids, nutritional status); and
- inconsistencies in concomitant wound therapy leading to possible confounding (e.g., debridement, use of topical and/or cleansing agents, use of dressings, use of pressure devices or turning therapy if applicable, use of topical or systemic antibiotics).

For outcome measures, each trial was evaluated to determine whether it:

- specified initial wound size by surface area and/or volume, and
- specified initial wound size by subject, group (without variance), or group with variance.

Individual study critiques are presented in section 4.3. All studies had at least 1 weakness, but not all were potentially confounded by these criteria.

### 9.2.2 Quantitative Analysis of Electrical Stimulation Normalized Healing Rates

Many wound healing studies assumed or implied that the rate of wound healing is linear. There is little evidence that this is true.

We observed that studies appear to exhibit exponential healing rates. We used an exponential decay model reported by Karba et al.\(^{956}\) and Stefanovska et al.\(^{957}\)

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\(^{956}\) Excluding case reports and background studies.
to describe the rate of wound healing. Using an exponential decay model enables one to express the healing rate as a constant independent of wound size. Karba et al. have described this constant as the normalized healing rate or theta (?), usually expressed as a value per week.

The normalized healing rate (?) is derived from the basic equation for an exponential decay:

\[ S_t = S_0 \times e^{-?t} \]

where \( S_t \) is the size of a wound at a time “t” and \( S_0 \) is the initial size of the wound (at time 0). Solving for theta:

\[
\begin{align*}
\frac{S_t}{S_0} &= e^{-?t} \\
\ln\left(\frac{S_t}{S_0}\right) &= -?t \\
\ln\left(\frac{S_0}{S_t}\right) &= ?t \\
? &= \frac{\ln\left(\frac{S_0}{S_t}\right)}{t}.
\end{align*}
\]

Time “t” is usually expressed in weeks. For example, if the initial size of a wound is 4 cm\(^2\) and the size 8 weeks later is 0.25 cm\(^2\), then \(? = \frac{\ln(4)}{\ln(0.25)} \div 8 = 0.3466/week\). Although ? is a good measure of wound healing, it does have weaknesses.

We calculated the normalized healing rate for all ES studies that provided sufficient data.

Based on these calculations, we concluded that there is evidence of the following:

- For direct current devices, there is evidence that PDC improves the healing rate of stage II or III decubitus ulcers compared to sham (placebo) therapy. However, there is only weak evidence that HVPC improves the healing rate of stage IV decubitus ulcers compared to sham therapy. This evidence is weak because of small study size.

- There is evidence that PEE stimulation improves the healing rate of stage II decubitus ulcers.

Based on these calculations, we concluded that there is weak evidence of the following:

- There is weak evidence that AC stimulation improves the healing of decubitus ulcers compared to “standard” therapy, but these results are suspect because the standard therapy was not specified.
• There is weak evidence that PEMF stimulation improves the healing rate of chronic venous ulcers compared to sham therapy, but these results are suspect because of possible inconsistencies in concomitant therapy.

Based on these calculations, we concluded that there is no evidence of the following:

• There is no evidence that DC stimulation improves the healing rate of chronic venous, decubitus, or diabetic ulcerations.

• There is no evidence that PC stimulation improves the healing rate of chronic venous or diabetic ulcerations.

• There is no evidence that AC (including TENS) improves the healing rate of chronic diabetic ulcerations.

• There is no evidence that Pemi stimulation (PEMF or PEE energy) improves the healing rate of chronic decubitus or diabetic ulcerations.

• There is no evidence that any other form of ES improves the healing rate of chronic lesions.

9.2.3 Meta-Analyses of Electrical Stimulation Studies

We performed 2 meta-analyses to determine

• whether ES increases the normalized wound healing rate (?), and

• whether ES increases the proportion of wounds that completely heal.

Both of our meta-analyses are designed to answer 2 critical questions:

• Does ES promote wound healing?

• If ES does promote wound healing, then is there a particular patient or treatment subgroup for whom ES is most effective?

