

Topical Opioids and Antimicrobials for the Management of Pain, Infection, and Infection-Related Odors in Malignant Wounds: A Systematic Review

Kathleen Finlayson, BN, MN, PhD, Laisa Teleni, APD, BBS(Hons), MND, and Alexandra L. McCarthy, PhD, MN, BN

Finlayson is a research fellow in the School of Nursing in the Institute of Health and Biomedical Innovation at Queensland University of Technology in Australia; Teleni is a project officer in the School of Nursing at Queensland University of Technology and in the Faculty of Health Sciences and Medicine at Bond University in Queensland, Australia; and McCarthy is a professor and chair in the School of Nursing at the University of Auckland in New Zealand and a professor in the Division of Cancer Services at Princess Alexander Hospital in Brisbane, Australia.

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All authors contributed to the conceptualization and design, data collection, analysis, and manuscript preparation.

Finlayson can be reached at k.finlayson@qut.edu.au, with copy to editor at ONFEditor@ons.org.

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Problem Identification: Patients with malignant wounds report pain, distress from odor and exudate, decreased self-esteem, and poor quality of life. This systematic review explores topical opioids, antimicrobials, and odor-reducing agents for preventing or managing malignant wound pain, infection, and odor.

Literature Search: MEDLINE®, EMBASE, the Cochrane Library, CINAHL®, and reference lists were searched to identify relevant studies.

Data Evaluation: Eligible study designs included interventions with pre- and postintervention data. Data extraction and risk-of-bias assessments were conducted using the Cochrane approach.

Synthesis: No studies evaluated opioid use. Five studies (four randomized, controlled trials) evaluated topical antimicrobials for infection and odor. All studies reported clinically (but generally not statistically) significant improvements in outcomes.

Conclusions: Although not as prevalent as before, 5%–10% of tumors, particularly in breast cancer, sarcoma, and melanoma, are expected to fungate. Gaps in the literature exist for use of topical opioids and antimicrobials for managing pain, odor, and infection control in malignant wounds.

Implications for Research: Current recommendations for topical control of malignant wounds are based on case reports and observational studies in patients with breast cancer. Robust, controlled trials of topical opioid and antimicrobial use are warranted in patients with melanoma, breast, or head and neck cancer.

A fungating cancer is any cancer-related skin lesion characterized by ulcerations (breaks on the skin or surface of an organ) and necrosis (death of living tissue) (National Cancer Institute, 2015). Cancer registries do not report the rate of fungating cancers. In the authors' clinical experience, advances in chemotherapy and radiation therapy mean that they are not as prevalent as they once were. Now considered relatively uncommon, fungating cancers are nonetheless still encountered in patients with melanoma, breast cancer, and squamous cell carcinomas (particularly in head and neck cancer), and in those with more advanced disease. Retrospective reviews of large hospital databases undertaken from 1990–2007 indicate that 5%–10% of such cancers are likely to fungate (Alexander, 2009). In Europe, an estimated 5% or greater of patients with cancer develop a fungating wound (European Oncology Nursing Society, 2015).

Fungating lesions develop rapidly; if their exuberant growth is not controlled, they can damage local skin and vascular and lymph structures. If the lesion undergoes necrosis, it also provides a favorable medium for bacterial growth and subsequent infection (da Costa Santos, de Mattos Pimenta, & Nobre, 2010) and infection-related odor. Although current cancer therapy can usually help debulk

the lesion, reduce the risk of infection, and provide palliative relief, these growths are unlikely to heal completely once entrenched. Therefore, patients with malignant wounds often report pain, distress from odor and exudate, decreased self-esteem, and poor quality of life (da Costa Santos et al., 2010). Pain, odor, exudate, and hemorrhage are the most common symptoms (Woo & Sibbald, 2010). For example, a study by Lo et al. (2011) of symptom burden in patients with malignant fungating wounds reported malodor and pain as the most troublesome symptoms. These symptoms are reported to present physical and emotional challenges for patients, and are significantly associated with decreased quality of life (European Oncology Nursing Society, 2015; Lo et al., 2011). In a study with 70 participants, 87% of total variance in quality of life was accounted for by age, psychological issues, and symptoms from malignant wounds (i.e., pain and malodor) (Lo et al., 2011). Symptom control is one of the most important challenges for healthcare providers caring for patients with malignant wounds.

