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Advanced Wound Care Therapies for Non-Healing Diabetic, Venous, and Arterial Ulcers: A Systematic Review

EXECUTIVE SUMMARY

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Prepared by:
Evidence-based Synthesis Program (ESP) Center
Minneapolis VA Medical Center
Minneapolis, MN
Timothy J. Wilt, M.D., M.P.H., Director

Investigators:
Principal Investigators:
Nancy Greer, Ph.D.
Neal Foman, M.D., M.S.
Timothy Wilt, M.D., M.P.H.

Co-Investigators:
James Dorrian, B.S.
Patrick Fitzgerald, M.P.H.
Roderick MacDonald, M.S.

Research Assistant:
Indy Rutks, B.S.

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PREFACE

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QUERI provides funding for four ESP Centers and each Center has an active VA affiliation. The ESP Centers generate evidence syntheses on important clinical practice topics, and these reports help:

- develop clinical policies informed by evidence,
- guide the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures, and
- set the direction for future research to address gaps in clinical knowledge.

In 2009, the ESP Coordinating Center was created to expand the capacity of QUERI Central Office and the four ESP sites by developing and maintaining program processes. In addition, the Center established a Steering Committee comprised of QUERI field-based investigators, VA Patient Care Services, Office of Quality and Performance, and Veterans Integrated Service Networks (VISN) Clinical Management Officers. The Steering Committee provides program oversight, guides strategic planning, coordinates dissemination activities, and develops collaborations with VA leadership to identify new ESP topics of importance to Veterans and the VA healthcare system.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP Coordinating Center Program Manager, at nicole.floyd@va.gov.

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EXECUTIVE SUMMARY

BACKGROUND

Chronic ulcers (i.e., ulcers that are unresponsive to initial therapy or that persist despite appropriate care) are estimated to affect over 6 million people in the United States. The incidence is expected to increase as the population ages and as the number of individuals with diabetes increases. Chronic ulcers negatively affect the quality of life and productivity of the patient and represent a substantial financial burden to the health care system.

Lower extremity ulcers, especially those attributed to either diabetes, venous disease, or arterial disease comprise a substantial proportion of chronic ulcers. Approximately 15% to 25% of individuals with diabetes develop a foot ulcer at some point in their lifetime and an estimated 12% of those patients require lower extremity amputation. Healing is complicated by diabetic neuropathy and susceptibility to infection. Venous disease accounts for the majority of chronic lower extremity ulcers. Venous hypertension secondary to various cuases results in damage to vessel walls and ultimately leads to skin breakdown. Arterial ulcers are less common and are a result of impaired circulation which can affect healing lead to ulceration.

Standard treatment for diabetic ulcers includes debridement of necrotic tissue, infection control, local ulcer care, mechanical off-loading, management of blood glucose levels, and education on foot care. For venous ulcers, standard treatment typically includes the use of mechanical compression and limb elevation to reverse tissue edema and improve venous blood flow. Care for ulcers caused by arterial insufficiency is centered on reestablishing blood flow and minimizing further loss of tissue perfusion.

If ulcers do not adequately heal with standard treatment, additional modalities may be required – these are often termed "advanced wound care therapies." Lower extremity ulcers are frequently classified etiologically as diabetic, venous or arterial, though overlap may exist. Treatment modalities and wound care therapies are often selected based on the ulcer characteristics as well as patient factors, past treatment, and provider preference. A large and growing array of advanced wound care therapies of different composition and indications have been developed though their efficacy, comparative effectiveness and harm is not well established.

The purpose of this review is to synthesize the evidence on therapies for non-healing diabetic, venous, and arterial lower extremity ulcers. This work was nominated by Rajiv Jain, MD (Chief Consultant, Office of Patient Care Services) and Jeffrey Robbins, DPM (Director, Podiatry Service) and is intended to provide an evidence base to guide clinical practice and policy needs within the VA. We recognize that a non-healing ulcer is likely a result of multiple factors and comorbid conditions. We group studies in the review according to the study authors' description of the included ulcer type. The review focuses on FDA-approved therapies and examines clinically relevant outcomes. We address the following key questions:

Key Question #1. What are the efficacy and harms of therapies for diabetic ulcers? Is efficacy dependent on ancillary therapies? Does efficacy differ according to patient demographics, comorbid conditions, treatment compliance, or activity level?

Key Question #2. What are the efficacy and harms of therapies for venous ulcers? Is efficacy dependent on ancillary therapies? Does efficacy differ according to patient demographics, comorbid conditions, treatment compliance, or activity level?

Key Question #3. What are the efficacy and harms of therapies for arterial ulcers? Is efficacy dependent on ancillary therapies? Does efficacy differ according to patient demographics, comorbid conditions, treatment compliance, or activity level?

Advanced wound care therapies included in this review are: collagen, biological dressings, biological skin equivalents, keratinocytes, platelet-derived growth factor, platelet-rich plasma, silver products, intermittent pneumatic compression therapy, negative pressure wound therapy, electromagnetic therapy, hyperbaric oxygen, topical oxygen, and ozone oxygen. We included studies that compared these therapies to standard care (as defined above) as well as to other advanced therapies. We recognize that collagen may be used as a vehicle for the delivery of other therapies (e.g., growth factors, silver). Under the collagen heading, we report findings from studies of collagen used as an inert matrix material.

METHODS

We searched MEDLINE (OVID) for randomized controlled trials (RCTs) published from 1995 through August, 2012 using standard search terms. We limited the search to studies involving human subjects over age 18 and published in the English language. Search terms included skin ulcer, foot ulcer, leg ulcer, varicose ulcer, diabetic ulcer, diabetic foot, wound healing, venous insufficiency, artificial skin, biological dressings, negative-pressure wound therapy, collagen, silver, topical oxygen, hyperbaric oxygen, electromagnetic, platelet-derived growth factor, platelet-rich plasma, and intermittent pneumatic compression devices. Investigators and research associates trained in the critical analysis of literature assessed for relevance the abstracts of citations identified from literature searches. We obtained additional articles from a search of the Cochrane Library, existing systematic reviews, and reference lists of pertinent studies.

Study, patient, ulcer and treatment characteristics, primary and secondary outcomes, and adverse events were extracted by trained research associates under the supervision of the Principal Investigator. Our primary outcome was the percentage of ulcers healed at study completion. Additional "primary outcomes" included time to complete ulcer healing, patient global assessment, and return to daily activities. Secondary outcomes included ulcer infection, amputation, revascularization surgery, ulcer recurrence, time to ulcer recurrence, pain or discomfort, hospitalization, progression to require home care, quality of life, all-cause mortality, adverse events, and adverse reactions to treatment. Where feasible, pooled analyses were performed for outcomes from studies of equivalent therapies used to treat like ulcer types. We calculated absolute risk differences for the primary outcome of ulcers healed. All other data were narratively summarized. We assessed quality of individual studies according to established criteria for randomized controlled trials. Strength of evidence was determined for primary outcomes.

DATA SYNTHESIS

We constructed evidence tables showing study, patient, and intervention characteristics; methodological quality; and outcomes, organized by ulcer type (diabetic, venous, arterial) and then by treatment. We analyzed studies to compare their characteristics, methods, and findings. We compiled a summary of findings for each ulcer type based on qualitative and semi-quantitative synthesis of the findings. We identified and highlighted findings from VA or Department of Defense (DoD) populations.

