Supplementary Material*


Supplement. Pressure Ulcer Treatment Strategies: Update to a Comparative Effectiveness Review

* This supplementary material was provided by the authors to give readers further details on their article. The material was reviewed but not copyedited.
Pressure ulcer treatment strategies: update to a comparative effectiveness review

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A systematic review on the comparative effectiveness of pressure ulcer treatment strategies was published in July 2013, based on searches conducted through October 2012 (1, 2). It found evidence that in comparison with standard care, placebo, or sham interventions, there was moderate-strength evidence that air-fluidized beds, protein-containing nutritional supplements, radiant heat dressings, and electrical stimulation improved healing of pressure ulcers. Alternating-pressure surfaces, hydrocolloid dressings, platelet-derived growth factor, and light therapy may improve healing, but the strength of evidence supporting these interventions was low. Evidence on harms was limited. This update was performed to identify new studies published since the original review and to determine their impact on strength of assessment and findings.

Methods

This update follows the protocol used for the original review, including the key questions and analytic framework, used for the original review. Details regarding the methods, including search strategies, and detailed inclusion criteria, are available in the original full report, available on the Agency for Healthcare Research and Quality website (1). The key questions addressed for this update were:

**Key Question 1.** In adults with pressure ulcers, what is the comparative effectiveness of treatment strategies for improved health outcomes including but not limited to: complete wound healing, healing time, reduced wound surface area, pain, and prevention of serious complications of infection?

- **Key Question 1a.** Does the comparative effectiveness of treatment strategies differ according to features of the pressure ulcers, such as anatomic site or severity at baseline?
- **Key Question 1b.** Does the comparative effectiveness of treatment strategies differ according to patient characteristics, including, but not limited to: age, race/ethnicity, body weight, specific medical comorbidities, and known risk factors for pressure ulcers, such as functional ability, nutritional status, or incontinence?
- **Key Question 1c.** Does the comparative effectiveness of treatment strategies differ according to patient care settings such as home, nursing facility, or hospital, or according to features of patient care settings, including, but not limited to, nurse/patient staffing ratio, staff education and training in wound care, the use of wound care teams, and home caregiver support and training?

**Key Question 2.** What are the harms of treatments for pressure ulcers?

- **Key Question 2a.** Do the harms of treatment strategies differ according to features of the pressure ulcers, such as anatomic site or severity at baseline?
- **Key Question 2b.** Do the harms of treatment strategies differ according to patient characteristics, including: age, race/ethnicity, body weight, specific medical comorbidities, and known risk factors for pressure ulcers, such as functional ability, nutritional status, or incontinence?
- **Key Question 2c.** Do the harms of treatment strategies differ according to patient care settings such as home, nursing facility, or hospital, or according to features of patient care settings, including, but not limited to, nurse/patient staffing ratio, staff education and training in wound care, the use of wound care teams, and home caregiver support and training?

**Data sources and searches**

The original review performed searches through October 2012. For this update, we updated searches on Ovid MEDLINE, the Cochrane Library, and CINAHL (EBSCOhost) from November 2012 through February 2014.
Study selection

English language articles that were relevant to a key question and met the inclusion criteria as defined in the original report were selected. Included studies were randomized trials and comparative observational studies of treatments for pressure ulcers in adults. We included non-comparative intervention series (n > 50) for surgical interventions and evaluation of harms. Exclusion criteria were wrong population (children; adolescents; and patients with non-pressure-related ulcers, including but not limited to venous ulcers and diabetic foot ulcers), studies without comparator interventions, hospice care settings unless complete wound healing was an outcome measured, and case reports.

Data extraction

Details about the study design, population, setting, interventions, analysis, follow-up and results were abstracted. Study quality was assessed using previously predefined criteria.

Data synthesis and analysis

Meta-analysis was not conducted due to methodological limitations in the studies and clinical heterogeneity. Based on new evidence identified for this update as well as the evidence previously reviewed for the original review, we assessed the overall strength of evidence of each body of evidence as “high,” “moderate,” “low,” or “insufficient” in accordance with the Agency for Healthcare Research and Quality Methods Guide for Comparative Effectiveness Reviews (3), based on the quality of studies, consistency between studies, precision of estimates, and directness of evidence.

