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Topical review

How are topical opioids used to manage painful cutaneous lesions in palliative care? A critical review

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1. Introduction

Cutaneous lesions can be painful, difficult to heal and negatively impact quality of life [22]. They are often unresponsive to systemic analgesics, leading to increases in analgesia. The growing consensus that topical opioids relieve inflammatory pain without systemic side effects is important because these patients typically have complex medical problems [2,11,12,14,15,20,21,29, 34,36,38,39].

Painful cutaneous lesions vary widely and require systematic assessment and management, including a standardised approach to administering topical opioids and measuring outcomes [22]. Clinicians often try a number different treatments in palliative care before finding the appropriate one. However, knowledge regarding the effectiveness of those treatments may not be disseminated [25]. Current unpublished guidance reveals different practices indicating the need to work towards an international consensus for the administration of topical opioids.

Important aspects of clinical decision making regarding the use of topical opioids for patients include wound aetiology and size [10], titration, dose concentration and formulation of the opioid preparation, presence of inflammation [30,31], patient monitoring and their experience of the treatment. Two reviews focussed on the effectiveness of topical opioids and a brief investigation of wound aetiology but did not assess the impact of titration or patients' views [10,21]. This review aims to critique clinical practice as reported in the literature and provide insights into the use of topical opioids in the management of painful cutaneous lesions.

2. Methods

2.1. Search strategy

An electronic database search for the period between 1980 to September 15, 2012, was conducted of the following: Embase, Medline, CINAHL, Cochrane Library, Biomed Central, NHS Evidence and British Nursing Index (BNI), as well as the grey literature (Appendix A). The review was guided by the following questions: What wound characteristics are associated with the use of topical opioids for effective symptom management? Does titration of topical opioids affect the outcomes of symptom management? How should the use of topical opioids be monitored? What are patients' views about the use of topical opioids?

Free text and (where available) subject heading searches were conducted using the following search terms: topical opioids *or* topical morphine *or* topical diamorphine; and skin ulcers *or* cutaneous ulcers *or* malignant wounds *or* fungating wounds *or* wound inflammation *or* wound management *or* local wound pain

2.2. Study selection and analysis

Studies were selected and analysed by 2 authors (TG and PG) and non-English-language articles by SP according to the following inclusion criteria: patients with painful cutaneous skin lesions, interventions with topical opioids, studies which found topical opioids to be both effective and noneffective and studies in English, German, French and Italian. We included all types of study design except reviews. Case reports were included because they provide data on how clinicians administer topical opioids but are often not included in trials. The following data were extracted from each study: wound aetiology and size, topical opioid used, details of titration, frequency of application, local and systemic side effects, systemic medication, outcomes and author comments. A narrative analysis was conducted.

3. Results

The search yielded 77 articles, 50 of which were excluded because they did not meet the inclusion criteria detailed above. The excluded studies focussed on the following: burns, wound healing, animals, topical analgesics other than topical opioids such as local anaesthetics creams, noncutaneous lesions including oral mucositis, cutaneous leishmaniasis, acute injuries, lacerations and surgical

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Table 1
Wound characteristics in studies that found topical opioids to be effective and ineffective.