PEER REVIEW

A draft version of this report was reviewed by clinical content experts, as well as clinical leadership. Reviewer comments were addressed and our responses are incorporated in the final report.

RESULTS

We screened 1,230 titles and abstracts, excluded 1,053, and performed a more detailed review on 177 articles. From these, we identified 68 articles representing 64 randomized controlled trials (RCTs) (35 trials involved patients with diabetic ulcers, 20 with venous ulcers, 1 with arterial ulcers, and 8 with mixed etiology or amputation ulcers) that addressed one of the key questions. Most studies compared advanced wound care therapies to standard care or placebo. Direct comparison of one advanced wound care therapy to another was done in 10 of 35 studies (29%) of diabetic ulcers, 4 of 20 studies (20%) of venous ulcers, and 2 of 9 studies (22%) of arterial or mixed ulcers. Overall, studies enrolled a diverse group of participants as determined by age, gender and race/ethnicity. The majority of enrollees were male, white, aged 60 years and older, and demographics did not differ markedly by ulcer type. However, studies rarely reported results separately by important baseline characteristics.

In studies of diabetic ulcers, mean ulcer sizes ranged from 1.9 to 41.5 cm^2, however, the mean ulcer size was greater than 10 cm^2 in only 6 of 29 studies reporting ulcer size. Mean ulcer durations ranged from 14.5 days to 21.6 months with durations of greater than 1 year in 6 of 21 studies reporting. In studies of venous ulcers, mean ulcer sizes ranged from 1.2 to 11.1 cm^2 in 16 studies reporting with 4 of 16 studies reporting mean ulcer sizes of greater than 10 cm^2. Ulcer durations ranged from 7 weeks to 626 weeks with durations of greater than 1 year in 6 of 11 studies reporting ulcer duration. The mean ulcer size in the single study of arterial ulcers was 4.8 cm^2; ulcer duration was not reported. In the single amputation wound study, the mean ulcer size was 20.7 cm^2 with of a mean duration of 1.5 months.

Key Question #1. What are the efficacy and harms of therapies for diabetic ulcers? Is efficacy dependent on ancillary therapies? Does efficacy differ according to patient demographics, comorbid conditions, treatment compliance, or activity level?

We identified 35 eligible trials of 9 different advanced wound care therapies for diabetic ulcers. In 26 of these trials the ulcer was described as a "foot" ulcer, in 7 trials the ulcer was described as

a "lower extremity" ulcer, and in 2 trials the ulcer was described only as a "diabetic ulcer." The ulcer type was further described as neuropathic in 11 trials, ischemic in 1 trial, neuroischemic in 1 trial, and mixed in 3 trials. Of the remaining trials, 16 had inclusion criteria related to adequate circulation or exclusion criteria related to severe arterial disease and 3 did not specify criteria related to circulation.

Collagen (4 RCTs)

Four RCTs (n=489 randomized) reported outcomes of interest. All were rated as fair quality. One study (n=86) found collagen (Graftjacket) to significantly improve ulcer healing compared to standard care (70% healed in the biological dressing group, 46% in the standard care group; ARD=23%, 95% CI 3% to 44%). This difference was maintained after adjusting for baseline ulcer size. Three trials found no significant difference between collagen matrix products and standard care in the percentage of ulcers healed (differences of 9% to 14% between groups). No study found collagen to improve time to complete ulcer healing at study completion (3 studies reporting, differences of 0.4, 1.1, and 1.2 weeks). Two studies reported no significant difference between collagen treatment and standard care for ulcers infected during treatment. No differences were observed in withdrawals due to adverse events (3 studies, 7% overall, 6% versus 0%, and 6% versus 5%) or all-cause mortality (two studies, 1.4% versus 4.3% and 0% overall). One study reported no difference between groups in amputation or need for revascularization surgery.

Biological Dressings (2 RCTs)

Two studies (n=124 randomized), both multisite RCTs, were identified. Both studies, one of which was a non-inferiority study, showed no difference between a biological dressing and other advanced wound care therapies. Neither study found a difference in mean time to healing and no statistical differences were seen between biological dressings and PDGF in the type or number of adverse events. Only one study reported on the possible effect of patient characteristics on efficacy. Results from an *a priori* subgroup analysis indicated that the biological dressing did not improve healing (p=0.14) of plantar surface ulcers more than the advanced therapy comparator (PDGF). A second subgroup analysis found that biological dressing significantly healed more ulcers in patients with type 2 (p=0.03) but not type 1 diabetes.

Biological Skin Equivalents (7 RCTs)

In three fair quality studies (n=576 randomized), Dermagraft statistically significantly improved ulcer healing compared to standard care in two of the trials (30% versus 18% in one study, 50% versus 8% in the other), one of which also reported a significant faster time to closure. The third trial found significant differences in ulcer healing only in patients receiving metabolically active Dermagraft. In this older trial, some Dermagraft samples had a level of metabolic activity outside of the therapeutic range. All of the trials allowed for up to 8 pieces of Dermagraft. A pooled analysis showed an overall non-significant benefit of Dermagraft compared to standard care for ulcer healing (RR=1.49, 95% CI 0.96 to 2.32, I^2=43%). A fourth study, a small trial (n=26) of poor quality, allowed for up to 3 grafts and found no difference in ulcer healing between Dermagraft and a biological dressing. Two fair quality studies (n=359 randomized) compared Apligraf to standard care and showed significant benefits in ulcer healing (55% versus 34%; ARD=21%, 95% CI 9% to 32%; RR=1.58, 95% CI 1.20 to 2.08, I^2=0%). One trial allowed up

to 5 treatments over 5 weeks while the other allowed up to 3 treatments over 8 weeks. A small (n=29 ulcers), poor-quality study compared up to 5 Apligraf treatments to cryopreserved split-thickness skin allograft and showed patients benefited from both therapies, although a larger percentage of ulcers healed with the allograft. No statistical analyses were provided. Two of the Dermagraft studies reported on factors associated with ulcer healing. In one study, neither patient age, gender, ulcer size or duration, diabetes type, ankle-arm index, nor HbA_1c were significantly associated with time to closure. In another study, an interim analysis showed a relationship between ulcer duration and healing and therefore the analysis focused on ulcers of greater than 6 weeks duration. This study also reported outcomes based on ulcer location. Although both analyses resulted in non-significant differences, there was a trend for more forefoot/toe ulcers (n=214) to heal with Dermagraft (29.5% versus 19.6%, p=0.065). For heel ulcers (n=31), 33% of those treated with Dermagraft achieved closure compared to 8% in the control group (p=0.01). Four studies found no difference in recurrence between either Dermagraft or Apligraf and standard care. One study reported fewer amputations in the Apligraf group compared to standard care; a second study reported no difference. Overall, the number of adverse events was low with no differences between treatment groups.