We used the Hedges' d statistic, which is the difference between the experimental and control groups expressed in units of standard deviation and corrected for errors in treatment effect estimations. We calculated d for each study in the meta-analysis. Values of d >0 imply that ES therapy promotes wound healing; values of d <0 imply that ES therapy hinders wound healing.
A $d = 0$ implies that ES therapy has no effect. Another important statistic we used in our meta-analysis is the $Q$ statistic, which tests the homogeneity of studies—that is, whether all studies in the meta-analysis share a common effect size. Using all applicable controlled studies from our literature searches, we performed both fixed- and random-effects analyses.

Although there are weaknesses in our meta-analyses (e.g., excluding outliers, small study sizes, literature weaknesses), we conclude the following:

- ES increases the normalized healing rate ($\phi$) of chronic ulcers.
- ES increases the proportion of complete healing of chronic ulcers.
- However, the relationship between outcomes and ES is not always simple. For example, the effect of ES on wound healing rates appears to be small in patients with larger wounds and is affected by the type of stimulator.
- There is weak evidence suggesting that decubitus ulcers have greater healing rates than venous ulcers by ES.
- ES appears more likely to enhance complete healing of decubitus ulcers.
9.3 Comparison of Electrical Stimulation Studies with Other Therapies for Wound Healing

9.3.1 Comparison of Qualities of Studies

The RCTs of ES therapy for wound healing have many design and reporting weaknesses. We wanted to determine whether these flaws are unique to ES studies or are common shortcomings throughout published studies of wound healing.

VENOUS ULCERS: CONVENTIONAL THERAPIES—We identified 40 conventional RCTs for the treatment of venous ulcers. Our definition of conventional RCT was any therapeutic study of venous ulcers which evaluated debridement, cleaning agents, topical agents, dressings, bandages, antibiotics (systemic or local), compression therapies, systemic medications, or nutritional supplements. We compared the quality of these conventional RCTs for wound healing to ES RCTs for healing of venous ulcers.

Based on our comparisons, we conclude the following:

- The shortcomings presented in RCTs for ES for venous ulcers are common throughout published studies of conventional therapies for venous ulcers. One ES study, however, appears inferior in quality.

VENOUS ULCERS: ALTERNATIVE THERAPIES—We identified 10 alternative RCTs for the treatment of venous ulcers. Our definition of alternative RCT was any therapy utilizing hyperbaric oxygen (HBO), growth factors, ultrasound (US), lasers, or ultraviolet light (UV). We compared the quality of these alternative RCTs for wound healing to ES RCTs for healing of venous ulcers.

Based on our comparisons, we conclude the following:

- The shortcomings presented in RCTs for ES for venous ulcers are common throughout published studies of alternative therapies for venous ulcers. However, 2 of the 3 ES studies may have been confounded by inconsistencies in concomitant therapy whereas none of the alternative studies was confounded. Therefore, ES study quality may be slightly inferior to those in other alternative-therapy studies of venous ulcers.

hh The term “conventional” is not meant to imply that the (experimental group) therapy or therapies in the RCT are accepted treatment regimens.
DECUBITUS ULCERS: CONVENTIONAL THERAPIES—We identified 16 conventional RCTs for the treatment of decubitus ulcers. We compared the quality of these conventional RCTs for wound healing to electrical stimulation RCTs for healing of decubitus ulcers.

Based on our comparisons, we conclude the following:

- The shortcomings presented in RCTs for ES for decubitus ulcers are common throughout published studies of conventional therapies for decubitus ulcers. However, because ES studies were usually blind and were usually not confounded by the inclusion of diabetic patients or concomitant therapy, particularly topical/cleansing agents and dressings, it appears that their quality may be slightly superior to RCTs of conventional therapies for decubitus ulcers—with the exception of 1 ES study.

DECUBITUS ULCERS: ALTERNATIVE THERAPIES—We identified 7 alternative RCTs for the treatment of decubitus ulcers. We compared the quality of these alternative RCTs for wound healing to ES RCTs for healing of venous ulcers.

Based on our comparisons, we conclude the following:

- The shortcomings presented in the RCTs for ES for decubitus ulcers are common throughout published studies of alternative therapies for decubitus ulcers. The quality of ES randomized controlled studies of decubitus ulcers appears to be similar to the quality of alternative therapy RCTs.

9.3.2 Comparison of Normalized Healing Rates

We calculated the $\delta$ values for ES RCTs. There was a significant difference in the normalized healing rates between some types of ES ($\delta_{tx}$) and control ($\delta_{con}$) groups. We determined that the effect sizes (Hedges' $d$) for some studies were significant.