Role of the funding source

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Results

Searches yielded 488 unique citations. Sixty-six potentially relevant studies were identified in the abstract review stage. After review of the full-text articles, seven studies were determined to meet inclusion criteria. Reasons for exclusion at the full-text stage were: wrong population, inappropriate design or lacking original data, wrong outcomes, or a systematic review update without additional included studies. Seven studies met our inclusion criteria addressing the effectiveness or harms of interventions to treat pressure ulcers (Table 1): There were two studies found in the categories of local wound applications (one comparing a foam to a collagen-foam dressing (4), and one comparing collagenase to hydrogel dressings (5), and nutrition (one comparing an L-Carnosine-Zinc complex with L-Carnosine alone or an untreated control (6), and one comparing an anabolic steroid, oxandrolone, to placebo (7)). There was one study in the categories of support surfaces (comparing two mattress overlays (8), and adjunctive therapies (comparing ultraviolet-C irradiation to placebo (9)). One new study reported on harms of different types of skin flap surgeries to treat pressure ulcers (10). Quality ratings are shown in Tables 2 (randomized trials) and 3 (observational studies). We found no new evidence addressing treatment or harm differences based on features of the pressure ulcers, patient characteristics, or clinical setting. There was one systematic review update on the effectiveness of electromagnetic therapy in the treatment of pressure ulcers but as no additional data was included, this review was excluded (11).

Support surfaces

Evidence from original report

The original report found 24 studies (21 trials and 3 observational studies) that provided evidence on various support surfaces, including air-fluidized beds, alternating-pressure beds and chair cushions, and low-air-loss beds (1-2). Of these, 4 were rated good-quality, 10 as fair-quality, and 10 as poor quality. We found 8 studies that compared types of support surfaces and found no differences in the outcome of complete wound healing (12-19). We found moderate-strength evidence based on 5 highly consistent
studies that wound improvement (including rate of reduction in wound size and ulcer stage) was superior with air-fluidized beds, although they were most often compared with standard hospital beds rather than other advanced support surface (20-24). Healing was similar between alternating pressure mattresses and other support surfaces (15, 25-27) (low-strength evidence), and different types of alternating pressure mattresses provided similar benefit (moderate strength evidence) (12, 19, 28-30). Evidence about the effectiveness of alternating-pressure seat cushions was insufficient because only 2 studies with very different populations were identified (31, 32). We found low-strength evidence that low–air-loss beds are similar to foam surfaces or foam mattresses (4 studies), and wound healing did not differ when comparing low–air-loss beds with low–air-loss overlays (1 study) (1, 2).

New evidence
One new, poor-quality trial (n=72) compared a 3-layer multifilament polyester-air interface-monofilament polyester overlay to a gel overlay, both used over a foam mattress in nursing home patients in Italy. (Table 1) (8). They found a larger percentage of patients showed improvement in the ulcer at 12 weeks (37% vs. 11%, p<0.005) but no difference was found in complete healing (9% vs. 14%, NS). There was no difference in the percentage of patients with a worsened ulcer (46% vs. 60%, NS). No trial in the original report compared the effectiveness of these two support surfaces. This study had several methodological shortcomings including an unclear description of randomization and allocation concealment methods, dissimilar groups at baseline with 22% versus 7% stage IV ulcers, and lack of blinding (Table 2). Given the poor quality of this one study, there is insufficient evidence to determine the effect of the 3-layer versus the gel overlay.

Nutrition
Evidence from original report
The original report found 16 studies (11 trials and 5 observational studies) that addressed nutritional support, including protein-containing nutritional supplementation and specific nutrient supplementation with vitamins or minerals, such as ascorbic acid (vitamin C) or zinc. Three trials were rated good-quality (33-36), 2 were fair-quality (33, 37, 38), and 6 were poor-quality (38-43). Four observational studies were rated fair-quality (44-47), and 1 was poor-quality (48). Eight studies considered the outcome of complete wound healing (33, 35-38).

Although the formulations varied greatly, most of the 12 studies of protein supplementation found greater reduction in ulcer size with supplementation than without, but not more complete wound healing. Because of the small number of head-to-head trials, the existing evidence base does not clarify whether any specific type of protein supplementation is superior to others. Low-strength evidence indicated no benefits in wound healing with vitamin C based on 1 good-quality study (n = 88) (36). Evidence about zinc supplementation was insufficient to draw conclusions based on one randomized trial (46).

New evidence
One new poor-quality non-randomized observational study (5) compared an L-carnosine-zinc preparation (n=10) to L-carnosine alone (n=18) and to an untreated control (n=14) in long-term care patients in Japan with stage II-IV pressure ulcers (6). They followed the ulcers for 4 weeks and found no differences between the two treatment groups but an improvement in mean weekly surface area in both of the treatment groups compared with the control (1.0+/-.1 vs 1.2+/-.0.2 vs. 0.6+/-.0.1 cm2) (6). This study does not change the conclusions of the original report that there is insufficient evidence to determine the effectiveness of zinc supplementation versus no zinc supplementation for the healing of pressure ulcers based on two randomized trials. There is also insufficient evidence to determine the effectiveness of L-carnosine versus no L-carnosine supplementation based on results from this one new study.