Platelet-Derived Wound Healing (Platelet-Derived Growth Factors [PDGF]) (9 RCTs)

Nine RCTs (n=990 randomized) compared PDGF to placebo gel or standard ulcer care (n=6), an advanced wound care therapy (n=2), or both (n=1). Two studies were of poor quality, five were of fair quality, and two were of good quality. Compared to standard care (7 trials), PDGF demonstrated a greater percentage of healed ulcers at study completion, although there was evidence of substantial heterogeneity (58% versus 37%; ARD=21%, 95% CI 14% to 29%; RR=1.45, 95% CI 1.03 to 2.05, I^2=85%). In five studies reporting, time to ulcer healing was significantly shorter in the PDGF treated groups in four studies (29 to 41 days; $p \leq 0.01$) with one study reporting no difference. However, when compared to silver sulfadiazine, sodium carboxymethylcellulose gel, or biological dressing there was no significant difference in percentage of ulcers healed or time to healing. Several studies looked at factors associated with ulcer healing. In one study, ulcers less than 9 cm^2, ulcers located on non-weight-bearing surfaces, and the use of antibiotics significantly improved healing. Another study reported that healing did not vary by age and baseline HbA_1c but that compliance with off-loading was positively associated with healing (p not reported). No studies reported significant differences between treatment arms for secondary outcomes or adverse events.

Platelet-Rich Plasma (PRP) (2 RCTs)

One poor quality and one fair quality study (n=96 randomized) evaluated the efficacy of PRP compared to placebo or another advance wound therapy (platelet poor plasma, PPP). PRP was applied twice per week for up to 12 weeks in one study and up to 20 weeks in the other study. Neither study demonstrated a significant effect on the percentage of ulcers healed (PRP compared to placebo: 33% versus 28% healed; PRP compared to PPP: 100% versus 75% healed). One study reported a significantly shorter time to healed ulcers for PRP compared to PPP (11.5 weeks versus 17.0 weeks, $p<0.005$) and the other showed no significant difference between PRP and placebo (43 days versus 47 days). One study reported on secondary outcomes of interest and adverse events with no difference between PRP and placebo.

Silver Products (4 RCTs)

We identified four fair quality RCTs (n=280 randomized) of silver products; three were versus another advanced wound care product. Three studies reported healed ulcers with mixed results. In one study (n=66), ulcers treated with silver ointment were more likely to heal than those treated with standard care (39% versus 16%; ARD=23%, 95% CI 2% to 43%); in the other 2 studies, there was no difference in healing between silver products (dressing or cream) versus oak bark extract or a calcium-based dressing. There were no differences between silver dressing and calcium dressing or silver cream and poly-herbal cream for time to ulcer healing. No differences between silver dressing or creams and either standard care or other advanced wound care therapies were observed for our secondary outcomes and adverse events of interest.

Negative Pressure Wound Therapy (NPWT) (3 RCTs)

Three RCTs (n=418 randomized) compared NPWT to standard care. One study was of good quality, one appeared to be of moderate quality but reporting was limited, one was a small pilot study. Only the good quality study (n=335 with primary outcome) reported on the percentage of healed ulcers finding improved healing in the NPWT group compared to standard care of advanced moist wound therapy (43% versus 29%; ARD=14%, 95% CI 4% to 24%). All three studies reported on the time to healing and found mixed results. In the good quality study, NPWT reduced second amputations compared to advanced moist wound therapy (4.1% versus 10.2%, p=0.04). The moderate quality study reported a significant positive effect of NPWT on mental and physical health compared to standard care. No differences in adverse events were observed in any study although reporting was sparse.

Hyperbaric Oxygen Therapy (HBOT) (5 RCTs)

Five RCTs of fair quality, enrolling a total of 326 subjects, met inclusion criteria. Four studies (n=240) compared HBOT to standard or sham therapy. The findings could not be pooled due to variations in follow-up duration. Three studies with at least one year of follow-up reported a significantly higher percentage of ulcers healed (using Fisher's exact test) among patients allocated to adjunctive HBOT (range 52% to 66%) than sham therapy or standard care (range 0% to 29%). In one of the studies, all of the standard therapy patients required some form of surgical management (i.e., debridement, graft or flap, or distal amputation) to achieve ulcer closure compared to 16% of patients in the HBOT group. A short-term trial found that, within 2 weeks of therapy, 2 of 14 patients had complete healing versus none of the 13 patients in the standard care control group; the difference was not significant. None of the studies reported mean time to healing. Two studies reported no difference in amputations required between HBOT and sham therapy; one study reported fewer amputations in the HBOT group compared to the standard therapy group. Adverse events were similar between the HBOT and standard care/sham groups. HBOT resulted in significantly less healing (25% versus 55%, p=0.008) than extracorporeal shock wave therapy (EST) in one poor quality study.

Ozone-Oxygen Therapy (1 RCT)

One RCT of fair quality (n=61 randomized) compared ozone-oxygen therapy to sham treatments and found no significant difference between groups in the proportion of patients with completely

healed ulcers (41% versus 34%, p=0.34). Post-hoc subgroup findings in patients with ulcers of 5 cm^2 or less found that active treatment resulted in 100% closure compared to 50% in the sham treatment group (p=0.006). No differences were reported between active and sham therapy for ulcers infected during treatment, amputation, or withdrawals due to adverse events.

Summary

Nine different advanced wound care therapies used for treatment of diabetic ulcers provided information on our primary and secondary outcomes. Most compared outcomes to standard care, placebo or sham treatments with few reporting comparative effectiveness findings versus other advanced wound care therapies. Advanced wound care therapies included collagen, biological dressings, biological skin equivalents, platelet-derived growth factors, platelet-rich plasma, silver products, negative pressure wound therapy, hyperbaric oxygen therapy, and ozone-oxygen therapy. We summarize our primary and secondary outcome findings below. We found insufficient evidence to address the question whether efficacy and comparative effectiveness differed according to patient demographics, comorbid conditions, treatment compliance, or activity level.

Primary Outcomes

Advanced wound care therapies using platelet-rich plasma or ozone oxygen therapy did not improve diabetic ulcer healing compared to standard care (2 studies) or another advanced care therapy (1 study). Other therapies provided mixed results. Four studies compared collagen products to standard care with only one study reporting significantly better healing in the collagen group (70% versus 46%, p=0.03). Pooled results from three studies indicate that the biological skin equivalent Dermagraft compared to standard care results in a non-significant improvement in ulcer healing favoring Dermagraft (35% versus 24%, low strength of evidence, see Executive Summary Table 1). We found moderate strength of evidence that the biological skin equivalent, bi-layer Apligraf, improved healing compared to standard care (55% versus 34%, p=0.001; 2 studies). While pooled results from studies of platelet-derived growth factor showed improvement in the percentage of ulcers healed compared to placebo or standard care (58% versus 37%, p=0.04; 7 studies) the strength of evidence was low due to high heterogeneity of results between studies. One good quality study provided moderate strength evidence that negative pressure wound therapy improved healing more than standard care (43% versus 29%, p<0.05). Three long-term, fair quality studies of HBOT reported significantly better healing with HBOT (52% to 66%) than sham therapy or standard care (0% to 29%).

Few studies reported time to ulcer healing and other primary outcomes. We found no benefit in time to ulcer healing for collagen, biological dressings, or silver products. We found mixed but generally negative results for biological skin equivalents (1 of 4 Dermagraft and 1 of 3 Apligraf studies showing benefit compared to standard care), platelet-derived growth factors (4 of 8 studies reporting showing benefit compared to placebo or standard care), platelet-rich plasma (1 of 2 studies showing benefit compared to another advanced therapy), and negative pressure wound therapy (1 of 3 studies showing benefit compared to standard care). Strength of evidence was low or insufficient for all findings related to time to ulcer healing. One study of a silver dressing versus a calcium dressing reported a global outcome of healed or improved ulcers with no difference between groups. No studies reported on return to daily activities.