However, these studies only demonstrate that patients treated by ES stimulation may heal faster than those undergoing no therapy at all. These outcomes, by themselves, are not clinically useful because they do not compare ES to wound healing therapies patients are likely to receive. The best way to determine whether ES therapy is effective is to conduct RCTs that compare stimulation therapy to common therapies for chronic wound healing. In the absence of such RCTs, we can only compare ES outcomes with outcomes from RCTs of other therapies.
We compared ES with non-ES therapies using the normalized healing rate (\( ? \)). This value allows us to assess whether one therapy appears to accelerate wound healing compared to another. Currently, it is the only way to determine whether healing rates of patients treated by ES is less than, roughly equivalent to, or greater than other therapies. For example, if the mean \( ? \) is +0.4199 (95% CI = +0.3571 to +0.4827) and we were treating a 10 cm\(^2\) lesion, we would expect it to heal (99%) in approximately 10.9 weeks (\( t = \left[ \ln \left( \frac{10 \text{ cm}^2}{.1 \text{ cm}^2} \right) \right] \div ? = 10.9 \)). Without the context of \( ? \) values from other therapies, one wonders if this is a poor or excellent healing time. If another therapy, such as hydrocolloidal dressing, typically has \( ? \) values between +0.1 and +0.2, then the identical lesion would require 23 to 46 weeks to heal. If, on the other hand, it typically has values between +0.6 and +0.7, then the same lesion would require 6.6 to 7.7 weeks.

Unfortunately, we cannot directly compare normalized healing rates from different studies because of heterogeneity, numerous variables, confounding factors—and too few studies. These weaknesses and the poor quality of published studies of wound healing circumvent any analysis that would account for different patient and wound characteristics. We can only conduct crude comparisons to assess whether \( ? \) values from ES studies appear greater, smaller, or similar to those for other therapies.

Therefore, we compared ES RCTs to non-ES RCTs that had (a) similar types of lesions (i.e., venous, decubitus) and (b) control groups with similar healing rates. We performed the latter by comparing \( ? \) values for ES study control groups with \( ? \) values for non-ES study control groups. If the 95% confidence intervals for the control groups of ES and non-ES studies overlapped, then we compared the experimental groups of the studies. This provides a crude estimate of ES therapy compared to non-ES therapy for venous and for decubitus ulcers.

VENOUS ULCERS: CONVENTIONAL THERAPIES—Twenty-one of the 40 conventional RCTs for the treatment of venous ulcers provided sufficient data to calculate normalized healing rates. Only 1 ES study showed a significant difference between ES (using PEMF therapy) and placebo groups.

Based on our crude comparison which did not consider possible patient and wound heterogeneity,

- PEMF produces a normalized healing rate roughly similar to most conventional RCTs.

VENOUS ULCERS: ALTERNATIVE THERAPIES—Three of the 10 alternative RCTs for the treatment of venous ulcers provided sufficient data to calculate normalized healing rates. Only 1 ES study showed a significant difference between ES and placebo (using PEMF therapy) and provided sufficient data for calculating \( ? \).

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286961.WGE
Based on our crude comparison, which did not consider possible patient and wound heterogeneity,

- the clinical value of PEMF therapy for accelerating wound healing is minimal.

**DECUBITUS ULCERS: CONVENTIONAL THERAPIES**—Seven of the 16 conventional RCTs for the treatment of decubitus ulcers provided sufficient data to calculate normalized healing rates. Four ES studies showed a significant difference between ES and placebo groups (1 PDC, 1 HVPC, 1 AC, and 1 PEE) and provided sufficient data for calculating \( \).

The following are based on these crude comparisons, which did not consider possible patient and wound heterogeneity:

- PEE therapy for stage II decubitus ulcers yields normalized healing rates that are indistinguishable from established therapies.
- PDC therapy for stage II or III decubitus ulcers yields normalized healing rates that are indistinguishable from established therapies.
- There is insufficient data to compare HVPC therapy for stage IV decubitus ulcers to conventional therapies.
- There is insufficient information to compare AC therapy to conventional therapies for decubitus ulcers.

