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Systematic review of topical interventions for the management of pain in chronic wounds

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Abstract

Chronic wounds adversely affect quality of life. Pain is associated with chronic wounds, and its impact can vary according to wound aetiology, condition, and patient factors. This systematic review examined the effectiveness of topical interventions in the management chronic wound–related pain guided by PRISMA recommendations of randomised controlled trials (RCTs) where pain reduction is the primary outcome. Inclusion criteria were adults (older than 18 years) with chronic venous, arterial, diabetic, or pressure ulcers where pain has been managed through topical administration of pharmacological/nonpharmacological agents. Searches were conducted in Ovid Embase, Ovid MEDLINE, EBSCOhost, CINAHL, CENTRAL, PubMed, Web of Science, and Scopus. Studies were screened for eligibility; risk of bias and data were extracted by 2 independent assessors. Searches retrieved 10,327 titles and abstracts (7760 after deduplication). Nine full texts (1323 participants) examining ibuprofen (n = 4), morphine (n = 2), BWD + PHMB [polihexanide-containing biocellulose wound dressing] (n = 1), and EMLA (n = 2) were included. Risk of bias was assessed using the Cochrane Risk of Bias 2 tool. Meta-analysis was not possible, but initial exploration suggests improved outcomes (reduced pain) for ibuprofen when compared with controls. Two studies involving morphine showed conflicting findings. Included studies often had small samples, and considering confounding factors (eg, comorbidities), the results should be interpreted with caution. Review of included studies suggests that topical interventions may provide pain relief in individuals with chronic wounds. Further adequately powered RCTs are recommended to assess the efficacy of topical interventions for the management of chronic wound–related pain.

Keywords: Review, Chronic wounds, Topical management, Pain, RCTs

1. Introduction

The prevalence of chronic wounds is conservatively estimated at 4% of the adult population in developed countries.[17,32] The incidence of chronic pain in individuals with a lived experience of chronic wounds is estimated to be as high as 85%, with pain reported to be one of the most distressing aspects of the chronic wound experience.[4,14,19,20,27] Chronic pain is defined by the International Association for the Study of Pain as "*An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.*"[31] Chronic pain affects many aspects of the individual's life and often exists concomitantly with conditions such as anxiety, depression, and cognitive impairment.[6,18,24]

Currently available therapeutics for the management of chronic pain are typically given as systemic preparations and include a wide variety of drug classes. Examples of commonly used

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analgesics include nonsteroidal anti-inflammatories (NSAIDS), opioid medications, and atypical analgesics including antiepileptics such as gabapentin, which is commonly used for neuropathic pain conditions.[34,35] There exists several topical-based preparations for the prevention, management, and treatment of chronic pain and wound-associated pain, including local anaesthetics, anti-inflammatory foam dressings, and topical opioid medication.[1,5,25,30] The therapeutic potential of topical cannabis-based medicines for the management of wound-associated pain and wound healing has been highlighted in several recent case reports.[7,21,22]

A previous Cochrane review of topical agents or dressings for pain limited to those with venous leg ulcers only identified 2 randomised controlled trials (RCTs) meeting their criteria.[5] One study showed significantly more participants in the ibuprofen group achieving >50% total maximum pain relief score between day 1 and day 5 compared with the control group, whereas the second study showed no statistically significant difference in the proportion of participants experiencing slight to complete pain relief on the first evening of treatment. The following systematic review aims to establish a robust understanding of the level of efficacy of topical interventions available for the management of wound-associated pain in individuals with a lived experience of chronic wounds.

2. Methods

A full protocol for this review has been submitted for publication.[16] Ovid Embase, Ovid MEDLINE, EBSCOhost, CINAHL, the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Web of Science, and Scopus were searched from inception to present with no limits on language alongside OpenGrey and Eudra CT for gray literature and registered clinical trials, respectively [All sources were searched between June 25, 2021, and July 1, 2021]. The most recent article was added on the 15th of November 2022.[28] Searches were developed iteratively with PRESS Guideline Evidence-Based Checklist[23] in mind. This was a stepped process, with terms being developed to capture 3 distinct concepts: different types of chronic wound, pain experienced because of chronic wounds, and interventions used to alleviate the wound-related pain.

2.1. Population

This review is limited to individuals older than 18 years who have chronic wounds including venous, arterial, mixed arterial venous, diabetic ulcer, or pressure ulcer. Studies which included individuals with surgical, acute, burn, or otherwise atypical wounds were excluded. Where more than one wound aetiology was reported, the article was included if a subset of the participants met the above criteria alongside the data being presented based on accordant aetiology.

2.2. Type of study

Only RCTs were included in this review. Allocation method was open provided it fitted the criteria of an RCT (eg, clustered). Quasirandomised studies, reviews, and case studies were excluded.

2.3. Comparators

Studies which compared any one intervention compared with another, or studies with any one intervention compared with a placebo were included.