One practice used to control pain in malignant wounds is the application of topical opioids (e.g., morphine mixed with a hydrogel). It is hypothesized that topical opioids relieve pain rapidly by inhibiting the propagation of action potentials around the lesion (Krajnik, Zylicz, Finlay, Luczak, & van Sorge, 1999; Miyazaki, Satou, Ohno, Yoshida, & Nishimura, 2014) and by reducing inflammation (Krajnik et al., 1999). It is also believed that topical opioids are preferable because they remain topical, meaning they are free of the side effects associated with systemic administration. Krajnik et al. (1999) reported that absorption of opioids is usually poor through intact skin, but local bioavailability reaches 75% where local inflammation and epithelial compromise exist, which are common in fungating tumors. However, small sample sizes and limited research in this area preclude definitive conclusions regarding these potential advantages.

Unfortunately, published articles that recommend topical opioids and antimicrobials to manage this problem inevitably cite poor-quality evidence, such as case reports (Gallagher, 2010). Hospital and organizational protocols advocate the practice based on such literature (Harvey, 2012). The European Oncology Nursing Society's (2015) *Recommendations for the Care of Patients With Malignant Fungating Wounds* notes that wound pain might be managed with topical application of 10 mg of morphine mixed with 8 g of hydrogel. This recommendation is based on a critical review of clinical case studies rather than intervention studies (Graham et al., 2013). There is no doubt that topical opioids, if they are effective, would be far preferable to systemic opioids to control wound-related pain, given the complex side effect profile of the

latter in many patients with cancer. However, the use of topical opioids is unsubstantiated. A systematic review by de Castro and Santos (2015) of topical metronidazole therapy for odor management reported a scarcity of studies, limiting the strength of evidence for its use, and a review by da Costa Santos et al. (2010) on topical treatments for odor of malignant wounds also reported a lack of high-quality studies.

Despite the lack of evidence, topical opioids and antimicrobials are often used to manage malignant wounds in clinical settings. The aim of this review is to inform clinical practice by determining whether pain, infection, and odor can be controlled in malignant wounds not related to surgery or radiation therapy. Specifically, the primary objective is to determine whether topical analgesics, with or without additional inert substances, are effective in managing pain associated with malignant wounds. The secondary objective is to determine whether antimicrobials, with or without odor-reducing topical agents, are effective for preventing or managing infection and infection-related wound odor.

Methods

This systematic review is reported per the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist (Moher, Liberati, Tetzlaff, & Altman, 2010).

Eligibility Criteria

To address the review objectives, the authors included intervention studies with at least 10 human participants who were diagnosed with cancer and a malignant wound (fungating, infiltrative, ulcerating) not related to surgery or radiation therapy. Study designs were randomized, controlled trials and non-randomized intervention studies with pre-/post-test outcomes. Systematic reviews, clinical guidelines, case series, and case reports were excluded. Interventions of interest included topical analgesics with or without additional inert substances for the management of pain and/or topical antimicrobials with or without additional odor-reducing topical agents for the prevention or management of infection and infection-related odors. Interventions were not limited by dose or duration. Primary outcome measures included pain (intensity, type, frequency, and overall experience), the use of adjuvant pain medications, and the use of breakthrough medications. Secondary outcome measures included indicators of systemic and/or localized infection and subjective measures of infection-related wound odor.