However, even this crude comparison may not be valid because most of the conventional RCTs used grades I through III ulcers or stage I or II lesions whereas all patients in HVPC were stage IV.

**DECUBITUS ULCERS: ALTERNATIVE THERAPIES**—Four of 7 alternative RCTs for the treatment of decubitus ulcers provided sufficient data to calculate normalized healing rates. Four ES studies showed a significant difference between ES and placebo groups (1 PDC, 1 HVPC, 1 AC, and 1 PEE) and provided sufficient data for calculating \( \).

The following are based on findings from conventional and alternative groups:

- PEE therapy for stage II decubitus ulcers yields normalized healing rates that are indistinguishable from established and alternative therapies.
- PDC therapy for stage II or III decubitus ulcers yield normalized healing rates that are indistinguishable from established or
alternative therapies.

- There is insufficient data to compare HVPC therapy for stage IV decubitus ulcers to conventional therapies. Normalized rates for HVPC may, however, be indistinguishable from PDGF-BB therapy.

- There is insufficient information to compare AC therapy with non-ES therapies for decubitus ulcers.
### 10.0 Appendix I: List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC</td>
<td>alternating current</td>
</tr>
<tr>
<td>ADP</td>
<td>adenosine diphosphate</td>
</tr>
<tr>
<td>AHCPR</td>
<td>Agency for Health Care Policy and Research</td>
</tr>
<tr>
<td>ATP</td>
<td>adenosine triphosphate</td>
</tr>
<tr>
<td>B</td>
<td>unstandardized regression coefficient</td>
</tr>
<tr>
<td>BCOHTA</td>
<td>British Columbia Office of Health Technology Assessment</td>
</tr>
<tr>
<td>bFGF</td>
<td>(basic) fibroblast growth factor</td>
</tr>
<tr>
<td>BID</td>
<td>two times a day</td>
</tr>
<tr>
<td>CI</td>
<td>(95%) confidence interval</td>
</tr>
<tr>
<td>CL&lt;sub&gt;lower&lt;/sub&gt;</td>
<td>lower limit of confidence interval</td>
</tr>
<tr>
<td>CL&lt;sub&gt;upper&lt;/sub&gt;</td>
<td>upper limit of confidence interval</td>
</tr>
<tr>
<td>COM</td>
<td>chronic osteomyelitis</td>
</tr>
<tr>
<td>d</td>
<td>Hedges’ $d$ = standardized measure of effect size</td>
</tr>
<tr>
<td>$d_o$</td>
<td>overall $d$</td>
</tr>
<tr>
<td>DC</td>
<td>direct current</td>
</tr>
<tr>
<td>dv</td>
<td>device variable</td>
</tr>
<tr>
<td>EGF</td>
<td>epidermal growth factor</td>
</tr>
<tr>
<td>ES</td>
<td>electrical stimulation</td>
</tr>
<tr>
<td>FGF</td>
<td>fibroblast growth factor</td>
</tr>
<tr>
<td>GaAs</td>
<td>gallium-arsenide laser (therapy)</td>
</tr>
<tr>
<td>HBO</td>
<td>hyperbaric oxygen</td>
</tr>
<tr>
<td>hEGF</td>
<td>(human) epidermal growth factor</td>
</tr>
<tr>
<td>HeNe</td>
<td>helium-neon laser (therapy)</td>
</tr>
<tr>
<td>hGF</td>