2.4. Primary outcomes

Studies required having pain as a primary outcome measure to be included. The primary outcomes were as follows:

(1) The proportion of participants with any reduction or improvement in pain intensity.
(2) Any assessments of pain intensity measured on a continuous scale (eg, numerical rating or visual analogue scales).

2.5. Secondary outcome measures

Based on a process of public patient involvement from the Alliance for Research and Innovation in Wounds and with reference to the recommendations by IMMPACT,[9] the following secondary outcomes were included:

(1) The proportion of participants with ≥30% reduction in pain intensity (equivalent to a moderate improvement defined by IMMPACT).[9]
(2) Reported changes in disability or physical functionality.
(3) Reported changes in emotional functionality or impact on mental health (eg, anxiety, depression, mood, etc).
(4) Reported changes to quality-of-life score, measured using any quality-of-life assessment tool.
(5) Adverse events. For this review, adverse events will include reported measures of harm, withdrawal because of adverse events or serious adverse events, patient-reported adverse events, and specific adverse events—especially central nervous system (CNS) and cardiovascular. We will describe how adverse events were addressed, how they were reported, and over what time the harm was experienced as per the PRISMA harms checklist.[36]
(6) Rescued analgesia requirements (eg, time to rescue).
(7) Patient-reported changes to sleep quality and duration.
(8) Analgesic effect onset and duration.
(9) Reported changes in cognitive functioning.

2.6. Procedure

After the conclusion of searches, deduplication was performed using EndNote and subsequently transferred to Rayyan (rayyan.qcri.org) for the second phase of deduplication and screening. Disagreements were resolved by discussion between 2 authors with referral to a third author when required. At least 2 members of the study team screened all titles and abstracts (randomly allocated). Full text of any studies or reports identified as potentially relevant was retrieved. All studies excluded from the review at this stage were listed as excluded, with reasons (PRISMA flowchart **Fig. 1**).

To create a more homogenous understanding of the screening process, team members who were involved with screening performed a pilot calibration exercise on a random sample of 100 references until 90% agreement was reached. Similarly, 2 review authors independently extracted data from included studies. Again, at least 2 review authors screened full-text studies for inclusion or exclusion. Any discrepancies were resolved by discussion until consensus was reached or through consultation with a third review author, when necessary.

3. Results

Searches retrieved 10,327 titles and abstracts (7,760 after deduplication). Eighteen studies were selected for full-text review, of which 9 (n = 1323 participants) examining the following were

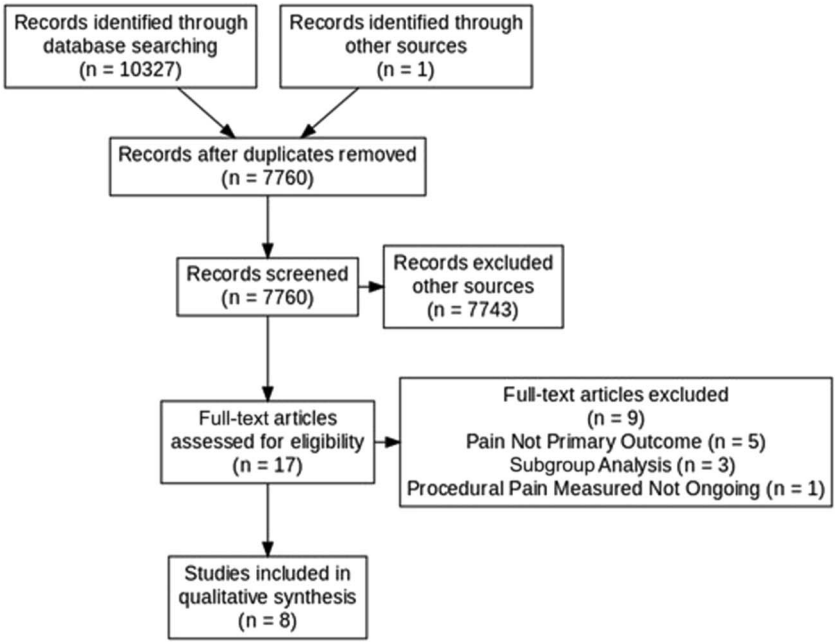

Figure 1. PRISMA flow diagram.

retained: ibuprofen (n = 4), morphine (n = 2), BWD + PHMB [polihexanide-containing biocellulose wound dressing] (n = 1), and EMLA (n = 2) (**Table 1** for further details). The results of these searches are presented in the PRISMA flowchart **Figure 1**. Of the 9 included trials, 3 were multicentre/multinational, with the remainder in Canada, Switzerland, Australia, Sweden, and the United States. Combined statistical or meta-analysis was not possible because of differences in frequency and dosage of interventions and differences in timing and methods used to assess (combined) outcomes, and thus, a narrative review is reported here.

3.1. Characteristics of included studies

Studies ranged in size from 13 to 853 participants with a mean of 147 and a median of 55. Studies involved predominantly female patients (52%–88%). The overall mean age was 71.9 years with a median of 70.3.