Secondary Outcomes

The most commonly reported secondary outcomes were ulcers infected during treatment and ulcer recurrence. No study reported a benefit for these outcomes for any of the advanced therapies reviewed. Fewer amputations were reported in three studies (one each of a biological skin equivalent, negative pressure wound therapy, and hyperbaric oxygen therapy all compared to standard care) while five studies reported no difference. Few studies reported other secondary outcomes of interest including revascularization or surgery, pain or discomfort, hospitalization, need for home care, or quality of life. No significant differences between treatment groups (including 12 studies comparing an advanced therapy to standard care, 3 studies comparing one advanced therapy to another advanced therapy, and 1 study with both standard therapy and advanced therapy comparison arms) were seen in all-cause mortality though studies were not designed to assess this outcome. We found no significant differences in study withdrawals due to adverse events or allergic reactions to treatment.

Executive Summary Table 1. Strength of Evidence - Advanced Wound Care Therapies for Diabetic Ulcers

Treatment	Control(s)	Outcome	Number of Studies (n for Primary Outcome)*	Comments	Strength of Evidence
Collagen	Standard care	Percentage of ulcers healed	4 (483)	One study reported significant improvement compared to standard care. Three studies reported no significant difference between collagen and standard care. Trials were rated as fair quality.	Low
		Mean time to ulcer healing		One trial found a significant difference favoring standard care; two found no difference.	Low
Biological Dressings	Advanced therapy control (*PDGF, BSE)*	Percentage of ulcers healed	2 (99)	Two fair quality trials showed no difference compared to other advanced wound care therapies.	Low
		Mean time to ulcer healing		No trial was significantly different versus control.	Low
Biological Skin Equivalents [BSE] – *Dermagraft*	Standard care	Percentage of ulcers healed	3 (505)	A trend toward statistically significant improvement compared to standard care (RR=1.49, 95% CI 0.96 to 2.32, I^2=43%). Trials were rated as fair quality.	Low
		Mean time to ulcer healing		Inconsistent results, with one trial reporting a significant difference versus standard care. Trials were rated as fair quality.	Low
BSE – *Apligraf*	Standard care	Percentage of ulcers healed	2 (279)	Two trials of fair quality found statistically significant improvement versus standard care (RR=1.58, 95% CI 1.20 to 2.08, I^2=0%).	Moderate
		Mean time to ulcer healing		One trial reported a significant difference between *Apligraf* and standard care.	Low
BSE – *Apligraf*	Advanced therapy control (*Skin allografts -Theraskin)*	Percentage of ulcers healed	1 (29 ulcers)	One fair quality trial found no significant difference versus *Theraskin*.	Low
		Mean time to ulcer healing		No significant difference versus *Theraskin*.	Low
Platelet Derived Wound Healing [PDGF]	Placebo /standard care	Percentage of ulcers healed	7 (685)	Overall statistically significant improvement versus placebo (RR 1.45 [95% CI 1.03 to 2.05]) but results were inconsistent (I^2 85%). Overall study quality was rated as fair.	Low
		Mean time to ulcer healing	5 (731)	Overall, PDGF demonstrated shorter duration of time to ulcer healing versus placebo.	Low
PDGF	Advanced therapy control (*BSE, silver, sodium carboxy-methylcellulose)*	Percentage of ulcers healed	3 (189)	No significant differences compared to an advanced therapy comparator. Trials were rated as fair quality.	Low
		Mean time to ulcer healing		No significant differences compared to an advanced therapy comparator.	Low
Platelet-Rich Plasma [PRP]	Placebo gel, Platelet-Poor Plasma	Percentage of ulcers healed	2 (96)	Neither of the studies (fair to poor quality) demonstrated a significant difference between PRP and its respective control.	Low
		Mean time to ulcer healing		Significantly shorter healing time compared to platelet-poor plasma. No significant difference versus placebo gel.	Low

Treatment	Control(s)	Outcome	Number of Studies (n for Primary Outcome)*	Comments	Strength of Evidence
Silver Products	Standard care or advanced therapy controls *(calcium-based dressing, oak bark extract, polyherbal cream*	Percentage of ulcers healed	4 (280)	One trial found silver ointment more effective than standard care. Two trials found no difference in healing between a silver cream or dressing and another advanced care product. Studies were of fair quality.	Low
		Mean time to ulcer healing	2 (174)	Two trials found no difference between silver and another advanced wound care product.	Low
Negative Pressure Wound Therapy [NPWT]	Standard care (*Advanced moist wound therapy, saline gauze*)	Percentage of ulcers healed	1 (335)	One trial of good quality found 43% in the NPWT group experienced ulcer healing compared to 29% treated with standard care (RR=1.49, 95% CI 1.11 to 2.01).	Moderate
		Mean time to ulcer healing	3 (432)	Results for time to healing were inconsistent based on 3 trials of mixed quality.	Low
Hyperbaric Oxygen Therapy (HBOT)	Sham or standard care	Percentage of ulcers healed	4 (233)	Three long-term studies of fair quality found significant improvement with adjunctive HBOT versus sham or standard care; one short-term study found no difference.	Low
		Mean time to ulcer healing	-	Outcome not reported.	Insufficient
HBOT	Advanced therapy control (*Extracorporeal shockwave therapy*)	Percentage of ulcers healed	1 (84)	One trial of poor quality found adjunctive HBOT less effective than extracorporeal shockwave therapy.	Low
		Mean time to ulcer healing	-	Outcome not reported.	Insufficient
Ozone-Oxygen Therapy	Sham	Percentage of ulcers healed	1 (61)	One trial of fair quality found no significant difference between ozone-oxygen and sham.	Low
		Mean time to ulcer healing	-	Outcome not reported.	Insufficient

*Number of ulcers evaluated for the primary outcome

The evidence is rated using the following grades: (1) high strength indicates further research is very unlikely to change the confidence in the estimate of effect, meaning that the evidence reflects the true effect; (2) moderate strength denotes further research may change our confidence in the estimate of effect and may change the estimate; (3) low strength indicates further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate, meaning there is low confidence that the evidence reflects the true effect; and (4) insufficient, indicating that the evidence is unavailable or does not permit a conclusion.

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Key Question #2. What are the efficacy and harms of therapies for venous ulcers? Is efficacy dependent on ancillary therapies? Does efficacy differ according to patient demographics, comorbid conditions, treatment compliance, or activity level?

We identified 20 eligible trials of 9 different advanced wound care therapies for venous ulcers. In 14 trials the ulcer was described as a "leg" ulcer, in 2 trials the ulcer was described as a "lower extremity" ulcer, and 3 trials did not report the ulcer location describing the ulcer only as a "venous ulcer." In 12 trials a diagnosis of venous ulcers was based on clinical signs or symptoms of venous insufficiency. The remaining 8 trials required either patients to have adequate arterial circulation or specifically excluded patients with known arterial insufficiency.

Collagen (1 RCT)

One fair quality small RCT (n=73 randomized) compared collagen to standard care. No significant differences were found between collagen and standard ulcer care for the percentage of ulcers healed by study completion (49% versus 33%, p=0.18; ARD=16%, 95% CI -7% to 38%) though the confidence interval was wide and cannot exclude a clinically meaningful difference. Fewer ulcers were infected during treatment in the collagen group. There were no significant differences between collagen and standard care for pain, the number of withdrawals due to adverse events, or allergic reaction to treatment. The effects of ancillary therapies or patient factors on outcomes were not reported.