<td>(human) growth factor</td>
</tr>
<tr>
<td>HVPC</td>
<td>high-voltage pulsed current</td>
</tr>
<tr>
<td>HVPG</td>
<td>high-voltage pulsed galvanic (direct current)</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz (1 cycle/second)</td>
</tr>
<tr>
<td>IL-(#)</td>
<td>interleukin-(factor #)</td>
</tr>
<tr>
<td>LIDC</td>
<td>low-intensity direct current</td>
</tr>
<tr>
<td>MENS</td>
<td>microcurrent electrical neuromuscular stimulator</td>
</tr>
<tr>
<td>NMES</td>
<td>neuromuscular electrical stimulator</td>
</tr>
<tr>
<td>NPUAP</td>
<td>National Pressure Ulcer Advisory Panel</td>
</tr>
<tr>
<td>ORN</td>
<td>osteoradionecrosis</td>
</tr>
<tr>
<td>PAF</td>
<td>platelet-activating factor</td>
</tr>
<tr>
<td>PC</td>
<td>pulsed current</td>
</tr>
<tr>
<td>PDC</td>
<td>pulsed direct current</td>
</tr>
<tr>
<td>PDGF(-BB)</td>
<td>platelet-derived growth factor(-BB)</td>
</tr>
<tr>
<td>PDWGF</td>
<td>(autologous) platelet-derived wound healing factors</td>
</tr>
<tr>
<td>PEE</td>
<td>pulsed electromagnetic energy</td>
</tr>
<tr>
<td>PEMF</td>
<td>pulsed electromagnetic field</td>
</tr>
<tr>
<td>PEMI</td>
<td>pulsed electromagnetic induction</td>
</tr>
<tr>
<td>PGF</td>
<td>placental growth factor</td>
</tr>
<tr>
<td>Q</td>
<td>$Q$ statistic = measure of homogeneity</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>$Q_E$</td>
<td>$Q$ statistic for multiple regression</td>
</tr>
<tr>
<td>$Q_1$</td>
<td>1st quartile (25th percentile)</td>
</tr>
<tr>
<td>$Q_3$</td>
<td>3rd quartile (75th percentile)</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>SCS</td>
<td>spinal cord stimulator (stimulation)</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SE</td>
<td>standard error</td>
</tr>
<tr>
<td>$T_c$PO$_2$</td>
<td>transcutaneous oxygen level</td>
</tr>
<tr>
<td>TENS</td>
<td>transcutaneous electrical nerve stimulation</td>
</tr>
<tr>
<td>TGF-α</td>
<td>transforming growth factor-alpha</td>
</tr>
<tr>
<td>TGF-β</td>
<td>transforming growth factor-beta</td>
</tr>
<tr>
<td>$\theta$</td>
<td>theta = normalized healing rate</td>
</tr>
<tr>
<td>$\theta_{con}$</td>
<td>normalized healing rate for control group(s)</td>
</tr>
<tr>
<td>$\theta_{tx}$</td>
<td>normalized healing rate for treatment group(s)</td>
</tr>
<tr>
<td>TID</td>
<td>three times a day</td>
</tr>
<tr>
<td>TNF</td>
<td>tumor necrosis factor</td>
</tr>
<tr>
<td>UHC</td>
<td>University Hospital Consortium</td>
</tr>
<tr>
<td>UMDNS</td>
<td>Universal Medical Device Nomenclature System</td>
</tr>
<tr>
<td>US</td>
<td>ultrasound (therapy)</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet (therapy)</td>
</tr>
<tr>
<td>WOCN</td>
<td>Wound Ostomy and Continence Nurses Society</td>
</tr>
<tr>
<td>WP</td>
<td>whirlpool</td>
</tr>
</tbody>
</table>