One new, good-quality trial (n=212) evaluated effects of oxandrolone (20mg/d), an anabolic steroid, compared with placebo in spinal cord injured patients admitted to a Veterans Affairs Rehabilitation center in the United States (7). They found no differences in the percentage of healed ulcers (24.1% vs. 29.8%) and no differences in the percentage of ulcers remaining healed at 8-weeks follow up (16.7% vs. 15.4%). They did find greater number of patients with elevated liver enzymes (32.4% vs. 2.9%, p<.001) but no difference in the percentage of patients who withdrew due to adverse events (19% vs.18%) (Table 1).
This trial provided low strength of evidence that oxandrolone is similar to placebo in wound healing of pressure ulcers and may be associated with adverse effects.

**Local wound applications**

**Evidence from original report**
The original report found 89 original studies examining the effectiveness of local wound applications for pressure ulcers. Of these, 11 were rated good-quality, 20 were fair quality, and 45 were poor-quality. Ninety-nine studies addressed the outcome of complete wound healing and found no differences when comparing types of local wound applications. We found 10 studies (1 good-quality (49), 2 fair-quality (50, 51), and 7 poor-quality (52-59) that compared hydrocolloid with gauze dressings and provided low-strength evidence indicating greater reduction in wound size with hydrocolloid dressings. Statistical heterogeneity precluded quantitative pooling of results across these studies. Complete wound healing was equivalent with hydrocolloid and foam dressings (pooled relative risk, 1.12 [95% CI, 0.88 to 1.41]; $I^2 = 16.4\%$; $P = 0.301$) (8 studies; moderate-strength evidence) (60-67). Radiant heat dressings produced more rapid reduction in wound size than other dressings based on moderately consistent results from 2 good-quality and 2 fair-quality trials, but there was no evidence of benefit in terms of complete wound healing (pooled relative risk, 1.23 [CI, 0.70 to 2.14]; $I^2 = 0.0\%$; $P = 0.916$) (68-71). Evidence about the comparative effectiveness of other dressing types was insufficient and there were no new studies to add to the body of evidence.

The most commonly evaluated topical therapies were debriding enzymes (primarily collagenase), phenytoin solution, dextranomer paste, and collagen applications. Low strength evidence showed that dextranomer is less effective than other wound dressings based on 1 good-quality trial (72) and 1 poor-quality trial (73). Evidence about enzymes and phenytoin was inconsistent and insufficient to draw conclusions.

The most commonly evaluated biological agent was platelet-derived growth factor, for which 1 fair-quality (74) and 4 poor quality (75-78) studies provided low-strength evidence of benefit compared with placebo in promoting healing of severe (stage III or IV) ulcers. Evidence about the effectiveness of other biological agents was insufficient.

In the original report, collagen applications did not seem to provide wound-healing benefit compared with standard care, based on low-strength evidence from 1 good-quality (80) and 2 poor-quality (81, 82) trials.

**New evidence**
One new poor-quality trial (79) compared collagenase to hydrogel in nursing home patients in the United States with stage III-IV pressure ulcers and followed them for 12 weeks. This was a continuation of a randomized controlled trial that was excluded for the first report due to the wrong outcome. All patients that had complete debridement of visible, nonviable tissue by the end of phase 1 (day 42) were rolled over into phase 2 of the trial and continued their assigned treatment. Of the 13 patients enrolled in phase 1 in the collagenase group, 11 rolled over into phase 2, and of the 14 patients enrolled in the hydrogel group during phase 1, 4 rolled over into phase 2. At 12 weeks they found the collagenase group had similar percentage of complete wound healing compared to the hydrocolloid group (82\% vs. 75\%). There are several methodological limitations to this study including a lack of intention to treat. Based on original enrollment into phase 1, collagenase was more effective in complete wound healing compared to hydrogel (9 of 13 (69\%) vs. 3 of 14 (21\%). Large loss to follow up, unclear randomization measures and allocation concealment, small and dissimilar sample sizes, and lack of blinding of the care provider and patient limit the methodological quality and interpretation of the results. There remains low evidence that the effectiveness of collagenase and other debriding enzymes is inconclusive.

One new fair-quality randomized controlled trial (4) compared collagen dressing covered with foam dressing to foam dressing alone ($n=10$) in hospitalized adults with stage III pressure ulcers in Germany. They found a faster rate of healing in the foam dressing group (healed at day 14: 40\% vs. 0\%) but no difference in the percentage of ulcers completely healed at day 21 (80\% vs. 100\%) (4). Although randomization was adequate, allocation concealment was unclear and there was a lack of masking of
outcome assessors, care providers, and patient. The additional study does not alter the conclusion that wound improvement was similar with topical collagen applications compared with hydrocolloid dressings or standard care.