Study	Aetiology	Wound size if reported and other characteristics
Effective (case series)		
Back and Finlay [4]	2 pressure ulcers and 1 malignant skin ulcer	No deterioration in the state of the skin noted
Krajnik and Zylicz [19]	Malignant tumour forming massive, confluent, elevated, cutaneous lesions	Severe tension pain. Inflamed. Possible blood extravasation
Krajnik et al. [20]	Patient A—Inflamed subcutaneous tibial infiltrate Patient B—Tumour infiltrating into the sacrum Patient C—Severe oral mucositis later developed a painful inflamed knee Patient D—Painful necrotic leg ulcers Patient E—Malignant ulcer Patient F—Fungating lesion and carcinoma of the vulva	Patient A—3 × 7 cm skin was red but intact. Patient B—During tenesmoidal episodes had rectal discharge Patient D—480 cm^2 Patient E—6 cm^2
Twillman et al. [33]	Patient A—Chronic *Pyoderma gangrenosum* ulcers Patient B, C and H—Pressure ulcer Patient D—Carcinoma of the right breast Patient E—Diabetic foot ulcer Patient F—Hydradenitis suppurativa lesions Patient G—Painful melanoma lesions of foot and lower leg Patient I—Red swollen scrotum—Not an open wound	Patient A—Skin graft for a wound that would not heal Patient B—Oral mucosal pain? Patient D—Large tumour 2.5 × 2.5 inches, ulcerated lesion leaking serosanguineous fluid Patient H—Plastic surgery to repair ulcer
Flock et al. [12]	Circumferential leg ulcers (stage 1–3)	Some leg ulcers were infected
Grocott [16]	Malignant wound across the chest wall	Treated with metronidazole for infection
Ballas [5]	Sickle cell anaemia	3.5 × 3.5 cm for 1 patient
Watterson et al. [36]	Epidermolysis bullosa	Case 1—Most painful areas of the skin were neck, buttocks and groin Case 2—Had an isolated large skin lesion on her thigh
Ashfield [3]	Pressure ulcer	Inflammation Large amount of exudate Treated for infection
Gairard-Dory et al. [14]	Grade 3 radiotherapy-induced esophagitis	Grade 3 esophagitis causes severe dysphagia or odynophagia with dehydration or weight loss.
Gallagher et al. [15]	Case1 and 2—Pressure ulcersCase 3—Malignant woundsCase 4—Infected wound	Case 1—Area of necrotic tissue large volume of exudate from the wound in addition to the gel Case 2—Open wounds with areas of eschar—powder analgesic clumped onto and increased the eschar so used both gel and powder to overcome this. Methadone power appears to be effective for exudative wounds as the powder adheres to dry wounds causing increased eschar. Case 3—Two wounds 7.5 × 5.5 × 3.5 and 4 × 2 × 0.5 cm both with necrotic edges and purple reddish tumour at the base. Both wounds were growing *Pseudomonas* and were foul smelling. Case 4 wound was oozing significantly, and no eschar was present
Platzer et al. [26]	5 patients with inflammatory mucosal lesions (oral, anogenital) and in 1 with a skin ulcer on the leg.	Mucositis (cancer patients)
Porzio et al. [27]	Patient 1—Malignant Patient 2—Pressure Patient 3—Malignant Patient 4—Pressure Patient 5—Malignant	Patient 1—Breast cancer/ulcer sited on sternum Patient 2—Cervical cancer/ulcer sited on right foot Patient 3—Colon cancer/ulcer sited on sternum Patient 4—Cervical cancer/ulcer sited on sacrum Patient 5—Vulval cancer/ulcer sited on vulva
Tran and Fancher [32]	Skin lesions from stage IIb mycosis fungoides	Widespread skin lesions ranging from mild erythematous patches to scaly plaques to open weeping ulcers. TO applied to lesions that >2.5 cm in diameter
van Ingen et al. [34]	Superficial ulcer with necrotic boarders surrounded by erythematous and oedematous skin. No would infection present	Superficial ulcer diameter of 5.5 × 4.5 cm morphine gel applied to several wounds, total area 25 cm^2
Barker [6]	*Pyoderma gangrenosum* affecting the right breast present for 6 weeks gradually enlarged to form an ulcer	45 × 35 mm on the inferior boarder of the right breast

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Table 1 (*continued*)