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11.0 Appendix II: Formulae Used in Meta-Analyses

11.1 Univariate Analysis

11.1.1 Formulae for Univariate Fixed Effects Models

11.1.1.1 Hedges' d

Meta-analyses were conducted by computing a Hedges' d for each study and then computing an average d weighted by the inverse of each study's variance. Statistical significance of this overall d (d_o) and of the d's from individual studies is determined from the 95% confidence limits around these d's. For each study, differences between experimental and control groups were initially converted into Hedges' g, then into Hedges' d.

Hedges' g standardizes the differences between the means of different studies by dividing each of these differences by the standard deviation. The effect of this standardization is to convert the between-group differences in each study into effect sizes that are all derived from population with a variance equal to 1, thereby eliminating dependence of the scores from their often unique units of measurement.

Unfortunately, Hedges' g overestimates the true effect size of small studies. This bias becomes apparent when the total number of patients in the experimental plus control groups is ≤10. Therefore, Hedges' g is corrected for this overestimate by converting it into Hedges' d.

The formula for computing each study's Hedges' g is:

\[ g = \frac{X_e - X_c}{s_{pooled}} \]

where \( X_e \) bar is the mean of the experimental group, \( X_c \) bar is the mean of the control group, and \( s_{pooled} \) is the pooled standard deviation of the experimental and control groups. In the analysis of complete wound healing, \( X_e \) bar and \( X_c \) bar were the proportion of wounds in the experimental and control groups that healed. In the analysis of normalized wound healing rates, average values of were calculated from published data of experimental and control groups.
The value of $S_{\text{pooled}}$ is given by the formula:

$$S_{\text{pooled}} = \sqrt{\frac{(n_e - 1) (s_e^2) + (n_c - 1) (s_c^2)}{n_e + n_c - 2}}$$

where $n_e$ and $n_c$ are the numbers of wounds in the experimental and control groups, respectively, and $s_e^2$ and $s_c^2$ are the variances of the experimental and control groups, respectively.

The formula used for calculating the experimental and control group variances for each study in the analyses of complete wound healing was:

$$s^2 = p(1-p)$$

where $s^2$ is the variance of either the experimental or control group and $p$ is the proportion of wounds in the experimental or control group. For analysis of wound healing rates, the experimental and control group variances were taken from published variances, standard errors, standard deviations, or 95% confidence limits.

Hedges’ $d$ for each study is then calculated from each study’s $g$, where:

$$d = (1 - \frac{3}{4N-9})g$$

where $N$ equals the sum of the number of wounds in the experimental and control groups, and where $g$ is taken from the above equation.

Ninety-five percent confidence limits of each $d$ are calculated from each study’s variance. The variance for each study, $v_i$, is calculated according to the formula:

$$v_i = \frac{n_e + n_c}{n_e n_c} + \frac{d_i^2}{2(n_e n_c)}$$

where $n_e$ and $n_c$ are defined above, and $d_i^2$ is the squared $d$ that was calculated for that study.
Because the square root of this variance equals the standard error, the 95% confidence limits for each study can be calculated from the equation:

\[ C_a = 1.96 \sqrt{v_i} \]

Adding \( C_a \) to \( d_o \) gives the upper 95% confidence limit; subtracting \( C_a \) from \( d_o \) gives the lower 95% confidence limit.

Calculating the overall \( d \) (\( d_o \)) for the collection of studies involves determining an average \( d \), where each study’s contribution to \( d_o \) is weighted by the inverse of its variance. Thus, for a collection of \( k \) studies, where the \( d \) for the \( i \)th study is \( d_i \) and the weight for the \( i \)th study is \( w_i \) (i.e., \( 1/v_i \)), the formula for the overall \( d \) is:

\[
d_o = \frac{\sum_{i=1}^{k} w_i d_i}{\sum_{i=1}^{k} w_i}
\]

To create 95% confidence intervals around the overall \( d_o \), one must first calculate the conditional variance, \( v_c \), according to the formula:

\[
v_c = \frac{1}{k} \sum_{i=1}^{k} (1/v_i)
\]

(This quantity is called the conditional variance because it is conditioned upon the studies at hand, and is to be distinguished from the unconditional variance used in random effects models.)

Now, from the conditional variance, one calculates the critical level, \( C_a \), according to the formula:

\[
C_a = 1.96(\sqrt{v_c})
\]

Adding \( C_a \) to \( d_o \) gives the upper 95% confidence limit and subtracting \( C_a \) from \( d_o \) gives the lower 95% confidence limit.
11.1.1.2  \( Q \) Statistic

The \( Q \) statistic is used to test whether the individual studies share a common population effect size. The \( Q \) statistic is most easily understood from the equation.

\[
Q = \sum_{i=1}^{k} \frac{(d_i - d_o)^2}{v_i}
\]

Here, it can be seen that each study’s deviation from \( d_o \) and each study’s variance is taken into account in calculating the \( Q \) statistic.

\( Q \) is statistically significant if its value exceeds the upper-tail critical value of chi-square on \( k-1 \) degrees of freedom. If \( Q \) is found to be statistically significant, the studies included in the meta-analysis are not measuring the same parameter (i.e., they are heterogeneous).

The \( Q \) statistic can also determine whether differences between categorical subgroups are statistically significant. However, this is only possible if \( Q \) is statistically significant. These calculations are based on a model analogous to analysis of variance, and the overall model is described by the equation:

\[
Q_T = Q_B + Q_W
\]

where \( Q_T \) is the \( Q \) statistic described above and is the “total fit” to the model of a single effect size, \( Q_B \) is the “between group fit”, and \( Q_W \) is the “within class fit”. If there are \( k \) studies and \( p \) categories, the degrees of freedom for \( Q_T \) equal \( k-1 \), the degrees of freedom of \( Q_B \) equal \( p-1 \), and the degrees of freedom of \( Q_W \) equal \( k-p \).