Four of the studies[8,12,13,33] were partially or fully funded by Coloplast A/S. All author groups, funded by Coloplast, declared no conflict of interest except for Fogh et al.[12] who included employees of Coloplast in their authorship list. The Research Council of Southeast Sweden funded one study.[2] A clinical research grant from Lohmann & Rauscher GmbH & Co. funded one study.[10] Three authors list conflicts of interests as members of the speaker's bureau and as consultants for the organisation.[10] Two studies were funded by the New South Wales Health Nursing and Midwifery Innovation Scholarship, the Australian Wound Management Research Foundation, and the Central Coast Health Research Advisory Committee CHARM Research Grant.[28,29] The remaining study lists no means of funding or conflicts of interest.[11]

3.2. Characteristics of excluded studies

Studies which were examined at the full-text stage and were subsequently excluded are presented here for clarity around their potential perceived relevance (**Table 2**).

3.3. Risk of bias assessment

The Cochrane Risk of Bias 2 tool[15] was used to assess the risk of bias (RoB) across 5 domains (plus one subdomain) within each study. The randomization process performed best across all studies because 75% had a low risk of bias. Fifty percent reported sufficient time between identification and eventual randomization and likewise for following intended interventions. The domain related to missing outcome data performed worst across studies because 50% had a high RoB, and one study did not provide information to make a determination. One study[13] had a low RoB across 5 of the 6 domains (and subdomains) and was thus deemed to have the lowest RoB of all studies (**Fig. 2**).

3.4. Primary outcome

The results were grouped according to the topical intervention and presented sequentially below.

3.4.1. Overview of ibuprofen interventions

Four studies were included that reported the use of ibuprofen foam as their intervention.[8,12,13,33] Two studies compared ibuprofen foam (ibuprofen concentration: 0.5 mg/cm^2) with a nonmedicated placebo foam.[12,13] Two hundred forty-two patients (n = 120[12]; n = 122[13]) were randomised across the 2 studies with 27 and 29 participants not completing each study, respectively. Fogh et al.[12] explicitly prohibited the use of per need medication while the study of Gottrup et al.[13] allowed regular medication; provided dose and timing remained consistent. The remaining 2 studies compared ibuprofen foam (ibuprofen concentration: 0.5 mg/cm^2) with local best practice.[8,33] 877 patients (n = 853[8]; n = 24[33]) were randomised across the 2 studies with 77 and 0 participants not completing each study, respectively.

3.4.2. Ibuprofen foam vs control

Both Gottrup et al.[13] and Fogh et al.[12] required participants at entry to have a minimum ulcer size of 1.6 cm in any direction and

Table 1

Summary of results table.

	Sibbald et al.,[33] 2007	Gottrup et al.,[13] 2008	Domenech et al.,[8] 2008	Fogh et al.,[12] 2012	Flock,[11] 2003	Bastami et al.,[2] 2012	Eberlein et al.,[10] 2012	Purcell et al.,[28] 2017	Purcell et al.,[29] 2017
No. of participants	24	122	853	120	13	21	50	60	60
Wound aetiology	Chronic painful exudation leg ulcer	Painful chronic VLU >8 wk	Painful wounds with moderate-to-severe levels of exudate	Painful, moderately to highly exuding, chronic VLU >8 wk	Inpatients with painful stage II or III pressure ulcers with surrounding erythema	Painful leg ulcer	Wounds of various aetiologies and minimal bacterial load	Chronic lower leg ulcer of at least 6-wk duration	Chronic lower leg ulcer of at least 6-wk duration Low-to-moderate CLU exudate
Eligibility criteria									
Ulcer size	0.5 × 0.5 cm	Length 1.6 cm, max 50 cm^2	1 cm^2	1.6 cm, max 11 cm in any direction	Full-thickness skin loss extending into subcutaneous tissue or into muscle, fascia, and/or bone	Not reported	<200 cm^2	Not reported	Not reported
Ankle brachial pressure index	Not reported	>0.8	Not reported	≥0.8	Not reported	Not reported	Not reported	Not reported	Not reported
Min wound-related pain	3/10	3/5	3/5	4/11	Not reported	4/11	4/11	Pain score ≥4	Pain score ≥4
Measures									
Measure of pain intensity	VAS 0–10	VAS 0–10	VAS 0–10	VAS 0–10	0–4	VAS 0–10	VAS 0–10	NRS 0–10	NRS 0–10
Timing of assessment	Morning/bedtime	Morning/evening	Twice daily	9 AM/8 PM	1 h, 12 h	2, 6, 12, 24 h	Days 1, 3, 7, 14, 21, 28	Weekly until week 4 Again, at weeks 8 and 12	Weekly until week 4 Again, at weeks 8 and 12
Study duration	7 d	5 d + follow-up at days 45, 47	7 d	5 d	1 d	1 d	28 d	4 wk+ follow-up at 8 and 12 wk	4 wk+ follow-up at 8 and 12 wk
Quality-of-life assessment	Not reported	Yes	Yes	Not reported	Not reported	Not reported	Yes	Not reported	Not reported
Interventions									
Intervention Comparator	Ibuprofen foam Local best practice	Ibuprofen foam Nonmedicated foam	Ibuprofen foam Local best practice	Ibuprofen foam Nonmedicated foam	Diamorphine gel Placebo gel	Morphine gel Placebo gel	PHMB dressing Silver dressing	EMLA cream Standard wound care	EMLA cream Standard wound care
Concomitant medication allowed	Yes	Yes	Yes	No	Yes	Yes	Not reported	Yes	Yes