Study	Aetiology	Wound size if reported and other characteristics
Stefancic et al. [29]	Unbearable pain in the shoulder and neck region after radiotherapy for lung cancer	Intense redness, swelling and induration of the painful region
Effective (larger studies)		
Abbas and Fatima [2]	Malignancy with grade 2 pressure sores	No details given—short report
Abbas [1]	Grade 2+ pressure ulcers	No details given—short report
Huptas et al. [17]	Patients with infected leg ulcers	Not reported
Effective (RCTs)		
Flock [11]	Painful stage 2 or 3 pressure ulcers	Stage 2—Partial thickness skin loss involving the epidermis and or dermis Stage 3—Full thickness
Zeppetella [39]	All patients had painful sacral pressure sores	Sores 4.5–14 cm^2. All patients had primary cancer
Zeppetella and Ribeiro [39]	Pressure × 13 and Malignant × 3 Sterling scores 2.2–3.2	Size: 5–38 cm^2
Ineffective (RCTs)		
Vernassiere et al. [35]	Arterial, venous, mixed, necrotic and pressure	Ulcer duration ranged 1–36 mo (average 13 mo) Reported ulcer characteristics: fibrinous, necrotic, granulation, dryness, exudation, depth extension and superficial extension (did a comparison between wound characteristics but found no significant difference between morphine and placebo groups)
Jansen et al. [18]	Arterial 78%Mixed venous-arterial 22%	7.5 ± 3.1 cm^2Reported inflammation characteristics:100% pain and loss of function,11% of ulcers had swelling and 44% heat
Bastami et al. [7]	Venous ×13Arterial × 1 Venous and Arterial × 1Not characterised × 2	Size ranged 0.4–94.5 cm^2Leg ulcers: ulcer size mean 28.6 ± 39.4 cm^2
Other		
Ribeiro et al. [28]	Skin ulcers	Skin ulcers >2 cm in diameter and 0.5 cm in depth; between 5 and 60 cm^2

RCT, randomized controlled trial.

repair. Twenty-seven articles were included in the review, reporting on a total of 170 patients.

3.1. Study characteristics

Seventeen case studies indicated that topical opioids are clinically useful for reducing pain for patients with cutaneous lesions but did not conduct statistical analyses of their results [3–6,12,14–16,19,20,26,27,29,32–34,36]. Three controlled studies [11,38,39] and 3 case studies with a large number of patients [1,2,17] reported statistically significant reductions in pain scores. Three controlled studies found that topical opioids were not effective [7,18,35]. One nonrandomized trial assessed the bioavailability of topical opioids [28].

3.2. Wound characteristics associated with the use of topical opioids for effective symptom management

There was wide variation in the size and aetiology of the wounds in the studies reporting positive responses to topical opioids. Most commonly analgesic relief was achieved for patients with pressure and malignant wounds (Table 1).

Three studies reported topical opioids were ineffective [7,18,35]. One study of patients with predominantly arterial leg ulcers and another with ulcers that were arterial, venous or mixed aetiology found no statistical difference between patients receiving topical morphine or the placebo [35]. A more recent study with mainly venous ulcers (some arterial ulcers and others not characterised) found the difference between topically applied morphine and placebo was only significant 2 h after dressing application [7].

3.3. Titration of topical and effect on symptom management outcomes

There were variations in the extemporaneous preparation and application of topical opioids. Doses ranged from 1.6 to 15 mg with varied concentrations. This variation appeared to depend on whether the wound was open or closed, the latter indicating locally inflamed skin whereby the inflammation alters the otherwise impermeable epithelial barrier permitting morphine absorption (eg, 1.6 mg used for an inflamed subcutaneous tibial infiltrate [20]). For open painful wounds, dosage varied between 6.25 and 15 mg, with the most common being 10 mg morphine in 8 g hydrogel (Table 2).

3.3.1. Altered dosage

Seven studies reported altered dosage of topical opioids [3,7,16,20,29,32,33]. Grocott [16] titrated the doses of diamorphine and hydrogel, and the frequency of application for a patient over 8 days until the scores for relief from stinging were reduced and maintained in twice-daily applications. The morning dose was mixed with metronidazole gel to combat wound malodour. Bastami et al. [7] varied the dosage for patients (mean dose 6.6 ± 5.06 mg) according to the size of the ulcer (mean size 28.6 ± 39.4 cm^2). The topical opioid demonstrated a significant difference in pain after 2 h but not after 6, 12 and 24 h, suggesting a need for an increased dose and frequency of application.