Biological Dressings (1 RCT)

We identified one multisite RCT enrolling 120 patients. This fair quality study found that biological dressing, OASIS Wound Matrix, increased complete ulcer healing at 12 weeks compared to standard care (55% versus 34%; ARD=20%, 95% CI 3% to 38%). The benefit of the biological dressing was significantly increased in patients who received ulcer debridement at baseline. At 6 months follow-up, recurrence was significantly less frequent in the biological dressing group than in the standard care group (0% versus 30%, p=0.03). No statistically significant differences were seen in adverse events between groups.

Biological Skin Equivalents (3 RCTs)

We identified three trials, all of fair quality (total n=380) and all comparing a biological skin equivalent to standard care with compression bandage. Two trials evaluated Dermagraft and one evaluated Apligraf. Both studies of Dermagraft were small in size and did not reach statistical significance for our primary efficacy outcomes when compared to standard care including compression bandages. The Apligraf study was a large (n=309), multicenter trial that found significant increases in the proportion of completely healed ulcers (63% versus 49%; ARD=14%, 95% CI 3% to 26%; p=0.02) and reduction in the time to complete healing (61 days versus 181 days, p=0.003) when compared to standard compression bandage therapy. Of the two studies reporting on adverse events, no significant differences were seen between treatment and control groups. One study reported subgroup analyses. In ulcers of more than 6 months duration, Apligraf resulted in faster healing than standard compression bandage therapy (p=0.001). A similar result was observed for patients with ulcers reaching muscle tissue (p=0.003). For both large ulcers (>1000mm^2; p=0.02) and small ulcers (<1000mm^2; p=0.04), Apligraf resulted in faster healing.

Keratinocytes (4 RCTs)

Four RCTs were identified (n=502 randomized). These trials had marked heterogeneity across several important parameters: keratinocyte source (autologous or allogeneic); cellular state of keratinocytes (fresh, frozen, or lysed), comparators (other keratinocyte product, standard of care); and study size, protocols, and quality. One large, fair quality trial demonstrated significant improvements in both proportion of ulcers healed (38% versus 22%, p=0.01) and time to complete healing (176 days versus more than 201 days, p<0.0001) when BioSeed-S (autologous keratinocytes in fibrin sealant) was compared to standard care. In the other studies, no statistical differences in ulcer healing were seen when cryopreserved, cultured epidermal allografts (CEA) were compared with standard compression therapy (fair quality study), cryopreserved CEA were compared to lyophilized CEA (poor quality study), and when lyophilized keratinocytes were compared to standard care in a large, fair quality, multinational study. Pooled results from the two studies with standard care as the comparator yielded a significant benefit of treatment with keratinocytes (38% versus 24%; ARD=14%, 95% CI 5% to 23%; RR=1.57, 95% CI 1.16 to 2.11, I^2=0%). One study reported recurrence with no different between keratinocyte therapy and standard care. Only the two large studies reported adverse events; one demonstrated similar type and frequency of events compared to standard care, and the other reported a total of 9 minor adverse events that were deemed at least "possibly" related to treatment over the 6 month study. In one study, subgroup analyses found the benefit of keratinocytes in achieving ulcer closure was more pronounced in patients with larger ulcers (>10 cm^2) at baseline (25.5% versus 7.7%, p=0.03). Ulcer duration (greater than 12 months versus less than 12 months) did not influence outcomes. A second study found that the likelihood of healing was higher in small ulcers (p<0.001), ulcers decreasing in size between screening and baseline visits (p=0.001), and ulcers in patients with a higher BMI (p=0.02).

Platelet Rich Plasma (PRP) (1 RCT)

One fair quality study (enrolling 86 patients) found no difference between platelet lysate (applied twice per week for up to 9 months) and standard care regarding the percentage of ulcers healed at study completion (79% versus 77%). When the effects of ulcer area, ulcer duration, gender, and ulcer history were analyzed, only ulcer size was a significant factor in time to heal. No other outcomes or harms of interest were reported.

Silver Products (6 RCTs)

Six studies (n=771 randomized) reported on the use of silver products. One good quality study and one fair quality study compared silver cream/ointment to standard care. One fair quality study compared silver cream to copper cream or to placebo copper cream. Overall, no statistically significant difference in ulcer healing was observed with silver therapy (range 21% to 63%) versus standard care or placebo (range 3% to 80%) with evidence of large heterogeneity (RR=1.65, 95% CI 0.54 to 5.03, I^2=84%). Compared to the copper-based cream, the silver-based cream significantly improved healed ulcers (21% versus 0%, p=0.01 with Fisher's exact test). Results were mixed for two studies, both fair quality, that compared a silver dressing to a similar non-silver dressing. One of the trials (n=42) found a higher rate of healing in the silver dressing group compared to the control dressing at 9 weeks (81% versus 48%; ARD=33%, 95%

CI 6% to 61%); a larger trial (n=204) found no difference (60% versus 57%). One study (n=281) comparing two silver dressings also found no difference (17% vs. 15%). Pooled data from two studies of silver versus non-silver dressings show a non-significant outcome and evidence of heterogeneity (RR=1.27, 95% CI 0.80 to 2.01, I^2=67%). Two studies, of fair quality, reported time to ulcer healing when a silver dressing was compared to a non-silver dressing. One found no significant difference; one did not report significance. No differences were observed between silver-based therapies and other treatments or standard care for other outcomes or adverse events. In one study, female gender (p=0.01), and smaller ulcer size (up to 3 cm diameter, p=0.008) were significantly related to ulcer healing. In another study, a significant difference in healing between treatment and control was observed for shallow ulcers (p=0.04) but not for deep ulcers (p=0.29)

Intermittent Pneumatic Compression Therapy (1 RCT)

One fair quality RCT (n=54 randomized) compared intermittent pneumatic compression (IPC) therapy to compression bandaging (Unna's boot). There was no significant difference between IPC and Unna's boot in the percentage of ulcers healed by study completion (71% versus 60%) or pain/discomfort. There were no significant differences between the number of withdrawals due to adverse events or allergic reactions to treatment. An analysis of ulcer healing by ulcer size found that 100% of ulcers less than 3 cm^2 were healed regardless of treatment group.

Electromagnetic Therapy (EMT) (2 RCTs)

Two fair quality trials of EMT versus sham treatment (n=63 randomized) produced mixed results for percentage of ulcers healed. One trial (n=37) reported a significant increase in the percentage of healed ulcers compared to sham after 90 days (67% versus 32%; ARD=35%, 95% CI 5% to 65%). The other trial (n=19) reported no significant difference after 50 days (20% versus 22%). One study also reported lower pain in the EMT group. No other outcomes or adverse events differed between groups.

Hyperbaric Oxygen Therapy (HBOT) (1 RCT)

One small (n=16 randomized) good quality RCT comparing HBOT to sham found no difference between groups. No other outcomes were reported.

Summary

We identified 20 trials of nine different advanced ulcer care therapies for patients with venous ulcers: collagen, biological dressings, biological skin equivalents, keratinocytes, platelet-rich plasma, silver products, intermittent pneumatic compression therapy, electromagnetic therapy, and hyperbaric oxygen therapy. Sixteen of twenty studies compared an advanced therapy to standard therapy.