**Surgery**

*Evidence from original report*

In the original report, surgical interventions for pressure ulcers identified in studies that met our inclusion criteria were primarily surgical flaps (most commonly myocutaneous and fasciocutaneous flaps). One poor-quality trial (83) and 5 fair-quality intervention series (84-86) including 1094 pressure ulcers in 647 patients, provided evidence on the effectiveness of surgical techniques to treat stage III or IV pressure ulcers. We found low-strength evidence for a lower rate of ulcer recurrence with sacral ulcers than ischial ulcers, a higher rate of recurrent ulcer among patients with spinal cord injuries than among others, and greater wound dehiscence rates with surgeries in which bone was removed.

Because of heterogeneity in patient populations and surgical procedures, there was insufficient evidence that 1 approach to closure of stage III or IV pressure ulcers was superior to another. We found low-strength evidence that more adverse events occur with surgery for ischial ulcers than for sacral or trochanteric ulcers (84, 85). Surgical flap failures requiring reoperation ranged from 12% to 24% (84, 87).

*New evidence*

One new fair-quality retrospective intervention series (10) compared the complications and complication rates of various skin flap procedures in paralyzed spinal cord injured patients with stage III-IV pressure ulcers in Germany (10). They found 21% complication rate of all skin flap surgeries with the highest overall rate from tensor fascia lata flaps (17 of 25, 49%) and the lowest from Rotation flaps (15 of 131, 12%). Other complications included infection (25%, most common with Conway, 20%, and posterior thigh flap, 11%), Hematoma (19%, most common with biceps femoris flap, 13%, and Limburg, 10%), partial necrosis (14%, most common with tensor fascia lata flap), and total flap necrosis (10.3%, most common with tensor fascia lata flap, 9%, biceps femoris flap, 5%, and gluteus maximus flap, 19%). Despite the methodological limitations of this intervention series, including lack of clarity regarding comparability of groups, identification of potential confounders, blinding of the assessors, and reporting of attrition, the study provides low strength evidence that tensor fascia lata flaps may be associated with higher complication rates and the rotation flap may be associated with the lowest complication rates compared to other flap procedures.

**Adjunctive Therapies**

*Evidence from original report*

In the original report, thirty-four trials (3 good-quality, 29 fair-quality, and 2 poor-quality) and 5 observational studies (2 fair-quality and 3 poor-quality) evaluating adjunctive therapies met our inclusion criteria. Adjunctive therapies identified in our review included electrical stimulation, electromagnetic therapy, therapeutic ultrasound, negative-pressure wound therapy, hydrotherapy, light therapy, and laser therapy. Evidence about other adjunctive therapies—including vibration, shock wave, and hyperbaric oxygen—was limited to small, single studies that provided insufficient evidence for comparative effectiveness conclusions. Seventeen studies addressed the outcome of complete wound healing (34, 79, 88-102). Moderately consistent results from 1 good-quality (88) and 8 fair-quality (89-93, 103-105) trials showed that electrical stimulation improved healing rates (moderate-strength evidence) but evidence about the effect of electrical stimulation on complete wound healing was insufficient because of heterogeneous findings across studies. There was also low-strength evidence that electromagnetic therapy (94, 95, 106, 107), therapeutic ultrasound (34, 79, 97), negative-pressure wound therapy (98, 108, 109, Ho, 2010 #895) and laser therapy (79, 102, 110) were no different from sham treatment or standard care in wound-healing outcomes. There was insufficient evidence to draw conclusions about hydrotherapy (109, 111).
We found low-strength evidence that light therapies provided benefit in terms of reduced wound size but not complete wound healing (99, 100, 112, 113).

New evidence
One new fair-quality randomized controlled trial compared ultraviolet-C to SHAM ultraviolet-C, n=58, in spinal cord injured adults in Canada with stage III-IV pressure ulcers of the pelvis or lower extremity. Patients were either inpatient at a rehabilitation center or outpatients (9). They found no differences in complete healing at 8 weeks (43% vs. 43%) and no difference in the number of weeks to complete closure (data not reported). The groups however were dissimilar at baseline, it was unclear if the care provider was blinded to the treatment, and there was no intention to treat analysis. There remains low evidence that light therapy is similar to sham in producing complete wound healing.

Discussion
The evidence identified for this update is summarized in Table 4, with updated strength of evidence ratings. We identified five new randomized trials and two new observational trials of interventions to treat pressure ulcers, including support surfaces (8), nutrition supplementation (6, 7), local wound applications (4, 5), surgery (10), and adjunctive therapies (79).