Information Sources

A search of MEDLINE[®], EMBASE, the Cochrane Library, and CINAHL[®] was performed from database

inception to September 8, 2015. Search terms included (cancer OR “Neoplasms” [MeSH] OR malignan*) AND (wound OR “Wounds and Injuries” [MeSH]) AND (“Analgesics” [MeSH] OR “Morphine” [MeSH] OR diamorphine OR “Ketamine” [MeSH] OR “Lidocaine” [MeSH] OR xylocaine OR antimicrobial agents OR “Anti-Infective Agents” [MeSH] OR “Charcoal” [MeSH] OR “Metronidazole” [MeSH] OR “Silver” [MeSH]) AND (Administration, Cutaneous [MeSH] OR Administration, Topical [MeSH]) AND “Pain” [MeSH] OR “Infection” [MeSH] OR “Sepsis” [MeSH] OR “Odors” [MeSH] OR odo*r. The reference lists of all identified reports and articles were searched for additional studies. Only studies of human participants published in English were considered for inclusion in this review.

Study Selection

Search results were imported into Covidence systematic review software (Sherman & Flaxman, 2002), where titles and abstracts were screened for eligibility. Full text was sought for studies that potentially met the inclusion criteria or where eligibility could not be determined because of insufficient data (e.g., missing abstract). The full text of relevant publications was reviewed to ensure they met the inclusion criteria of the review.

Data Extraction

Because of the inclusion of nonrandomized studies, data extraction was conducted using standardized Mi-

crosoft® Excel templates developed by the authors for each study type. Generally, data extracted included descriptions of general study information, methods, participants, interventions, co-interventions, comparators (if applicable), outcomes, study results for each outcome, and time of assessment.

Risk-of-Bias Assessment

The tool for risk-of-bias assessment varied according to study type. For randomized, controlled trials, the Cochrane Collaboration tool for assessing risk of bias (Higgins et al., 2011) was used. This tool assesses random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting to provide an overall rating of low, high, or unclear risk of bias. For nonrandomized trials, a Cochrane Risk of Bias Assessment Tool: For Non-Randomized Studies of Interventions, version 1.0.0, was used (Sterne, Higgins, & Reeves, 2014). This tool assesses bias because of confounding, participant selection, intervention departure, missing data handling, outcome measures, and reporting against a hypothetical “target” randomized trial.

Data Synthesis

All article screening, full-text review, data extraction, and risk-of-bias assessment was conducted independently by two reviewers. Any disagreements between reviewers were resolved through consultation with a third reviewer. Because of clinical heterogeneity, a synthesis of the studies’ results is presented in narrative form.

Results

The authors identified a total of 980 unique articles (see Figure 1). Two review authors independently screened each title and abstract for relevance. Of the 980 articles, 946 were excluded as irrelevant to the review. The full text of the remaining 34 articles was independently evaluated by two review authors. Twenty-nine articles were excluded, leaving five studies that met the inclusion criteria. Intervention and key characteristics are summarized in Table 1.

Included Studies

Of the five studies that met the inclusion criteria, no studies evaluated topical opioids mixed with inert substances for managing pain. All studies (total of 137 participants) evaluated topical antimicrobials and odor-reducing topical agents for preventing or managing infection and infection-related odors. Four were randomized trials (Bower et al., 1992; Lian, Xu, Goh, & Aw, 2014; Lund-Nielsen et al., 2011; Upright, Salton,