3.3.2. Frequency of application

Frequency of application varied in 4 studies. Abbas [1] reported that patients had their dressings changed every 12 to 24 h but did not report the frequency of administration. In another study the patient required 12 hourly application of topical morphine (as opposed to 24 hourly administration reported by previous authors) [16]. For one patient, Krajnik et al. [20] reported a reduction in the frequency of topical morphine applications (0.08% gel 1.6 mg) to twice a day and later discontinued as pain did not recur. For

Table 2
Administration details and side effects of topical opioids by study type.

Study	No. of patients	Topical treatment used	Frequency of application	Details of titration to achieve pain control	Systemic drug regimen if reported	Local and systemic adverse effects	Author comments/outcome
Effective (case series)							
Back and Finlay [4]	3	10 mg Diamorphine in IntraSite gel	No details reported	Omitted, then reintroduced	Systemic opioids Diclofenac	No details reported	Topical opioids may have clinically useful analgesic effects
Krajnik and Zylicz [19]	1	Morphine 0.08% in hydrogel, ~4 g gel containing 3.2 g morphine applied to 100 cm^2 of scalp	No details reported	None reported	Paracetamol suppositories 1 g and controlled release morphine (Kapanol) 20 mg 2 × per day	No details reported	Topical morphine may be effective in the management of painful skin lesions
Krajnik et al. [20]	6	Patient A—2 mL of morphine gel 0.08% (1.6 mg) Patient B—5 mL Morphine gel 0.3% (15 mg morphine per dose) 3 times a day Patient C—Morphine gel 0.08% for mouth 3 mL (2.4 mg morphine per dose). Also intra-articular injection 3 mg morphine in 2 mL saline for painful knee Patient D—30–50 mL morphine gel 0.08% spread over 480 cm^2 wound Patient E—0.08% Morphine gel Patient F—10 mg Diamorphine in IntraSite gel then added 1% silver sulphadiazine cream	Patients A and B—3 × per day Patient C 3–4 × per day (at dressing changes)	Patient A—Topical morphine applications 0.08% gel 1.6 mg) was decreased to twice daily Patient B—After 7 days frequency reduced to 2× per day Occasional omission of dose resulted in symptoms reappearing. Increased morphine gel 0.5% to 7 mL (35 mL morphine per dose) 3 × per day Patient D—Morphine gel 0.08% increased to 0.16% (40–80 mg morphine per dose) so that dressing could be changed twice daily	Not reported?	No symptoms of toxicity observed for patient A No adverse effects observed for patient E	Topical morphine provided rapid relief for all but 1 case with no or minimal side effects. If clinical trials can confirm effectiveness a number of potential applications exist
Twillman et al. [33]	9	Morphine 0.1%-0.15% in IntraSite gel	Applied at dressing changes—usually 2× per day	Patient B—"Titrated for comfort" but no other details given Patient E—Increased the morphine concentration from 0.1% to 0.15% Patient F—Increased the morphine concentration from 0.1% to 0.15% only reason given for increase was because it was used by previous patient (E)	Systemic opioids—varied with each patient	No details reported	Seven of 9 patients experienced a substantial degree of analgesia. The others experienced a lesser (but still significant) degree of analgesia. Further research with different wound types needs to be conducted
Flock et al. [12]	1	Diamorphine gel 0.1% (1 mg/1 mL IntraSite gel) also 1 mg diamorphine/ 1 mL metronidazole	No details reported	Not reported	Oral morphine, Diclofenac and Acetaminophen	No systemic side effects reported. Patient developed signs of opioid toxicity so systemic opioids were discontinued and only topical opioids used	Our case supports previous reports that topical opioids have an analgesic effect without systemic side effects and also indicates that they can be combined with metronidazole which is helpful for painful infected wounds
Grocott [16]	1	40 μg diamorphine split into 2 applications of 30 g of hydrogel. Evening doses were applied in 30 g of topical metronidazole or odour management	22 × per day	The doses of diamorphine and hydrogel, together with the frequency of application, were titrated over a period of 8 days until the scores for relief from stinging were reduced and maintained	MST continuous 200 μg daily reduced to 100 mgs after patient became drowsy. Hydroxyzine Hydrochloride 25 mgs for irritation	No details reported	Topical diamorphine treatment was effective for local wound management of a patient with fungating malignant wounds
Ballas [5]	2	Oral oxycodone and Meperidine tablets dissolved into 1–2 mL	No details reported	None reported	Patient A—Oxycodone Patient B—Meperidine	No details reported	Topical opioids (other than morphine) are effective in sickle cell ulcers