Primary Outcomes

For collagen, platelet-rich plasma, intermittent pneumatic compression therapy, and hyperbaric oxygen therapy, no eligible studies reported a significant improvement in the number of ulcers healed. Strength of evidence was low for each of those comparisons with only one trial for each advanced wound care therapy (see Executive Summary Table 2). For biological dressings, we

found low strength of evidence of improved healing compared with standard care (55% versus 34% healed). The biological skin equivalent Apligraf significantly increased healed ulcers compared to compression bandaging in one trial (63% versus 49%) but the strength of evidence was low. In two trials, Dermagraft was not significantly better than compression bandaging. One trial comparing a keratinocyte product to standard care found improved healing versus standard care although a second trial found no difference. The pooled risk ratio was significant with healing in 38% versus 24% (RR=1.57, 95% CI 1.16-2.11; p=0.003). Two trials of keratinocyte therapies found no difference in ulcer healing when compared to another advanced wound care therapy. Silver creams improved healing in two studies (one comparing silver cream to standard care and one comparing silver cream to a copper-based cream) while three studies of silver dressings found mixed results (significant benefit in one study of silver dressing compared to non-silver dressing and no differences in two studies with non-silver or alternative silver dressings as the comparator). Strength of evidence was low for these outcomes. Two trials of electromagnetic therapy found mixed results; strength of evidence was low.

Few studies reported time to ulcer healing. Two studies of the biological skin equivalent Apligraf found shorter time to ulcer healing as did the study comparing a keratinocyte product to standard care. Two other keratinocyte studies reported no significant differences in time to ulcer healing as did a study comparing a silver dressing to a non-silver dressing. Strength of evidence was low for these comparisons. Two studies of silver products reported higher global assessment outcomes in the silver groups; a study of electromagnetic therapy reported no difference between groups. Only studies of electromagnetic therapy reported patient activity levels; one finding no difference between treatment groups and one noting improvements pre- to post-treatment.

Secondary Outcomes

The most commonly reported secondary outcomes were ulcers infected during treatment (8 studies), ulcer recurrence (7 studies), and pain (9 studies). The collagen treatment study reported fewer ulcers infected in the collagen group. No other study reported a difference between treatment groups. The biological dressings study reported fewer recurring ulcers in the active treatment group compared to standard care. No other differences were reported. One of the EMT studies reported a significant reduction in pain from baseline to 30 days in patients receiving EMT. Other studies reporting pain found no differences between treatment groups. No studies reported amputation, revascularization or other surgery, time to recurrence, or need for home care. Two studies reported hospitalization and one reported quality of life with no difference between treatment arms in the studies. No significant differences were observed in all-cause mortality, study withdrawals due to adverse events, or allergic reactions to treatment.

Executive Summary Table 2. Strength of Evidence - Advanced Wound Care Therapies for Venous Ulcers

Treatment	Control(s)	Outcome	Number of Studies (n for Primary Outcome)*	Comments	Strength of Evidence
Collagen	Standard care	Percentage of ulcers healed	1 (73)	One fair quality RCT found no significant differences between treatment groups.	Low
		Mean time to ulcer healing		Outcome not reported.	Insufficient
Biological Dressings	Standard care with compression bandage	Percentage of ulcers healed	1 (120)	One fair quality study found biological dressing (OASIS) more effective at 12 weeks but not 6 months versus standard care.	Low
		Mean time to ulcer healing		Outcome not reported.	Insufficient
Biological Skin Equivalents [BSE] – *Dermagraft*	Standard care with compression bandage	Percentage of ulcers healed	2 (44)	Data from two small trials (fair quality) found *Dermagraft* was not more effective than standard care.	Low
		Mean time to ulcer healing		Outcome not reported.	Insufficient
Biological Skin Equivalents [BSE] – *Apligraf*	Standard care with compression bandage	Percentage of ulcers healed	1 (275)	One large fair quality trial found significant improvement with *Apligraf* versus standard compression therapy.	Low
		Mean time to ulcer healing		Significant improvement with *Apligraf* versus standard compression therapy.	Low
Keratinocyte Therapy	Standard care with compression bandage	Percentage of ulcers healed	2 (418)	Keratinocyte therapy was more effective than standard care (RR=1.57, 95% CI 1.16 to 2.11, I^2=0%). The trials were rated fair quality.	Moderate
		Mean time to ulcer healing		Inconsistent results, one trial found a significant difference versus standard care and one found no difference between groups.	Low
Keratinocyte Therapy (*Cryopreserved*)	Advanced therapy control (*Lyophilized keratinocytes)*	Percentage of ulcers healed	1 (50)	One poor quality trial reported no differences between treatment groups.	Low
		Mean time to ulcer healing		No difference between groups.	Low
Keratinocyte Therapy	Advanced therapy control *(Pneumatic compression)*	Percentage of ulcers healed	1 (27)	One fair quality trial reported no differences between treatment groups.	Low
		Mean time to ulcer healing		Outcome not reported.	Insufficient
Platelet-Rich Plasma	Placebo	Percentage of ulcers healed	1 (86)	One fair quality trial reported no differences between treatment groups.	Low
		Mean time to ulcer healing		Outcome not reported.	Insufficient

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Treatment	Control(s)	Outcome	Number of Studies (n for Primary Outcome)*	Comments	Strength of Evidence
Silver, Dressings	Controls *(non-silver dressing, ionic silver vs. lipido-colloid silver)*	Percentage of ulcers healed	3 (536)	Inconsistent results from two fair quality trials, one found a significant difference versus non-silver dressing and one found no difference. One fair quality trial found no difference between two silver dressing groups.	Low
		Mean time to ulcer healing	2 (250)	Two fair quality trials; one found no significant difference between silver and non-silver dressings; one did not report significance	Low
Silver, Cream/ Ointment	Controls *(placebo, non-adherent dressing, standard care)*	Percentage of ulcers healed	3 (199)	One fair quality trial found significant benefit compared to standard care; one fair and one good quality trail found no benefit compared to placebo or standard dressing.	Low
		Mean time to ulcer healing		Outcome not reported.	Insufficient
Silver, Cream	Placebo, tri-peptide copper cream	Percentage of ulcers healed	1 (86)	One three-armed trial of fair quality trial found silver more effective than tri-peptide copper cream but not placebo.	Low
		Mean time to ulcer healing		Outcome not reported.	Insufficient
Intermittent Pneumatic Compression (IPC)	Unna's boot dressing	Percentage of ulcers healed	1 (53)	One fair quality trial found no significant difference between groups.	Low
		Mean time to ulcer healing		Outcome not reported.	Insufficient
Electromagnetic Therapy (EMT)	Sham	Percentage of ulcers healed	2 (56)	Inconsistent results between trials. Study quality was fair.	Low
		Mean time to ulcer healing	1 (37)	Comparable between groups.	Low
Hyperbaric Oxygen Therapy (HBOT)	Sham	Percentage of ulcers healed	1 (16)	One good quality trial found no significant difference between groups.	Low
		Mean time to ulcer healing		Outcome not reported.	Insufficient

*Number of ulcers evaluated for the primary outcome.

The evidence is rated using the following grades: (1) high strength indicates further research is very unlikely to change the confidence in the estimate of effect, meaning that the evidence reflects the true effect; (2) moderate strength denotes further research may change our confidence in the estimate of effect and may change the estimate; (3) low strength indicates further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate, meaning there is low confidence that the evidence reflects the true effect; and (4) insufficient, indicating that the evidence is unavailable or does not permit a conclusion.