FIGURE 1. PRISMA Diagram of Search Strategy

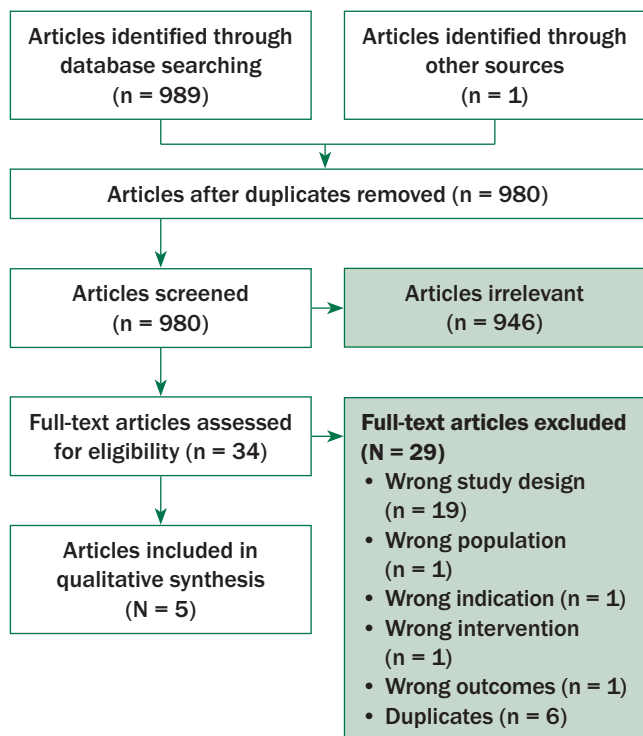


TABLE 1. Characteristics and Key Findings of Included Studies

Study	Design and Sample	N	Intervention	Findings
Bower et al., 1992	Phase 1: Double-blind RCT Phase 2: Open-label, single-arm study Sample consisted of 9 patients with breast cancer, 1 with ovarian cancer, and 1 with lung cancer.	Phase 1: 4 intervention and 5 control Phase 2: 11 intervention and no control	Phase 1: 0.8% metronidazole gel at a dose of 1 g/cm ² lesion applied daily for 7 days versus placebo Phase 2: 0.8% metronidazole gel at a dose of 1 g/cm ² lesion applied daily for 4 days versus no control	Phase 1: No significant difference in odor between groups Phase 2: Significant decrease in odor from phase 2 baseline (p < 0.01)
Kalinski et al., 2005	Open-label, single-arm study with 7 patients with head and neck cancer, 5 with groin cancer, 3 with breast cancer, and 1 with lung cancer	16 intervention	0.75% metronidazole gel applied daily for 14 days	Significant decrease in odor from baseline (p < 0.05)
Lian et al., 2014	Unblinded RCT with 24 patients with breast cancer, 2 with neck cancer, 2 with groin cancer, 1 with spine cancer, and 1 with anus cancer	15 intervention and 15 control	Green tea irrigation plus dressing containing green tea bag versus normal saline irrigation, metronidazole powder, and dry, absorbent dressing applied daily for 7 days	No significant difference in odor between groups
Lund-Nielsen et al., 2011	Open-label RCT with 55 patients with breast cancer, 8 with head and neck cancer, and 6 with other cancers	34 intervention and 35 control	Manuka honey-coated bandages, absorbent dressing, and foam bandages versus nanocrystalline silver-coated bandages and foam bandages as required for 4 weeks	No significant difference in malodor, exudate, or pain between groups; significant improvement over time for combined group in malodor (p < 0.05)
Upright et al., 1994	Crossover RCT with 9 patients with breast cancer, 1 with neck cancer, and 1 with ovarian cancer	11 participants	Hypertonic dressing of dry mesalt versus isotonic dressing of continuous wet saline applied daily for 8 weeks (4-week crossover)	Significant increase in odor control in the intervention group compared with the control group; no significant difference in infections between intervention and control

RCT—randomized, controlled trial

Roberts, & Murphy, 1994), and one was a nonrandomized study (Kalinski et al., 2005).

Randomized Trials

Bower et al. (1992) had an unclear risk of bias (see Table 2). It was a two-phase study that recruited 11 community-dwelling patients; 9 patients completed the study. The mean age was 68 years, and 91% were women. All patients had open, fungating primary or metastatic tumors with an odor score of 6 or greater on a visual analog scale from 0 (no odor) to 10 (worst odor imaginable). Tumor sites included breast (n = 9), ovary (n = 1), and lung (n = 1). The first phase (days 0–7) was a double-blind, randomized, placebo-controlled trial comparing daily application of 0.8% metronidazole gel at a dose of 1 g/cm² lesion (n = 4) with placebo control gel (n = 5). Wound odor was assessed daily by patients

and medical staff on the visual analog scale from 0 (no odor) to 10 (worst odor imaginable). The mean odor score remained greater than 6 at all time points in the control group. In the metronidazole group, patient and staff scores decreased from baseline to day 6 (p > 0.1). During the second open-label phase, all patients received the intervention. Mean odor scores reported by staff and patients for all patients significantly improved by day 11 (p < 0.01).