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Table 2 (*continued*)

Study	No. of patients	Topical treatment used	Frequency of application	Details of titration to achieve pain control	Systemic drug regimen if reported	Local and systemic adverse effects	Author comments/outcome
		water					
Watterson et al. [36]	2	10 mg diamorphine in 8 g IntraSite gel. Changed to 15 mg in 15 g of gel to make a larger volume required to cover the surface area	At dressing changes and on alternate days for 1 patient not detailed for the other patient—presume it was once a day?	None reported	Case 1—Oral ibuprofen and slow release morphine Case 2—Opioid naive	Blood plasma substantially below the range of plasma levels	A long lasting peripheral opioid analgesia with an additional healing effect. This apparent efficacy and lack of adverse effects warrant further systematic study
Ashfield [3]	1	10 mg diamorphine to 10 g IntraSite gel, then 15 mg diamorphine in 15 g IntraSite gel	No details reported	They first used 10 mg diamorphine in the 8 g of IntraSite gel as provided by the manufacturer (0.125%). They then used 15 g containers of IntraSite gel with 15 mg morphine (0.1%) to make a larger volume of gel needed to cover the surface area of both wounds. No other reason was given for the reduction in dosage other than the size of containers provided by the manufacturer and the need to produce more gel	Diclofenac, Clonazepam Fentanyl patches	No details reported	Diamorphine-infused gel has been used effectively to relieve pain. Further research is needed if more patients are to benefit from this treatment
Gairard-Dory et al. [14]	3	2–10 mL of 0.2% morphine gel	3 times a day before eating	No details reported	Omeprazole, acetaminophen, controlled release morphine magnesium aluminium hydrochloride. Ketoprofen, Fentanyl patches	1 patient reported nausea which disappeared after taking small volumes. This was probably due to the primary disease and the chemotherapy	Major advantages of topical morphine administration include simplicity, low side effects and cost Clinical trials needed
Gallagher et al. [15]	4	100 mg Methadone powder in 10 g Stomahesive powder. Approximate concentration was 25 mg per 15 cm of wound (225 cm^2)	No details reported	No details reported	Systemic opioids	Monitored serum methadone level—absorption was variable and likely depends on surface area of the wound available for absorption and not covered by eschar	Topical methadone powder can be effective for pain relief on open exudative wounds with little eschar
Platzer et al. [26]	6	0.1% Morphine gel (1 mg/mL)	Several times daily—no other details given?	No details reported	Due to nociceptive pain: 25 μg/h Fentanyl transdermal, 25 mg Amitriptyline hydrochloride (1 x/day), 5 mg/d Metamizol (drops), Xylocaine gel (local)	No details reported	Reported pain reduction for 6 case series
Porzio et al. [27]	5	Morphine sulphate injection 10 mg in 8 g IntraSite gel	3 times daily	No details reported	Systemic Opioids	No details reported	Satisfactory level of analgesia was obtained without escalation of systemic opioids and without adverse effects
Tran and Fancher [32]	1	10 mg Morphine sulphate injection with 8 g of a neutral water-based gel	Applied gel 2–3 times a day	Presented a sample treatment algorithm with titration up to 10 mg of morphine sulphate injection. There is also no data on the effect of the titration. Starting does and maximum doses are listed but no details of how this should be monitored	Systemic opioids	No details reported	Many patients likely to benefit from morphine gel
van Ingen et al. [34]	1	0.5% morphine gel and sporadic subcutaneous morphine as escape	Up to 4 times daily applied to several wounds—total area 25 cm^2	No details reported	Fentanyl patches Subcutaneous morphine	Morphine and its metabolites were detectable mean blood level was 16.4 μg/L, which was considered safe	Results suggest that topical opioids are an attractive approach to treating cases of painful scleroderma