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Key Question #3. What are the efficacy and harms of therapies for arterial ulcers? Is efficacy dependent on ancillary therapies? Does efficacy differ according to patient demographics, comorbid conditions, treatment compliance, or activity level?

We identified only one small (n=31), fair quality study of advanced wound care therapies for patients specifically identified as having arterial ulcers. This small study suggested that biological skin equivalent, may improve ulcer healing when used on ischemic foot ulcers or partial open foot amputations following revascularization surgery. At 12 weeks, healing was reported in 86% of the biological skin equivalent group and 40% of the standard care control group ($p<0.01$). Median time to healing was shorter in the biological skin equivalent group (7 weeks versus 15 weeks; p=0.002). Other outcomes did not differ significantly from standard care. The mean age of patients was 70 years and 75% of enrollees were men. Race/ethnicity data were not reported. Authors did not report on the effect of baseline patient characteristics, treatment compliance, or activity level on ulcer healing.

In studies of mixed ulcer types, a collagen matrix product (one fair quality study comparing collagen to standard care, n=24 randomized) improved ulcer healing (86% versus 29%, p=0.01). Improved healing was also observed in two studies of biological dressings - one fair quality study comparing biological dressing to standard care (n=50; 80% versus 65%, $p<0.05$), one poor quality study comparing biological dressing to another advanced wound care therapy (hyaluronic acid dressing, n=54; 81% versus 46%, $p<0.001$). Silver products (2 studies reporting, both fair quality and comparing a silver foam dressing to a non-silver foam dressing and a silver dressing to an advanced iodine-based dressing, n=410 randomized) and negative pressure wound therapy (1 study comparing NPWT to standard care, n=60) did not improve healing. There were mixed results for time to ulcer healing and, overall, no differences between investigational treatment and either standard care (5 studies) or another advanced care therapy (2 studies) on other outcomes. Only one study (of fair quality and comparing a silver dressing to an iodine-based advanced care dressing) looked at the effects of ulcer duration and ulcer size finding no difference in healing for ulcers of less than 12 weeks versus more than 12 weeks or ulcers of 3.6 cm^2 or less versus greater than 3.6 cm^2.

One good quality study of wounds associated with partial foot amputation (n=162) found that NPWT (compared to standard care) improved wound healing (56% versus 39%, p=0.04) and decreased mean time to healing (56 days versus 77 days, p=0.005). There were significantly more infections in the NPWT group (17% versus 6%, p=0.04), but the incidence of other adverse events did not differ between the NPWT and standard care groups. The effects of ancillary therapies, baseline characteristics, activity level and compliance were not explored.

Summary

For arterial ulcers, one small, fair quality study found that a biological skin equivalent, may improve the incidence and rate of complete ulcer healing when used on ischemic foot ulcers following revascularization surgery. Other outcomes did not differ significantly from standard care. The effects of ancillary therapies or baseline patient characteristics were not explored in the study. We found no RCTs that included any of the other therapies of interest exclusively in patients with arterial lower extremity ulcers.

In seven studies of mixed ulcer types, collagen and biological dressings were found to improve ulcer healing; silver products and negative pressure wound therapy did not. There were mixed results for time to ulcer healing and, overall, no differences between investigational treatment and control on other outcomes. The studies were of poor to fair quality.

One good quality study of ulcers associated with partial foot amputation showed a benefit of NPWT with respect to healed ulcers and mean time to healing. There were significantly more infections in the NPWT group but the incidence of other adverse events did not differ between the NPWT and standard care groups.

DISCUSSION

Chronic lower extremity ulcers are a common and serious health problem. A wide range of standard treatment approaches to achieve ulcer healing are used (e.g., off-loading, compression, leg elevation, etc.) based on patient and ulcer factors and provider preferences. While many ulcers heal completely within several weeks, a significant portion either do not heal or increase in size, depth, and severity. These chronic ulcers can result in considerable clinical morbidity and health care costs.

Many types of advanced wound care therapies exist but all represent considerably greater product costs compared to standard therapy. These costs may be justified if they result in improved ulcer healing, reduced morbidity, fewer lower extremity amputations, and improved patient functional status. In addition to the treatment selected, many potential factors contribute to the success or failure of the ulcer healing process including ulcer etiology; ulcer area, depth, duration, and location; patient comorbid conditions; and patient compliance with the treatment protocol. Much of the existing research on advanced wound care therapies has attempted to minimize the influence of many of these factors by limiting enrollment to patients with ulcers of a particular size, including only patients with adequate circulation, and excluding patients taking certain classes of medications. Furthermore, many of the trials are industry sponsored (55% of the studies included in our review) and the role of the sponsor is typically not stated, definitions of "chronic" ulcers vary widely, and few studies are of sufficient duration to assess whether healing is maintained.

Our systematic review of randomized controlled trials found discouragingly low strength evidence regarding the effectiveness and comparative effectiveness of advanced wound care therapies for treatment of lower extremity ulcers. This was primarily due to the fact that for each ulcer type (diabetic, venous, or arterial) individual categories of advanced wound care therapies were only evaluated in a few studies, often in highly selected populations, and frequently had conflicting findings. Furthermore, within each category of wound care therapies several different types of interventions were used making it difficult to determine if results were replicable in other studies or generalizable to broader clinical settings. Additionally, most studies compared advanced wound care therapies to standard care or placebo. Therefore there is little comparative effectiveness research evaluating one advanced wound care therapy to another. It has been noted that standard care is an inappropriate comparator for studies of advanced therapy since patients have likely already failed standard care. For arterial ulcers we identified only a single study of any advanced wound care therapy (and this was compared to standard care) despite the clinical importance of arterial ulcers.

However, based on the available findings we conclude that for patients with diabetic chronic ulcers, there is moderate strength of evidence that the biological skin equivalent Apligraf and negative pressure wound therapy improve healing compared to standard care. There is low strength evidence that advanced wound care therapies improved the percentage of ulcers healed compared to standard care for the following therapies: collagen (notably Graftjacket), the biological skin equivalent Dermagraft, platelet-derived growth factors, silver cream, and hyperbaric oxygen therapy but results were not uniform for any treatment group. Most beneficial effects were derived from single or few studies so we recommend caution regarding translating these findings of effectiveness into broader clinical application. Pooled analyses were possible for several therapies and demonstrated a significant improvement in ulcer healing compared to standard care for Apligraf (a biological skin equivalent), platelet-derived growth factors, and negative pressure wound therapy; no improvement was observed for Dermagraft (a biological skin equivalent). Few studies compared one advanced treatment to another but in those studies, no differences in percentage of ulcers healed were found between the two treatment arms. For time to ulcer healing, the pattern of findings was similar and strength of evidence was low for all treatment comparisons reporting that outcome. No studies reported a significant difference in adverse events for any treatment comparison.

Findings for venous ulcers were similar. Although some individual trials of biological dressings (notably OASIS), biological skin equivalents (Apligraf), keratinocytes, silver cream and dressing, and electromagnetic therapy noted significant benefit of the therapy in percentage of ulcers healed compared to standard care, overall the results for each therapy were mixed. In pooled analyses only keratinocytes resulted in significantly better healing compared to standard care. Strength of evidence was moderate for the benefit of keratinocyte therapy and low for the other therapies. Few studies of venous ulcers compared two advanced therapies and, where reported, typically found no differences. Time to ulcer healing was reported infrequently. No advanced wound care therapy was observed to result in an increase in adverse events.