The one new trial comparing a 3-dimensional multifilament polyester-air interface-monofilament polyester overlay with a gel overlay found no differences in the percentage of healed ulcers but was of poor-quality and provided insufficient evidence to draw conclusions (8).

Two new studies were included in the nutrition category. The non-randomized observational study comparing an L-carnosine/zinc supplement with L-carnosine alone or an untreated control found no differences in surface area when zinc was added but both active groups showed greater mean weekly improvement in wound surface area compared with the untreated control (6). Although this study is consistent with the fair-quality study showing no difference in wound healing with zinc supplementation, the evidence remains insufficient to make conclusions on the effect of zinc due to methodological limitations and small sample size. The addition of L-carnosine was associated with greater mean weekly improvement in wound surface area compared with no treatment but the evidence remains insufficient to draw conclusions.

One new study compared oxandrolone, an anabolic steroid, with placebo, and found no difference in complete wound healing or percentage of ulcers remaining healed at 8 weeks of follow up, but there was an association with elevated liver enzymes in the oxandrolone group (32.4% vs. 2.9%, p<.001) (7). This was a good-quality study of 212 patients and provides low strength evidence that oxandrolone is similar to placebo in the healing of pressure ulcers, and is associated with elevated liver enzymes.

Two new studies contribute to our understanding of topical applications, one regarding collagenase, a debriding enzyme, and one regarding collagen added to the wound bed. Due to methodological limitations with dissimilarity of treatment groups, lack of consideration of confounders and small sample size, the new trial on collagenase did not change the conclusion that the evidence remains insufficient to determine the effectiveness of collagenase or other debriding enzymes (5). The new trial on collagen plus foam dressing compared with foam dressing alone was of fair quality but very small sample size (n=10) and does not change the overall low strength of evidence that wound improvement is similar when comparing collagen with standard care or hydrocolloid dressings (4).

One new fair-quality trial comparing ultraviolet-C with sham ultraviolet-C was consistent with two previously reviewed studies finding no difference in complete wound healing (9). There remains low strength of evidence that light therapy is similar to sham light therapy in complete wound healing.

Only one new study reported on surgery and adds to the body of evidence. This retrospective intervention series comparing various types of skin flap procedures performed on stage II-IV pressure ulcers in patients with spinal cord injuries reported on complication rates and found the greatest complications with
tensor fascia lata flaps compared with others, and the least complication rates with rotation flaps (10). Although the evidence is limited by the design itself, this was a fair quality study that provides a low strength of evidence that tensor fascia lata flaps may be associated with greater complications.

We identified no new trials on other treatment interventions reviewed in the original report and no new evidence addressing treatment or harm differences based on features of the pressure ulcers, patient characteristics, or clinical setting.

In summary, new evidence on pressure ulcer treatment is most notable for a new trial that found that oxandrolone is similar to placebo in the outcome of complete wound healing and is associated with elevated liver enzymes. It is also notable that tensor fascia lata flaps may be associated with greater complication rates. Conclusions regarding other treatment interventions and harms is otherwise largely unchanged.
References

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Table 1. New trials of interventions to treat pressure ulcers