Upright et al. (1994) had a low risk of bias. The study comprised an eight-week randomized crossover trial, crossing over at four weeks. Eleven patients with ulcerating metastatic skin lesions of the breast (n = 9), neck (n = 1), and ovary (n = 1) were recruited from metropolitan outpatient, inpatient, and community settings. Nine patients completed the study. The mean age was 63 years, and 91% were women.

TABLE 2. Risk-of-Bias Assessment for Randomized Trials

Study	Random Seq. Gen.	Alloc. Conceal.	Blinding of PP	Blinding of OA	Inc. Outcome Data	Selective Reporting	Other Sources of Bias	Overall Bias
Bower et al., 1992	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Unclear
Lian et al., 2014	Low	Low	High	Unclear	Low	Low	Low	Low
Lund-Nielsen et al., 2011	Low	Low	High	High	Low	Low	Unclear	Unclear
Upright et al., 1994	Unclear	Unclear	Low	Low	High	Low	Unclear	Unclear

alloc—allocation; conceal—concealment; gen—generation; inc—incomplete; OA—outcome assessment; PP—participants and personnel; seq—sequence

Note. The assessment tool used was the Cochrane Collaboration Tool for Assessing Risk of Bias (Higgins et al., 2011).

An isotonic dressing of continuous wet saline (dry gauze soaked in normal saline) was compared with a hypertonic dressing of dry mesalt (bleached cotton gauze impregnated with crystalline sodium chloride). Wound odor was assessed daily by patients and medical staff using a visual analog scale from 0 (no odor) to 10 (worst odor imaginable). Comfort, ease of dressing application and removal, patient preference, and infection were also reported. Odor control and ease of dressing application were rated significantly higher for the mesalt dressing than the continuous wet saline (values not reported). There was no difference between groups for comfort or ease of removal ratings. No infections developed in either group.

Lund-Nielsen et al. (2011) had an unclear risk of bias. The study was an open-label, randomized comparative trial of 75 outpatients (88% female) with a median age of 65.6 years and a median malignant wound size of 130.9 cm². Sixty-nine patients completed the study. Manuka honey-coated bandages with an absorbent dressing and foam bandages (n = 34) were compared with nanocrystalline silver-coated bandages and foam bandages (n = 35) for four weeks. Both groups received wound cleaning, relaxation training, and psychosocial support with one hour of cognitive behavioral therapy. Malodor, exudate, and pain were all secondary outcomes. Malodor and exudate were assessed by the authors and patients using a verbal rating scale and visual analog scale from 0 (no odor) to 10 (worst odor imaginable), respectively. Pain was self-reported using a visual analog scale from 0 (no pain) to 10 (worst pain imaginable). There were no significant differences between groups at baseline or after the four-week intervention for any outcome. The combined sample had a significant decrease in malodor after four weeks (p = 0.036).

Lian et al. (2014) had a low risk of bias. The study was a non-blinded, randomized, controlled trial of 30 hospitalized patients with malodorous, fungating malignant wounds of the breast (n = 24), neck (n = 2), groin (n = 2), spine (n = 1), and anus (n = 1). Twenty-nine patients completed the study. The mean age was 46 years for the control group and 55 years for the intervention group, and 90% of participants were women. Wound size ranged from 21–960 cm². Irrigation with a green tea solution followed by an absorbent dressing containing a green tea bag (n = 15) was compared with a normal saline irrigation followed by sprinkling metronidazole powder (400 mg per 50 cm² lesion) and dressed with a dry, absorbent dressing (n = 15) for seven days. Wound odor was assessed daily by patients and nurses using a visual analog scale from 0 (no odor) to 10 (worst odor imaginable). Mean odor scores significantly decreased, and quality of life significantly improved in both groups, with no statistically significant differences between groups (p > 0.05).