(*continued on next page*)

Table 1 (*continued*)

Summary of results table.

	Sibbald et al.,[33] 2007	Gottrup et al.,[13] 2008	Domenech et al.,[8] 2008	Fogh et al.,[12] 2012	Flock,[11] 2003	Bastami et al.,[2] 2012	Eberlein et al.,[10] 2012	Purcell et al.,[28] 2017	Purcell et al.,[29] 2017
Outcomes									
Timing of assessment	Daily by patient	At dressing change days 2, 5, 45, 47	Daily by patient	Daily by patient	1 h, 12 h	2, 6, 12, 24 h	Days 1, 3, 7, 14, 21, 28	Weekly until week 4 Again, at weeks 8 and 12	Weekly until week 4 Again, at weeks 8 and 12
Measures of pain intensity	Sum of intensity differences from baseline	Differences over 5 d, score (unclear)	Summed time-weighted pain intensity differences from baseline	Not reported	Difference in pain scores from baseline	Mean pain score within patient and between groups	Total mean pain score comparing day 0–28, pain reduction	Mean pain scores were analysed from baseline to week 4	Mean pain scores were analysed from baseline to week 4 from week 4 to 12 after the cessation of EMLA and resumption of standard care in the intervention group
Other information	Separate morning and evening measures	Repeated measurement analysis of variance was applied	Ordinal logistic regression	GLM with time	Wash out period and crossover of treatment (2 treatments/patient)	Wash out period and 2 times crossover (4 treatments/patient)	Not reported	Pain was assessed immediately before the dressing change began, during.	Pain was assessed immediately before the dressing change began, during the dressing procedure, and within approximately 10 min after the dressing change

NRS, numeric rating scale; VAS, visual analogue scale.

Table 2

Characteristics of excluded studies.

Authors	Title	Journal	Exclusion reason
Agrifoglio et al. (2000)	EMLA anesthetic cream for sharp debridement of venous leg ulcers: A double-masked, placebo-controlled study	Phlebology, 15(2), 81–83	Pain not primary outcome
Alvarez et al. (2012)	An RCT to compare a bio-cellulose wound dressing with a non-adherent dressing in VLUs	Journal of Wound Care, 21(9), 448–453.	Pain not primary outcome
Arapoglou et al. (2011)	Analgesic efficacy of an ibuprofen-releasing foam dressing compared with local best practice for painful exuding wounds	Journal of Wound Care, 20(7), 319–325.	Subgroup analysis
Chatterjee et al. (2019)	Randomized controlled trial of topical mupirocin versus mupirocin with sucralfate combination in chronic skin ulcers	Indian Journal of Pharmacology, 51(5), 316	Pain not primary outcome
Dimikakos et al. (2011)	An ibuprofen-releasing foam dressing provided clinically relevant pain relief for exuding, painful, chronic, and traumatic wounds of different aetiology	EWMA Journal. 2011; Vol. 11:2 Suppl	Subgroup analysis
Hansson et al. (1993)	Repeated treatment with lidocaine prilocaine cream (emla(r)) as a topical anesthetic for the cleansing of venous leg ulcers—a controlled-study	Acta Dermato-Venereologica, 73(3), 231–233	Procedural pain was assessed and not ongoing wound pain.
Jorgensen et al. (2005)	The silver-releasing foam dressing, Contreet Foam, promotes faster healing of critically colonised venous leg ulcers: a randomised, controlled trial	International Wound Journal, 2(1), 64–73	Pain not primary outcome
Purcell et al. (2018)	Eutectic mixture of local anesthetics (EMLA) as a primary dressing on painful chronic leg ulcers: a pilot randomized controlled trial	Pilot and Feasibility Studies, 4(1), 1–13.	Pain not primary outcome
Romanelli et al. (2009)	Ibuprofen slow-release foam dressing reduces wound pain in painful exuding wounds preliminary findings from an international real-life study	Journal of Dermatological Treatment 2009; 20(1):19–26	Subgroup analysis

an ankle brachial pressure index of >0.8 as well as a minimum pain score of moderate on a 5-point scale. Dressing changes occurred on a 48-hour interval[13] and was not specified by Fogh et al.[12] The primary outcome assessed in the study of Gottrup et al.[13] was both pain relief and pain intensity. Pain relief was assessed using a 5-point verbal rating scale and intensity using an 11-point numeric box scale. Patients rated both measures after dressing change and wound cleaning on day 2 and day 5 as well as days 45 and 47. Fogh et al.[12] used a 5-point pain relief scale self-documented twice daily (morning and evening) day 1 through day 5.