<table>
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<tr>
<th>Author, Year</th>
<th>Setting</th>
<th>Study Type</th>
<th>Quality Rating</th>
<th>Country</th>
<th>Followup</th>
<th>Intervention (N)</th>
<th>Baseline Demographics</th>
<th>Pressure Ulcer Change</th>
<th>Adverse Effects</th>
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<tr>
<td><strong>Support surfaces</strong></td>
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<td>Cassino 2013(8)</td>
<td>Long term care ward in Italy</td>
<td>RCT</td>
<td>Poor</td>
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<td>12 weeks</td>
<td>A: 3-dimensional multifilament polyester-air interface-multifilament polyester overlay, n=35</td>
<td>Mean age: 85 vs. 86 years&lt;br&gt;Sex: 80% vs. 73% female&lt;br&gt;Race: Not reported&lt;br&gt;Stage I-IV pressure ulcer</td>
<td>Healed ulcer: 8.6% vs 13.5%, NS&lt;br&gt;Improved ulcer: 37.1% vs 10.8%, p&lt;0.005&lt;br&gt;Worsened ulcer: 45.7% vs 59.5%, NS</td>
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<td>B: gel overlay, n=37</td>
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<td><strong>Nutrition</strong></td>
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<tr>
<td>Sakae 2013(6)</td>
<td>Long term care hospital and nursing home in Japan</td>
<td>Non-randomized observational study</td>
<td>Poor</td>
<td>Long term care hospital and nursing home in Japan</td>
<td>4 weeks</td>
<td>A: control untreated, n=14&lt;br&gt;B: Polaprezinc (L-carnosine 116mg with zinc34 mg), n=10&lt;br&gt;C: L-carnosine 116mg, n=18</td>
<td>Mean age: 68 vs. 65 vs. 62 years&lt;br&gt;Sex: 36% vs. 56% vs. 30% female&lt;br&gt;Race: Not reported&lt;br&gt;Stage II-IV pressure ulcer x 4 weeks &lt;br&gt;Size: 8.8 +/-6.8 vs 6.3+/-6.0 vs 9.0+/-6.7 cm²</td>
<td>Mean weekly improvement in (p&lt;.05 vs control):&lt;br&gt;PUSH score: 0.8 +/-0.2 vs 1.6 +/-0.2 vs 1.8 +/-0.2&lt;br&gt;Surface area: 0.6 +/-0.1 vs 1.0 +/-0.1 vs 1.2 +/-0.2 cm²</td>
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<td>All groups received surgical debridement prior to study start as needed. All groups received standard wound care including repositioning, alternating pressure air mattress, pressure-redistributing seat cushion, topical treatments with povidone-iodine and silver hydrofiber dressing sealed with adhesive polyurethane film.</td>
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<tr>
<td>Bauman 2013(7)</td>
<td>Veterans Affairs hospital - spinal cord injury (SCI) ward United States</td>
<td>RCT</td>
<td>Good</td>
<td></td>
<td>24 weeks</td>
<td>A: placebo, n=104&lt;br&gt;B: Oxandrolone 20mg/d, n=108&lt;br&gt;All groups received standard wound care and repositioning</td>
<td>Mean age: 57 vs 58 years&lt;br&gt;Sex: 0% vs 1.8%, female&lt;br&gt;Race: 65% vs 61%, white&lt;br&gt;Level of SCI: 43% vs 48% tetraplegia&lt;br&gt;Stage III-IV PU of pelvis</td>
<td>Healed: 29.8% % vs 24.1%&lt;br&gt;8-week follow up: 15.4% vs 16.7% healed&lt;br&gt;Elevated liver enzymes: 2.9% vs 32.4%, p&lt;0.001&lt;br&gt;Withdrew because of adverse event: 18% vs 19%</td>
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Local wound applications

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<th>Author, Year</th>
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<th>Baseline Demographics</th>
<th>Pressure Ulcer Change</th>
<th>Adverse Effects</th>
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<tbody>
<tr>
<td>Piatkowski</td>
<td>Hospital</td>
<td>Germany</td>
<td>RCT</td>
<td>Fair</td>
<td>A: Foam dressing, n=5</td>
<td>Mean age: 63 vs. 67 years</td>
<td>Healed at day 14: 40% vs 0%</td>
<td>Healed at day 21: 80% vs 100%</td>
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<td>B: Collagen dressing covered with foam dressing, n=5</td>
<td>Sex: 20% vs. 40% female</td>
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<td>All groups had stagnating pressure ulcers of at least 4 weeks duration.</td>
<td>Race: Not reported</td>
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<td></td>
<td>All groups received repositioning and foam mattress</td>
<td>Stage III sacral ulcers</td>
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<td>Mean age: 63 vs. 67 years</td>
<td>Sex: 20% vs. 40% female</td>
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<td>Race: Not reported</td>
<td>Stage III sacral ulcers</td>
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<td></td>
<td>Size: 9.3 vs 11.4 cm median diameter</td>
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<tr>
<td>Milne 2012(5)</td>
<td>Long-term care facility</td>
<td>United States</td>
<td>Phase 2</td>
<td>Poor</td>
<td>A: collagenase, n=11</td>
<td>Mean age: not reported</td>
<td>Healed at 12 weeks: 9 of 11 (82%) vs 3 of 4 (75%)</td>
<td>ITT from phase 1: 9 of 13 (69%) vs 3 of 14 (21%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>B: Hydrogel, n=4</td>
<td>Sex: not reported</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Included all subjects who completed phase 1 of study at 6 weeks</td>
<td>Race: not reported</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All groups received standard wound care and repositioning</td>
<td>Stage: III-IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean age: not reported</td>
<td>Sex: not reported</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Race: not reported</td>
<td>Stage: III-IV</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Size: not reported. No difference in wound size at onset of phase 2, p=0.26</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All groups received standard wound care</td>
<td></td>
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</tr>
</tbody>
</table>