One performs this test by first calculating \( Q_T \) (i.e. \( Q \)). If this value is large or statistically significant, then the studies are partitioned into groups, and one calculates \( Q_B \) and \( Q_W \) as described above for \( Q \). If \( Q_W \) is not statistically significant, then the process stops because the model of a different effect size for each category is consistent with the data. In this case, the \( d \) for that category (calculated as described for \( d_o \)), represents the effect size for that category, and \( Q_B \) represents to which the effect sizes among classes differ. A large \( Q_W \) indicates that further, analogous partitioning is required. One performs this partitioning using the same logic. Alternatively, if one suspects that there are more than 2 categories of effects sizes, one can partition the data into these categories and use the chi-squared test to determine whether these are statistically significant differences among the categories. In this case, the \( d \) for each category and its associated 95% confidence limits are calculated as describe above for \( d_o \) and using \( C_a \).
11.1.1.3 Rosenthal's Method of Focused Contrasts

Rosenthal's method of focused contrasts is appropriate if one is interested in whether there is a relationship between a continuous variable and \( d \). Here, each \( g \) is converted to a \( z \)-score using the formula:

\[
\begin{align*}
    z_i = \frac{d_i}{(d_i - CL_{lower})/1.96}
\end{align*}
\]

where \( d_i \) is the value of \( d \) for the \( i \)th study and \( CL_{lower} \) is the lower 95% confidence limit for that study.

These \( z \) scores are then inserted into the formula:

\[
Z = \frac{\sum_{i=1}^{k} \lambda_i z_i}{\sqrt{\sum_{i=1}^{k} \lambda_i} \sqrt{\sum_{i=1}^{k} n_i - 3}}
\]

where \( n_i \) is the number of patients in each study and \( \lambda_i \) is a contrast weight for each study chosen from a table of orthogonal polynomials. If \( Z \) exceeds 1.96, the relationship between the continuous variable and \( d \) is statistically significant.

11.1.2 Formulae for Univariate Random Effects Models

Calculations for univariate random effects models are similar to those for fixed effects models. The major difference is in the calculation of variances. In the fixed effects model, the overall variance is simply the conditional variance. However, in the random effects model the overall variance, called the unconditional variance, is the sum of the conditional and random effects variances or:

\[
v_u = \sigma_r^2 + v_c
\]

where \( v_u \) is the unconditional variance, \( \sigma_r^2 \) is the random effects variance, and \( v_c \) is the unconditional variance. The random effects variance is, in turn, calculated from the equation:

\[
\sigma_r^2 = \frac{Q - (k - 1)}{c}
\]
where $Q$ is the value of the $Q$ statistic calculated as described in equation (10), $k$ is the number of studies, and $c$ is a quantity calculated from the formula:

$$c = \sum_{i=1}^{k} \frac{w_i}{\sum_{i=1}^{k} W_i} \sum_{i=1}^{k} W_i^2$$

16

The calculations, including weighting and construction of 95% confidence limits, proceeds as outlined above for the fixed effects approach—except that each study’s variance, $v_i^*$, is calculated according to the formula:

$$v_i^* = \sigma_i^2 + v_i$$

17
11.2 Multivariate Analysis

11.2.1 Formulae for Multivariate Fixed Effects Models

Multiple regressions are conducted using a computer program. In constructing these models, the d’s are the dependent variables and the regression is weighted by the inverse of the variance of each study (i.e. 1/vᵢ).

The regression output yields the $Q_E$ statistic, which is the test for model specification. $Q_E$ is the residual sum of squares, and one obtains its significance by using chi-square tables on k-p-1 degrees of freedom, where k = the number of studies and p = the number of predictor variables in the model.

The computer output also contains the correct unstandardized regression coefficients ($B$’s) for each of the predictor variables. However, the standard errors for these coefficients are not correct. To obtain the correct standard errors one divides them by the square root of the residual mean square of the analysis. Now, one can multiply these corrected standard errors by 1.96 and construct confidence limits as described above, divide the unstandardized regression coefficient by the corrected standard errors to convert the coefficient into a $z$ score, or divide the coefficient by the corrected standard error multiplied by 1.96 to obtain a t-test.