We identified only one study of patients with arterial ulcers despite the clinical importance of this population. It is possible that patients with arterial disease were included in the studies of diabetic ulcers or venous ulcers (i.e., mixed etiology). In one study of patients with non-healing lower extremity ulcers or amputation wounds following a revascularization procedure, Apligraf increased ulcer healing and decreased time to healing compared to standard care with no difference in adverse events.

For amputation wounds, one study of negative pressure wound therapy versus standard care found significantly better healing with no difference in adverse events.

Despite finding benefits of some therapies compared to standard care, the methodological quality of individual studies reviewed was predominantly fair or poor. Common factors limiting the quality were inadequate allocation concealment, no blinding (including no blinding of outcome assessment), failure to use intention-to-treat analysis methods, and failure to adequately describe study dropouts and withdrawals. With methodological flaws, few trials reporting, and heterogeneity in the comparators, study duration, and how outcomes were assessed, the overall strength of evidence was low. While a wide range of patients were enrolled in studies most were older than age 60 years, male, of white race, likely compliant with treatment protocols, and possessed ulcers

that were relatively small as measured by surface area. However, authors rarely reported outcomes by patient demographic, comorbidity or ulcer characteristics. Therefore, we found insufficient evidence to guide clinicians and policy makers regarding whether efficacy differs according to patient demographics, comorbid conditions, treatment compliance, or activity level.

APPLICABILITY AND COST EFFECTIVENESS

It is not well known how outcomes reported in studies of selected populations will translate to daily practice settings including in Veterans Health Administration facilities. There is evidence of good success in ulcer healing with strict adherence to off-loading for diabetic ulcers and compression therapy for venous ulcers. The patients enrolled in trials were likely more compliant than typical patients and received very close monitoring. Therefore, results from these studies may overestimate benefits and underestimate harms in non-study populations.

Our review was limited to studies of FDA approved products. We excluded studies with wounds of multiple etiologies (e.g., vascular, pressure, trauma, surgery) if they did not report results by etiology. We also excluded studies if they did not report our primary outcomes of healed wounds or time to complete healing. Many studies report change in ulcer size but the clinical benefit of change in ulcer size has not been established.

Furthermore, we did not conduct cost effectiveness analyses or assess additional costs of care associated with chronic ulcers. Despite the high costs of advanced wound care therapies it is possible that they may be cost effective or even cost saving if found to improve ulcer healing; reduce ulcer associated morbidity, hospitalizations, medical care and amputations; and improve functional status and quality of life. Based on our findings from randomized controlled trials the decision of if, when, and in whom to use advanced wound care therapies as well as the type of advanced wound care therapy selected is difficult. Additionally, because little comparative effectiveness research exists to guide choices, decisions may be based on other factors including wound care product cost, ease of use, and patient and provider preferences (the latter also influenced by personal experience with ulcer and patient characteristics).

FUTURE RESEARCH

Our review highlights several much needed areas for future research. Most studies compared an advanced therapy to either standard ulcer care or placebo treatment. Few studies (10 of the 35 eligible studies of diabetic ulcers, 4 of the 20 eligible studies of venous ulcers, and none for arterial or mixed ulcers) directly compared two advanced therapies. Furthermore, few studies provided a run-in period with carefully monitored standard care to exclude patients for whom carefully monitored standard care would obviate the need for advanced therapy. Therefore, additional randomized trials of advanced wound care therapies versus standard care are needed to replicate or refute current findings. Comparative effectiveness research is also needed to evaluate the relative benefits and harms of different advanced wound care therapies. In both effectiveness and comparative effectiveness research, the sample sizes should be adequate to report specific outcome reporting according to key patient and ulcer characteristics including age, race, gender, and ulcer size, location, and depth. We note below the limitations of the existing research by type of ulcer and therapy assessed.

Of the studies of diabetic ulcers included in this review, only two focused on biological dressings (using different products) and two on platelet-rich plasma. We identified no studies of topical oxygen or electromagnetic therapy. No studies reported on return to daily activities or the need for home care related to ulcer treatment and only one study reported quality of life or hospitalization. The need for amputation or revascularization and the incidence of and time to ulcer recurrence require further investigation. The majority of studies described the ulcers as diabetic foot ulcers with only six providing greater detail about ulcer location. Future research should report healing by ulcer location. Future research should also examine microvascular disease to more clearly distinguish diabetic ulcers from arterial ulcers.

For venous ulcers, we identified only one study of the following advanced wound care therapies: collagen, biological dressings, platelet rich plasma, intermittent pneumatic compression, and hyperbaric oxygen therapy. There were no studies of platelet-derived growth factors or typical oxygen. We found no studies that reported on amputations, time to ulcer recurrence, or need for home health care related to the ulcer. One study reported hospitalization, one study reported quality of life, and two studies reported return to work or daily activities.

We identified only one study of patients with arterial disease requiring advanced wound care following revascularization. Only this study and one other included patients with partial foot amputations with delayed healing. Neither of these studies reported on return to daily activities, pain, quality of life, or need for home health assistance related to the wound. There is a paucity of research on advanced wound care therapies in patients with strictly arterial disease.

In addition to specific topics needing further research, several organizations have outlined overall methodological standards for future research of wound healing therapies. The standards focus on study design, patient population, comparators, outcomes and outcome assessment, and potential sources of bias. Randomized trials, with allocation concealment and, at a minimum, blinding of third-party outcomes assessors, are recommended. The patient population should be appropriate for the treatment being studied and exclusion criteria should be minimal to enhance generalizability. Endpoints should be selected based on the purpose of the intervention (i.e., closure versus preparation for surgery) and adequate follow-up should be included to confirm healing. Dropouts and study withdrawals should be documented, including withdrawals due to ulcer deterioration. Additional research, conducted in accordance with the standards, is needed to establish the safety and efficacy of advanced wound care therapies. Finally, future research is needed to determine the effectiveness, comparative effectiveness and harms of advanced wound care therapies as used in general clinical practice settings (e.g., vascular and dermatology clinics) where patients may have more severe and larger ulcers, greater comorbidities, or increased difficulty with treatment compliance.

ABBREVIATIONS TABLE

ABI	Ankle-Brachial Index
ARD	Absolute Risk difference
BD	Biological Dressing
BMI	Body Mass Index
BSE	Biological Skin Equivalent
CI	Confidence Interval
CMS	Centers for Medicare and Medicaid Services
Col	Collagen
EMT	Electromagnetic Therapy
EST	Extracorporeal Shock Wave Therapy
FDA	Food and Drug Administration
HbA_1c	Hemoglobin A_1c
HBOT	Hyperbaric Oxygen Therapy
IPC	Intermittent Pneumatic Compression
NPWT	Negative Pressure Wound Therapy
PAD/PVD	Peripheral Artery Disease or Peripheral Vascular Disease
PDGF	Platelet-derived Growth Factor
PPP	Platelet-Poor Plasma
PRP	Platelet Rich Plasma
RCT	Randomized Controlled Trial
RR	Risk Ratio
VA	Veterans Affairs
VAMC	VA Medical Center