Gottrup et al.[13] reported significant improvements for the ibuprofen group on pain relief starting from the first evening and continuing to day 5 ($P < 0.05$). Seventy-four percent of the ibuprofen group experienced pain relief compared with 58% in the comparator group. Pain intensity was likewise better for the

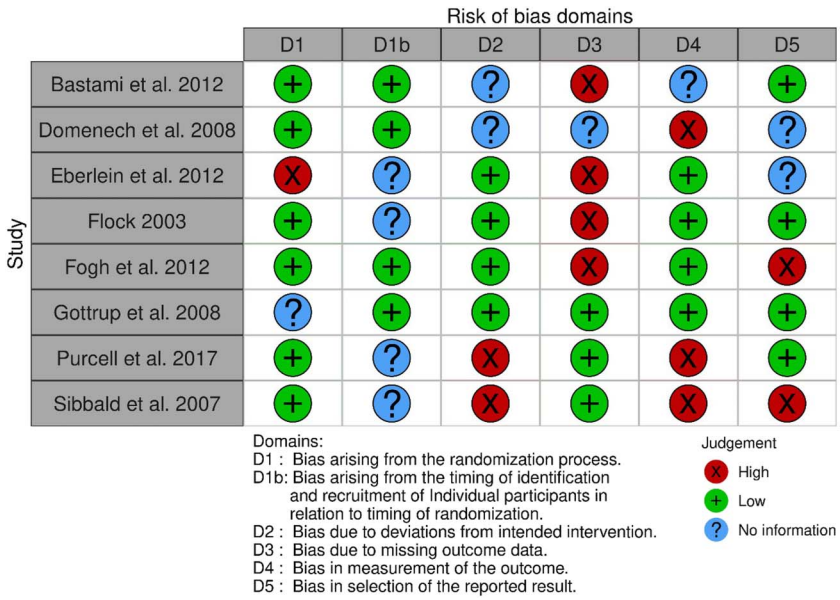

Figure 2. Risk of bias table of studies.

ibuprofen group days 1 to 5 ($P < 0.003$) with a reduction from 6.8 at baseline to 4.1 for the ibuprofen (40% reduction) while a 6.6 to 4.6 (30% reduction) was seen in the comparator. The wound pain intensity decreased for all patient's overtime from days 1 through 5 ($P < 0.001$).

Fogh et al.[12] reported significantly greater pain relief in the intervention group ($P = 0.044$). This was found when calculating cut-off points of at least 50% improvement in pain relief. Evening responder data were analysed separately with findings remaining consistent in favour of the ibuprofen foam group ($P = 0.006$) with 35% of the foam group experiencing at least 50% pain relief compared with 16% in the comparator group. However, they did not report on the changes between baseline and subsequent pain relief or improvement on which the combined outcome was based.

3.4.3. Ibuprofen foam vs local best practice

Sibbald et al.[33] and Domenech et al.[8] required a minimum wound area of 0.5 cm × 0.5 cm and 1 cm^2, respectively. All patients in the study of Sibbald et al.[33] at study entry experienced at least 3 on a 10-point verbal analogue scale. The study of Sibbald et al.[33] comprised a 1-week intervention period with pain relief and pain intensity scores recorded twice daily (morning and evening). Pain relief was assessed using a 5-point verbal rating scale while intensity was measured using an 11-point numeric box scale. Domenech et al.[8] similarly comprised a 1-week intervention period where participants recorded pain relief twice daily (morning and evening).

Sibbald et al.[33] despite measuring pain relief and reporting as a primary outcome does not provide data on this outcome. Pain intensity scores improved in favour of the ibuprofen group ($P = 0.04$) in the morning with evening values showing similar results ($P = 0.02$). The pooled data (morning and evening) was likewise in favour of the ibuprofen group ($P = 0.02$). No additional information on percentage or frequency of improvement was provided.

Domenech et al.[8] reported significant pain relief scores in favour of the intervention group ($P < 0.0001$) with almost 80% of patients experiencing relief within the first 24 hours compared with 59% in the local best practice group. Pain intensity decreased for both groups over time but with a larger reduction exhibited in the intervention group ($P < 0.0001$). Baseline intensity scores were 6.2 for the intervention group and 5.2 for the local best practice. After day 7, mean scores had reduced by 3.7 (60% reduction) in the intervention group and 1.5 (28% reduction) in the local best practice.