Barker [6]	1	10 mg morphine in 8 g IntraSite gel	4 times per week	No details reported	Paracetamol Tramadol	None reported	Our case shows that topically applied opiates may provide effective analgesia
Stefancic et al. [29]	2	5 mg morphine in 2 mL saline solution of intracutaneous injections into inflamed tissue for equal distribution over a large surface area	On average 4 equal doses were required	Increased from 5 mg to 6 mg then 8 mg diluted in 2 mL saline to achieve pain relief	Fentanyl patches, Metamizol, Sevredol, Diclofenac, Morphine sulphate	None observed	Morphine administered locally produced satisfactory pain relief. Absence of both side effects and tolerance and relatively low doses are advantages to this treatment
Effective (larger studies)							
Abbas and Fatima [2]	13	Dressings applied with 5–10 mg morphine and IntraSite gel with a 4 × 4 dressing	Dressings were changed 12–24 hourly but why was not reported	Dressings applied with 5–10 mg morphine and IntraSite gel with a 4 × 4 dressing	Systemic Opioids	All patients were on strong oral opiates with minimal response. Tolerance of topical opioids was not a problem in the first week	Mean pain intensity reducedafter application ($P \leqslant .002$)Diamorphine–IntraSite gel is an effective treatment in open pressure sores. More research is needed on right dosage and type of topical opioid
Abbas [1]	17	Dressings were applied with diamorphine 5–10 mg and IntraSite gel on a 4 × 4 dressing	Dressings were changed every 12–24 h	Dressings were applied with diamorphine 5–10 mg and IntraSite gel on a 4 × 4 dressing. No details about decision to change dosage or frequency of administration	Systemic Opioids	No details reported	Mean pain intensity reducedafter application ($P \leqslant .002$) Diamorphine-IntraSite gel may be an effective treatment in open pressure ulcers
Huptas et al. [17]	30	developed a new morphine gel with polyhexanide as a preservative	No details reported	None reported	No details reported	No details reported	Mean pain intensity reduced after the application $P < .0001$
Effective (RCTs)							
Flock [11]	13	Diamorphine gel 0.1% with IntraSite gel	Applied once daily and covered with a standard dressing	No details reported	Paracetamol Opioids	One patient experienced new side effects Found no difference in side effects between 2 treatment groups	Pain score improved ($P < .05$). The results suggest diamorphine gel is effective for pain associated with stage 2 and 3 pressure ulcers
Zeppetella [39]	5	10 mg morphine sulphate in 8 g IntraSite gel or placebo (water for injection)	Applied once daily	No details reported	Morphine; Diclofenac and extended release. No changes were allowed in scheduled analgesia—rescue analgesia was available	Two patients noted itching and burning but not attributable to morphine. No systemic adverse effects were reported	Mean pain scores lower in morphine group ($P < .01$). This pilot study suggests that morphine applied topically is an effective method of producing local analgesia
Zeppetella and Ribeiro [39]	21	10 mg morphine sulphate in 8 g IntraSite gel or placebo (water for injection)	No details reported	No details reported	Not reported	Patients noted some itching and burning but not attributable to the morphine. No systemic adverse effects were reported	Lower pain scores in the morphine treatment group ($P < .001$)Topical morphine appears to be safe and well tolerated by patients
Noneffective (RCTs)							
Vernassiere et al. [35]	18	Morphine hydrochloride mixed with hydrogel	No details reported	Dosage varied—no other details reported	Systemic Opioids	Systemic tolerance was good	No significant difference between the placebo and morphine group Topical morphine cannot be an alternative to systemic treatment
Jansen et al. [18]	9	0.5% morphine hydrogel Morphine hydrochloride 6.25 g Three different treatments (1) Morphine gel plus placebo infusion (2) Placebo plus morphine infusion (3) Placebo gel plus placebo infusion	Twice a day	No details reported	All patients had tried acetaminophen and NSAIDS; 7 patients has also used systemic opiates, including morphine, Oxycodone and Fentanyl patches without success	Most patients reported a mild stinging/burning after application of the gel which was attributed to the hydrogel and not the morphine itself	No significant difference between the 3 different treatments Reported that the absence of heat sensation and swelling in most of the patients may indicate that inflammation was not present and therefore opioid receptors were not expressed