**Adjunctive Therapies**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Setting</th>
<th>Country</th>
<th>Study Type</th>
<th>Quality Rating</th>
<th>Interventions (N)</th>
<th>Baseline Demographics</th>
<th>Pressure Ulcer Change</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nussbaum,</td>
<td>Rehab center and outpatient</td>
<td>Canada</td>
<td>RCT</td>
<td>Fair</td>
<td>A: SHAM Ultraviolet C, n=28</td>
<td>Mean age: 54 vs 55 years</td>
<td>Healed at ≤ 8 weeks: 43% vs 43%, NS</td>
<td>Weeks to closure: no difference</td>
</tr>
<tr>
<td>2013(9)</td>
<td>and outpatient in Canada</td>
<td></td>
<td></td>
<td></td>
<td>B: Ultraviolet C, n=30</td>
<td>Sex: 11% vs 25% female</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All groups received standard wound care</td>
<td>Race: not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Setting: 5% vs 25% outpatients</td>
<td>Setting: III-IV</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stage: III-IV</td>
<td>Size: 4.22-4.27 vs 2.24 vs 4.45 cm² of stage II and stage III ulcers respectively</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Size: 4.22-4.27 vs 2.24 vs 4.45 cm² of stage II and stage III ulcers respectively</td>
<td>Ulcer duration: 89% vs 50% &lt; 9 weeks</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All patients had paralysis from spinal cord injuries.</td>
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</tr>
</tbody>
</table>

**Harms associated with interventions**

Downloaded From: http://annals.org/pdfaccess.ashx?url=/data/journals/aim/933271/ on 07/31/2018
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Setting</th>
<th>Intervention (N)</th>
<th>Baseline Demographics</th>
<th>Pressure Ulcer Change</th>
</tr>
</thead>
</table>
| Biglari 2013(10)   | Outpatient followup | Skin flaps, nPU=421, n patients=352 | Mean age: not reported  
Sex: 29% female  
Race: not reported  
Stage: III-IV  
Size: not reported  
All patients had paralysis from spinal cord injuries | Overall Complications: 87 reported (21%)  
Suture line dehiscence: 31%, most common with PTF (15%) and TFF (14%)  
Infection: 25%, most common with Conway (20%) and PTF (11%)  
Hematoma: 19%, most common with BFF (9%) and Limburg (10%)  
Partial necrosis: 14%, all in TFF  
Total flap necrosis: 10.3%, most common in TFF 9%), BFF (5%), and GMF 4%  
Highest overall rate: TFF 17 of 35 (49%)  
Lowest overall rate: Rotation flaps 15 of 131 (12%) |
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</tr>
</thead>
<tbody>
<tr>
<td>Cassino, 2013(8)</td>
<td>Unclear</td>
<td>Unclear</td>
<td>No 3-D group with more stage IV ulcers (22% vs 7%)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>None noted</td>
</tr>
<tr>
<td>Bauman, 2013(7)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Good</td>
</tr>
<tr>
<td>Piatkowski, 2012(4)</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>None noted</td>
<td>Fair</td>
</tr>
<tr>
<td>Milne, 2012(5)</td>
<td>Unclear</td>
<td>Unclear</td>
<td>No – phase 2; Yes – phase 1</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>None noted</td>
<td>Poor</td>
</tr>
<tr>
<td>Nussbaum, 2013(9)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>None noted</td>
<td>Fair</td>
</tr>
</tbody>
</table>
Table 3. Quality Assessment: Observational Studies

<table>
<thead>
<tr>
<th>Lack Author, year</th>
<th>Country</th>
<th>Study Type</th>
<th>1) Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?</th>
<th>2) Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching?)</th>
<th>3) Did the study maintain comparable groups through the study period?</th>
<th>4) Did the study use accurate methods for ascertaining exposures and potential confounders?</th>
<th>5) Were outcome assessors and/or data analysts blinded to the exposure being studied?</th>
<th>6) Did the article report attrition?</th>
<th>7) Did the study perform appropriate statistical analyses on potential confounders?</th>
<th>8) Is there important differential loss to followup or overall high loss to followup?</th>
<th>Overall Quality Rating</th>
<th>Funding Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saka, 2013[6]</td>
<td></td>
<td>Non-randomized trial</td>
<td>Unclear</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Poor</td>
<td>Not reported</td>
</tr>
<tr>
<td>Biglari, 2014[10]</td>
<td>Intervention series</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Fair</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
### Table 4. Summary of Evidence