3.4.4. Overview of morphine interventions

Two studies were included which reported morphine as the intervention and compared it with a control.[2,11] 34 participants (n = 13,[11] 2003; n = 21[2]) were randomised across both studies with 6 and 4 participants not completing each study, respectively. Flock[11] assessed pain scores using a 5-point scale through nursing staff asking participants to rate their ulcer-related pain. Pain was assessed before, 1 hour, and 12 hours after gel application. Bastami et al.[2] used an 11-point visual analogue scale (VAS) assessed directly after gel application as well as at 2, 6, 12, and 24 hours.

Flock[11] noted similar pain scores between groups before application and significant improvement for the intervention group at 1 ($P = 0.003$) and 12 hours ($P = 0.005$) of follow-ups. All patients (n = 6) had improved pain scores both at 1 and 12 hours with 4 patients being pain-free after 1 hour. Bastami et al.[2] noted no significant difference between intervention and placebo condition when analysed as a whole ($P = 0.172$) despite higher mean pain scores in the placebo group (4.3 ± 2.8) vs morphine (3.8 ± 2.7).

3.4.5. PHMB vs local silver dressing

One study compared the efficacy of BWD + PHMB vs a best local standard silver dressing (Ag) (Eberlein et al.,[10]). Fifty patients were randomised, of whom 38 individuals (BWD + PHMB, n = 21; Ag, n = 17) with a total of 42 wounds (BWD + PHMB, n = 24; Ag n = 18) were included in the final analysis. Dressing changes occurred every second day or every third day over the weekends. Pain was assessed using a 10-point VAS comparing day 0 (start) and day 28 (end) and pain reduction over time.

For trial inclusion, all patients had to have a baseline pain score of >4 or 4 on a 10-point scale where 0 was no pain to 10 being worst possible pain. At day 0, those in BWD + PHMB reported a mean VAS pain score of 6.13 ± 1.43 vs 5.42 ± 1.43 in Ag group. These significantly reduced by day 28 for both groups ($P < 0.001$). Between-group comparisons are reported as VAS scores continuing to decrease by significantly greater amounts and faster over the 28-day study period for BWD + PHMB compared with AG-treated patients, although the results of between-group analysis to support this are lacking.

3.4.6. EMLA vs usual care/local best practice

Purcell et al.[29] compared the efficacy of 12 weeks of local usual care (dressing type and frequency determined by individual practitioner) with the usage of daily dressing change combined with a dose of EMLA cream (1–2 g/10 cm^2). This was performed for 4 weeks before reverting to usual care for the remaining 8 weeks of the trial.[29] Pain was assessed before dressing change, during the procedure, and within 10 minutes after the change of dressing. 60 patients were randomised, of whom 59 were included for analysis (intervention, n = 30; usual care, n = 29). Collected group demographics were comparable (eg, age, ulcer type, pain medications) except CLU duration in weeks which varied between groups (intervention, M = 26.4; usual care, M = 20.5).

Participants in both groups similarly reported congruent levels of wound-related pain at baseline assessment (intervention, M = 7.26, SD = 1.89; usual care, M = 7.36, SD = 1.89). Pain scores before dressing changes decreased across both groups over time with participants in both groups reporting similar pain throughout the duration. This indicates the intervention did not influence pain before dressing change (eg, week 2, intervention, M = 3.04, SD = 2.26; usual care, M = 3.64, SD = 2.22; $P = 0.34$).

This was in opposition to a previously conducted pilot study of Purcell et al.[28] which found mean pain scores after dressing change were significantly lower for the intervention group over the 4-week period.

3.5. Secondary outcomes

3.5.1. The proportion of participants with any reduction or improvement in pain intensity

Flock[11] notes that 85% of patients (6 of 7) experienced an improvement in pain intensity 1 and 12 hours after morphine gel application. 57% (4 of 7) were pain-free after 1 hour, and 43% (3/7) remained so after 12 hours had passed.

3.5.2. Reported changes in disability or physical functionality

Domenech et al.[8] report on overall mobility improvement in their study as reported by patients. Thirty-seven percent of the ibuprofen treatment group experienced increase in mobility compared with 18% in the comparator group ($P < 0.001$). There were also lower levels of deterioration for the treatment group (9%) vs the comparator group (16%).

3.5.3. Reported changes in emotional functionality or impact on mental health (eg, anxiety, depression, mood, etc)

Domenech et al.[8] report well-being improved significantly more in the ibuprofen treatment group 40% (n = 187) vs the comparator group 15% (n = 58) ($P < 0.001$). There were also lower levels of deterioration for the treatment group (4%) vs the comparator group (9%). Gottrup et al.[13] reported on mood but found no significant differences between groups.

3.5.4. Reported changes to quality-of-life score, measured using any quality-of-life assessment tool

Quality-of-life (QoL) metrics were reported in 3 studies.[8,10,13] Domenech et al.[8] used the WHO-5 Well-Being Index[3] and observed improvements in the ibuprofen foam group vs non-medicated control in 4 health parameters (appetite [22% vs 9% improvement], overall well-being [40% vs 15% improvement], mobility [37% vs 18% improvement], and social activities [17% vs 6% improvement]).