11.2.2 Formulae for Multivariate Random Effects Models

Random effects multiple regression is similar to fixed effects regression—except for calculating variances for each study. To obtain these variances, one first conducts an ordinary, unweighted regression. Then, the residual mean square is used to calculate the random effects variance, $s_r^2$, according to the formula:

$$
s_r^2 = MS_{\text{residual}} - v \tag{18}
$$

where v is given by the formula:

$$
v = \frac{\sum_{i=1}^{k} v_i}{k} \tag{19}
$$

Here, the vᵢ’s are the variances calculated from the univariate fixed effects model described above, and k is the number of studies being analyzed.
The weights for each study in the multiple regression are then calculated from:

\[ w_i = \frac{1}{v_i + \sigma_i^2} \]

As in the fixed effects model, the unstandardized regression coefficients are correct and the standard errors for these coefficients must be corrected by dividing them by the square root of the residual mean square. Statistical tests on the regression coefficients can then be conducted as described for the fixed effects multiple regressions.
11.3 Formulae for Publication Bias

**ROSENTHAL'S METHOD**—The Rosenthal method for assessing publication bias first involves converting each $d$ to a $z$ score as described in equation (12). An overall $z$ score, $z_o$, is then calculated from:

$$z_o = \frac{\sum_{i=1}^{k} z_i}{\sqrt{k}}$$

where $k$ equals the number of studies in the meta-analysis and $z_o$ is used to calculate the number of studies needed to overturn the results, $k_o$, according to:

$$k_o = k + (z_o/1.96)^2$$

**ORWIN'S METHOD**—The Orwin method for calculating $k_o$ is given by:

$$k_o = \frac{k(d_o - d_c)}{d_c}$$

where $d_o$ is the overall $d$ of the fixed effects model, $k$ is the number of studies in the meta-analysis, and $d_c$ is the critical value of $d$ that has been chosen to be negligible.

Determining where a negligible level therapeutic effectiveness lies has the potential to raise ethical problems when this line of reasoning is applied to medicine, but it is possible to make some assumptions that might be less objectionable than others. Thus, we assumed that a negligible level of effectiveness is no effectiveness (i.e. a $d$ of 0), and that the confidence limits of a meta-analysis conducted on any unpublished studies would have the same confidence limits that we report here. This means that the maximum statistically non-significant value for a negligible effect equals the upper confidence limit of these unpublished studies.

**CONTROVERSY REGARDING PUBLICATION BIAS**—Begg has argued that the assumption that the results of missing studies are centered about a $d$ of 0 is artificial (to this we add that our assumption in the Orwin method that the confidence limits of unpublished studies are equal to those we observed in our meta-analyses is equally artificial), and that the methods are weak because they are not influenced by bias in the data (e.g. by the shape of the funnel plot). It is
the conclusion of Begg as well as others\textsuperscript{959} that statistical methods for assessing publication bias are still under development, and should not be widely used.
12.0 Appendix III: AHCPR Strength-of-Evidence Rating System

The Agency for Health Care Policy and Research strength-of-evidence rating system is as follows:

Rating A • Results of two or more randomized controlled clinical trials on ulcers in humans provide support.

Rating B • Results of two or more controlled clinical trials on ulcers in humans provide support, or when appropriate, results of two or more controlled trials in an animal model provide indirect support.

Rating C • This rating requires one or more of the following: (1) results of one controlled trials; (2) results of at least two case series/descriptive studies on ulcers in humans; or (3) expert opinion.

Evidence ratings are based on the number of studies (quantity), quality of research, number of replications, and consistency of findings.
13.0 Appendix IV: External Reviewer Comments

127-002
14.0 Citations

For your convenience, each citations is provided in its entirety each time it is referenced in the text of the report.


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92. University Hospital Consortium (UHC), Technology Advancement Center. Guidelines for the use of pressure relief devices in the treatment and prevention of pressure ulcers. Oak Brook (IL): UHC; 1990. [various pagings].


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14.1 Citations from ECRI Databases and Publications

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