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Table 2 (*continued*)

Study	No. of patients	Topical treatment used	Frequency of application	Details of titration to achieve pain control	Systemic drug regimen if reported	Local and systemic adverse effects	Author comments/outcome
Bastami et al. [7]	17	Morphine hydrochloride and hydrogel	Each patient treated twice	Dosages varied in patients (mean dosage 6.6 mg ± 5.06) according to ulcer size; 0.5 mg morphine applied on 1 cm^2 of ulcer	Paracetamol, NSAIDS and/or opioids (mostly oxycodone). Two of the 21 patients had to use rescue medication	Nine patients in the morphine arm reported smarting pain/ burning pain but the incidence was the same in both treatment groups. Redness reported around the ulcers in 3 cases	Pain reduction was observed but difference was only significant 2 h and not after 6, 12 and 24 h
Other							
Ribeiro et al. [28]	6	10 mg Morphine sulphate in 8 g of IntraSite gel (topically) 10 mg Morphine sulphate (injection)	One application for ulcers Subcutaneously over 4 h	No details reported	Paracetamol Fentanyl and Tramadol	In 5 patients morphine and its metabolites were undetectable. In 1 patient with the largest ulcer morphine (20%) and MG6 (21%) and MG3 (below lower limit of quantification) was detected No adverse effects reported	Topically applied morphine was not absorbed in the majority of patients suggesting analgesic effect would be mediated locally rather than systemically

NSAIDS, nonsteroidal anti-inflammatory drug; MG6, morphine-6-glucuroride; MG3, morphine-3-glucuroide.

another patient, the frequency of topical morphine 0.3% was reduced from 5 mL 3 times a day to twice a day. Increasing pain was controlled by increasing morphine gel 0.5% to 7 mL (35 mg morphine per dose) 3 times a day. In another case study, a patient with a questionable response had the topical morphine omitted, but as pain increased, it was reintroduced with beneficial effect [4].

3.4. Monitoring the use of topical opioids

The studies revealed 3 aspects of topical morphine usage that require careful monitoring: local adverse effects, systemic absorption and drug interactions.

3.4.1. Local adverse effects

Three studies reported itching, burning and discomfort but argued that these were not attributable to the topical morphine [18,38,39]. In another study, the frequency of adverse effects (drowsiness, itching, redness and smarting) was similar between both treatment groups [7]. Flock [11] assessed 8 side effects (skin irritation, itching, constipation, nausea and/or vomiting, drowsiness, hallucinations and jerking) and found no significant difference between 2 treatment groups. Flock argued that the adverse effects were caused by systemic opioids and not topical morphine.

3.4.2. Systemic absorption

Six studies found systemic uptake of topical opioids at levels considered safe [8,15,24,28,34,36]. Ribeiro et al. [28] found topical morphine was not absorbed systemically in the majority of patients but may occur with ulcers with large surface areas. Gallagher et al. [15] found methadone absorption was variable and probably dependent on wound surface area and presence of eschar.