Gottrup et al.[13] recorded data on quality-of-life indicators at baseline, day 5, and day 43. Both intervention and control influenced the patients' well-being and individual quality-of-life parameters positively. All patients' overall QoL improved during the trial from day 5 to day 43. Percentage of participants who experienced improvements from baseline in the ibuprofen group are as follows: sleep 53%, mood 45%, well-being 39%, and appetite 24%. However, no statistically significant differences were evident between groups.

Eberlein et al.[10] assessed QoL using the Wurzburger quality-of-life score which consists of 19 different questions related to patients with chronic wounds. As pain was the primary outcome of the study, the authors modified the Wurzburger tool and removed the questions related to pain resulting in 17 questions remaining. Authors report that the dressings used in both the PHMB and silver dressing groups contributed to an improvement of various aspects of the patients' reported QoL with the same 4 subscores improving significantly over the study period (day 1, 2, 3, 14) ($P < 0.05$). Further detail is not provided.

Purcell et al.[29] used the Cardiff Wound Impact Schedule (CWIS)[26] which noted similar levels of health-related QoL scores at baseline. Scores in all subscales increased throughout the study in both groups; however, in the intervention group, only well-being reached significance ($P = 0.03$) and only from baseline to week 4. The effect dissipated after the conclusion of the intervention.

3.5.5. Adverse events

Adverse events have been reported with consideration given to the PRISMA harms checklist where appropriate.[36] The frequency of adverse events was reported in all studies. Two studies reported no adverse events having occurred in either group.[10,33]

Gottrup et al.[13] reported 7 (12%) participants experiencing 10 adverse events in the ibuprofen foam group and 12 (19%) participants experiencing 21 adverse advents in the control group. In the ibuprofen group, the following were experienced: combined urticaria and eczema, n = 1; eczema alone, n = 1; and blisters, n = 2. In the comparator group, the following were experienced: eczema alone, n = 2, and blisters, n = 2. A breakdown of the severity of the adverse events was provided (**Table 3**).

Domenech et al.[8] reported 23 adverse events in the ibuprofen foam group, primarily consisting of supplementary wound infection (n = 6) and increased pain levels (n = 7). Other adverse events included (erythema, n = 2; increased ulcer size, n = 1; erysipelas, n = 1; hospitalizations, n = 4). This study reported 9 adverse events in the control group including wound infection (n = 3) and increased pain intensity levels (n = 3). Other adverse events included (erythema, n = 1, and hospitalizations, n = 2). The authors noted on one adverse event (local wound infection) as dressing-related.

Bastami et al.[2] reported adverse events from patients and medical staff during the study period. In total, 36% of control patients and 27% of morphine intervention patients experienced adverse events with the majority consisting of increased pain (58% control and 66% intervention). Adverse events were reported as follows in the morphine intervention group: itching, n = 0; drowsiness, n = 1; redness, n = 2; smarting pain/burning, n = 6. Other adverse events were reported as follows in the placebo group: itching, n = 2; drowsiness, n = 2; redness, n = 1; smarting pain/burning, n = 7.

Purcell et al.[29] specified no reports of spreading infection, erythema, pallor, itching, edema, purpuric, or petechial lesions, allergic reaction, central nervous system reactions, or toxicity from any participant in the intervention group. Some participants (n = 3) in the intervention group reported an increase in pain after application of EMLA, and treatment was ceased. 13 participants with low-exudate CLUs across both groups (intervention, n = 7; usual care, n = 6) experienced an increase in pain as a result of adherence of the secondary dressing.

Flock[11] reported on the number of patients who developed new symptoms but does not specify these as "adverse events." The occurrence of symptoms was congruent across both arms of

Table 3

Adverse events presented on severity and device relatedness.[13]

Type	Ibuprofen foam				Comparator group			
	Unrelated	Possibly related	Related	Total	Unrelated	Possibly related	Related	Total
Mild (N/%)	1 (5)	3(14)	4 (19)	8 (38)	0 (0)	1 (10)	2 (20)	3 (30)
Moderate (N/%)	2 (10)	1 (5)	7 (33)	10 (48)	1 (10)	2 (20)	4 (40)	7 (70)
Severe (N/%)	0 (0)	1 (5)	2 (10)	3 (14)	0 (0)	0 (0)	0 (0)	0 (0)
Total (N/%)	3 (14)	5 (24)	13 (62)	21 (100)	1 (10)	3 (30)	6 (60)	10 (100)

the study. Most side effects are attributed to one participant who experienced opioid toxicity as a result of an increased dosage of a concomitant fentanyl patch a day before study entry. The total amount of side effects over the initial 3-day period are as follows: placebo group—skin irritation, n = 4; pruritus, n = 2; nausea, n = 1; drowsiness, n = 2; and nightmares, n = 1; diamorphine intervention group—skin irritation, n = 5; pruritus, n = 2; constipation, n = 1; nausea, n = 2; drowsiness, n = 3; nightmares, n = 2; hallucinations, n = 2; and myoclonus, n = 1.