<p>| Strength of evidence of findings from original AHRQ report | Number and type of studies identified (number of new trials) | Number of subjects (number in new trials) | Overall quality | Consistency (High, Moderate, Low) | Directness (Direct or Indirect) | Precision (High, Moderate, Low) | Overall strength of evidence rating, including new evidence | Summary of findings |
|---|---|---|---|---|---|---|---|---|---|
| 3-D polyester overlay vs. gel overlay | 1 randomized trial (1) | N=72 (72) | Poor | Cannot determine (1 study) | Direct | Low | Insufficient | One trial found a greater percentage of ulcers showing improvement in the 3-layer static air overlay versus a gel overlay (37.1% vs. 10.8%, p&lt;0.005) but no difference in the percentage of healed ulcers (8.6% vs. 13.5%, NS). There was no difference in the percentage of worsened ulcers (45.7% vs 59.9%) |
| Zinc supplementation vs. no zinc supplementation | 2 randomized trials (1) | N=112 (42) | Poor-Fair | Moderate | Direct | Low | Insufficient | Zinc supplementation compared to placebo in one fair quality study found greater improvement in stage III and IV ulcers, not stage II (p&lt;0.05) but no difference in surface area and complete healing was not reported. One poor quality study compared a combination of L-carnosine (116mg) plus zinc (34mg) with L-carnosine alone (116 mg) and with an untreated control. No difference was found between the L-carnosine with zinc and the L-carnosine alone group in mean weekly improvement in surface area. |
| L-carnosine vs. no L-carnosine supplementation | 1 randomized trial (1) | N=42 (42) | Poor | Cannot determine (1 study) | Direct | Low | Insufficient | One poor quality study compared a combination of L-carnosine (116mg) plus zinc (34mg) with L-carnosine alone (116 mg) and with an untreated control. Mean weekly improvement in surface area was found compared to control but no difference was found between the L-carnosine plus zinc and the L-carnosine alone group Surface area: 1.0+/-0.1 vs. 1.2+/-0.2 cm² vs. 0.6+/-0.1 |</p>
<table>
<thead>
<tr>
<th>Strength of evidence of findings from original AHRQ report</th>
<th>Number and type of studies identified (number of new trials) / Number of subjects (number in new trials)</th>
<th>Overall quality</th>
<th>Consistency (High, Moderate, Low)</th>
<th>Directness (Direct or Indirect)</th>
<th>Precision (High, Moderate, Low)</th>
<th>Overall strength of evidence rating, including new evidence</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxandrolone vs. placebo Overall strength of evidence: No studies</td>
<td>1 randomized trial (1) N=212 (212)</td>
<td>Good</td>
<td>Cannot determine (1 study)</td>
<td>Direct</td>
<td>Low</td>
<td>Low</td>
<td>One good-quality study compared oxandrolone (20mg/day) to placebo and found no difference was found in complete wound healing (24% vs. 30%) or percentage of ulcers remaining healed at 8 weeks follow up (17% vs. 15%). More patients experienced elevated liver enzymes (32.4% vs. 2.9%, p&lt;.001) but no difference was found in withdrawal due to adverse events (19% vs. 18%)</td>
</tr>
<tr>
<td>Debriding enzymes compared with dressings or other topical therapies Overall strength of evidence: Insufficient</td>
<td>6 randomized trials (1) N=245 (27)</td>
<td>Fair</td>
<td>Low</td>
<td>Direct</td>
<td>Low</td>
<td>insufficient</td>
<td>Evidence about the effectiveness of collagenase and other debriding enzymes was inconclusive due to differences in the enzymes studied and in outcomes measured (six studies)</td>
</tr>
<tr>
<td>Collagen applications similar to sham or standard care (complete wound healing) Overall strength of evidence: Low</td>
<td>4 randomized trials (1) N=179 (10)</td>
<td>Fair</td>
<td>Moderate</td>
<td>Direct</td>
<td>Low</td>
<td>Low</td>
<td>Wound improvement was similar with topical collagen applications compared with hydrocolloid dressings or standard care based on 4 studies</td>
</tr>
<tr>
<td>Light therapy similar to sham light therapy Overall strength of evidence: Low</td>
<td>3 randomized trials (1) N=437 (58)</td>
<td>Fair</td>
<td>Moderate</td>
<td>Direct</td>
<td>Low</td>
<td>Low</td>
<td>Light therapy was similar to sham in producing complete wound healing based on three studies (44% vs. 40% [Dehlin 2003], 54% vs. 59% [Dehlin 2009], 43% vs. 43% [Nussbaum 2013])</td>
</tr>
<tr>
<td>Overall complication rate highest with tensor fascia lata flaps and lowest with Rotation flaps versus other surgical skin flaps Overall strength of evidence: No studies</td>
<td>1 interventional series (1) N=352 (352) N pressure ulcers =421 (421)</td>
<td>Fair</td>
<td>Cannot determine (1 study)</td>
<td>Indirect</td>
<td>Low</td>
<td>Low</td>
<td>One fair quality intervention series found 21% complication rate of all skin flap surgeries with the highest overall rate from tensor fascia lata flaps (17 of 25, 49%) and the lowest from Rotation flaps (15 of 131, 12%)</td>
</tr>
</tbody>
</table>

*Strength of evidence as reported in references 1 and 2.