3.4.3. Impact of topical opioids on use of systemic medication

Four studies reported patients were able to reduce or withdraw their systemic medications after applying topical opioids [5,6,15,20]. Barker [6] found the patient was able to stop Tramadol medication and start immunosuppressant treatment. In another study, the patient's fentanyl dose patch was reduced after topical morphine application and pain reduction was achieved [20]. Gallagher et al. [15] reported a reduction in the use of oral morphine and fentanyl patches in 3 of the 4 cases. In another study, 2 patients required reduced systemic doses of analgesia (Oxycodone and Meperidine) after applying topical morphine to sickle cell ulcers [5]. One study found that analgesia was maintained without escalation of systemic doses [27].

3.5. Patients' views about the use of topical opioids

Patients' views were under represented. We found only 1 study which reported 2 patients' comments on topical opioid treatment, namely 'improved healing after 4 weeks of morphine gel application' and that the 'area under the gel healed more quickly than usual' [36].

4. Discussion

The results from this review indicate that topical opioids are clinically useful and safe for controlling inflammatory pain in wounds. The finding that systemic absorption of topical opioids occurs at a safe level is reassuring, particularly as the doses of topical opioids are small. This addresses concerns regarding the potential growth-promoting effect of opioids in lung cancer [13].

Wide variation in wound terminology was noted. This indicates a need for consistency if clinical guidelines are to be meaningful and transferable. Evidence was found that topical opioids are less effective for arterial and venous ulcers. However, a lack of differential diagnosis was reported between pain from wound infection and pain from inflamed tissue. In the study that assessed inflammation

[18], patients with arterial and mixed venous–arterial ulcers had erythema, pain and loss of function but swelling and heat were present for only 11% and 44%, respectively. The authors argue that the absence of heat and swelling may indicate inflammation was absent, and therefore opioid receptors were not expressed. Given research demonstrating the pharmacodynamic characteristics of topical opioids via activation of peripheral opioid receptors in the skin in the presence of inflammation [30,31], it appears crucial that standard approaches to assessment and differential diagnosis of inflammation and infection are adopted. Guidance on the assessment and diagnosis of wound infection in acute and chronic wounds has been published in an international consensus document [37]. This can assist clinical decision making in frail patients where the classic signs may be less obvious.

Two studies reported that wound size appears to affect the pharmacokinetics—absorption in particular—of topical opioids. This reinforces the need to collect data on wound characteristics and patient factors to accrue evidence on patients who benefit from topical opioids for the management of inflammatory pain. These findings are endorsed by Farley's [10] argument that the absorption of opioids from cutaneous lesions is related to wound surface area.

Seven studies titrated doses to achieve pain control although titration did not appear to follow any systematic method. We also found that doses varied widely with little explanation as to why. This lack of consistency makes it difficult to extrapolate standardised dosages. There are rigorous ways to determine dosage (see the Dixon up-and-down method [9]). However, there is conflicting evidence on whether a dose–response relationship exists for topical opioids [8,24].

In conclusion, systematic approaches to establishing the effectiveness and dose–response relationship of topical opioids are required to inform clinical guidelines. There is also a need for study designs that can evaluate topical opioids with patients with multiple variables and heterogeneous presentation of inflamed lesions. An *n*-of-1 study design offers a means of doing this, generating within and between patient data [23]. We also recommend routine systematic assessment and documentation of the lesions, inflammation and infection and patient variables that can inform decision making, and research protocols.

Conflict of interest statement

The authors report no conflict of interest.

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Appendix A. Grey literature sources

- PalliativeDrugs.org.
- ScottishIntercollegiateGuidelinesNetwork (SIGN).
- Macmillan guidelines for patients.
- OpenGrey (System for Information on Grey Literature) (http://www.opengrey.eu).
- HMIC (The Healthcare Management Information Consortium).
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