3.5.6. Rescue analgesia requirements (eg, time to rescue)

Not reported.

3.5.7. Patient-reported changes to sleep quality and duration

Gottrup et al.[13] reported on sleep. There was no significant difference of improvement between the ibuprofen treatment group 53% (n = 26) vs the comparator group 29% (n = 25).

3.5.8. Analgesic effect onset and duration

Not reported.

3.5.9. Reported changes in cognitive functioning

Not reported.

4. Discussion

This review initially screened 10,327 titles and abstracts resulting in the review of 18 full texts and final inclusion of 9 articles. Of these 9 studies, 8 reported improvements in pain which was suggested to be due to the pain treatment. However, the included studies assessed pain intensity using a variety of time points and outcome assessments, which makes it difficult to compare studies and limits the possibility to perform a combined (statistical) analysis with the reported data. Similarly, well-defined eligibility criteria and patient-relevant outcomes are absent in some articles, whereby not only the basic requirement of repeatability of research is lacking but also relevance (for patients).

This review suggests that topical application of interventions may provide pain relief in individuals with chronic wounds specifically with evidence toward ibuprofen being a potentially beneficial treatment. The results from Bastami et al.[2] conflict with the findings of Flock.[11] Bastami et al.[2] suggest that topically applied morphine is not an effective intervention strategy for pain relief in participants with chronic painful leg ulcers. As such, there is insufficient evidence to assess the usefulness of topically applied morphine in this context.

The recommended core outcome measures for clinical trials of chronic pain treatment efficacy and effectiveness as proposed by IMMPACT are listed across 6 domains.[9] In their consensus document, pain intensity should be assessed using an 11-point (0–10) numerical rating scale or a categorical scale in circumstances in which numerical ratings may be problematic. It is positive therefore to note that in all studies except one, a similar scale has been used, representing consistency in the use of methods to assess outcomes. However, IMMPACT do not recommend a time point to assess this pain and do make reference to time points being influenced by the condition and intervention being studied. Herein lies a difficultly and an opportunity because it relates to chronic wound care management. Studies in our review used various time points to assess outcomes, and we would argue that there is a need now to move forward in gaining consensus as to the optimal time points at which the application of topical interventions to manage pain in chronic wounds should be assessed and that this time point should not only be clinically meaningful but should be informed by patient opinion.

Physical functioning is an important consideration of the impact of pain on the individual, and its assessment in clinical trials of pain is recommended.[9] Measures of physical functioning include activities of daily living and more specifically disturbed sleep. Only one trial incorporated assessment of sleep as an outcome measure.[13] In the trial by Gottrup et al.,[13] 53% (ibuprofen group) vs 49% (control group) of participants reported an improvement in their pattern of sleep assessed after 1 week. Other aspects of physical functioning were incorporated in the assessment of quality of life or well-being across 3 trials.[8,10,13] But again, the lack of standardisation on how and when these were measured varied significantly, and thus, conclusions on the impact of interventions cannot be made.

Reporting of adverse events or lack thereof was good as represented by all trials reporting on this outcome. Of note, the main adverse event reported was that of increased pain. It would have been helpful to understand the measures taken to address this pain such as further investigation and need for rescue analgesia in addition to a description of pain quality. Assessment of pain qualities at baseline also makes it possible to determine whether certain patterns of pain characteristics moderate the effects of treatment.[9]

All the other domains recommended to assess clinical trials of chronic pain treatment efficacy and effectiveness as recommended by IMMPACT were either not reported or poorly considered among the studies in our review. We would recommend therefore that the design of future clinical trials related to wound pain should incorporate the core outcome measures as recommended by IMMPACT.[9]

4.1. Differences between final review and protocol

We have completed this review as per submitted protocol.[16] In addition, as 4 of the included studies reported on pain relief in addition to pain intensity, a decision was made to include reporting of this outcome to provide as much information to inform future practice.

4.2. Strengths and limitations

This review was conducted according to the preplanned protocol at every stage. Further strengths of our study include the explicit eligibility criteria for inclusion in the review, with independent duplicate adjudication and duplicate data extraction. Our review was not restricted to 1 wound aetiology or to language. Although all languages were included, it is possible that some studies in other databases or published in other language were overlooked.

5. Conclusion

This review suggests that topical application of interventions may provide pain relief in individuals with chronic wounds. However, combined statistical analysis or meta-analysis was not possible, therefore limiting the strength of our conclusions. Clinical trials of pain in chronic wounds should be informed by available core outcome measures for chronic pain. As such, our review shows

an urgent need to gain consensus on the timing of pain assessments, and this work should be informed by patient opinion where possible.

Disclosures

The authors have no conflict of interest to declare.

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