Nonrandomized Study

The nonrandomized study (Kalinski et al., 2005) in the current review had a low risk of bias (see Table 3). This was a single-center, open-label, single-arm trial of 16 patients with malodorous, fungating malignant wounds of the head and neck (n = 7), groin (n = 5), breast (n = 3), and lung (n = 1). The intervention involved daily application of 0.75% metronidazole mixed with stabilized propylene glycol and hydroxypropyl methylcellulose to produce a gel that was applied directly to the wound and covered with nonadherent primary dressing and absorbent gauze for 14 days. Within 24 hours of application, there was a statistically significant decrease (p < 0.05) in patient- and investigator-rated wound odor, with

further significant decreases ($p < 0.05$) at days 7 and 14. Although differences in wound exudate before and after treatment were clinically evident, they were not statistically significant ($p = 0.096$)

Discussion

These five small studies, including four randomized trials, investigated interventions for infection and infection-related odor. There were five different interventions tested in the studies, and different outcome measures were reported. Although all studies reported clinical improvement from the interventions, most were underpowered and unable to show statistical significance.

The primary objective of this review was to evaluate the effectiveness of topical analgesics for the management of pain associated with malignant wounds. The authors identified no studies that fit the inclusion and exclusion criteria of this review and addressed this outcome. The primary reason studies on this topic were excluded from the review was study design, because studies found in the literature search with this population were predominantly case studies.

Topical antimicrobials, such as metronidazole, the most common intervention studied, are widely available. Exploring their clinical use would be valuable because they are cheaper and less invasive than systemic antimicrobials and have fewer side effects. Only five topical antimicrobial studies were identified, four of which were randomized. When the analysis of these five studies was completed, an additional study was identified. Watanabe et al. (2016) published a multicenter, open-label, noncontrolled phase 3 study of 21 patients with stage III or IV breast cancer with fungating, malodorous tumors. Mean wound area was 69 cm², and baseline odor scores were 2 or greater on a scale from 0–4, with higher scores indicating more odor. Daily or twice daily, patients applied 0.75% metronidazole gel up to a maximum dose of 30 g for 14 days. The percentage of patients with an odor score of less than 2 on day 14 was 95.2% (90% confidence interval [79.3, 99.8]). A nonsignificant decrease was found in

Knowledge Translation

- No studies that evaluated opioid use with samples of greater than 10 participants were found.
- Five studies reported clinically (but generally not statistically) significant improvements in outcomes.
- Current recommendations for topical control of malignant wounds are based on case reports and observational studies in patients with breast cancer.

mean pain score, and anaerobic bacteria were detected in 9 patients on day 0 and in 1 patient on day 14, with no change in aerobic bacteria. The publication of these data after the literature search and analysis does not alter the essential findings. That is, the sample sizes of the studies reviewed (range = 7–69 participants) were small. Therefore, the randomized trials in this review were underpowered. Taken overall, a trend was seen toward odor reduction and potentially patient comfort in all of the studies assessing topical antimicrobial efficacy, but the effect of the agent on microorganism colonization and infection-related odor is not clear. Meaningful statistical and clinical conclusions about cause and effect cannot be drawn from the findings of any of the studies reviewed.

Fungating tumors are probably not as common as they once were, and they are likely not as advanced on presentation. This could be attributed to earlier detection and more effective control with radiation therapy and chemotherapy. However, with a conservative estimate that 5%–10% of some common cancers will fungate despite improved treatment options (Alexander, 2009), malignant wounds remain a concern in clinical practice. The lack of intervention studies evaluating the use of topical opioids in malignant wound pain management and topical antimicrobials to manage infection and infection-related odor is problematic.

Strengths and Limitations

This review was conducted systematically from database inception. All stages of the review were

TABLE 3. Risk-of-Bias Assessment for Nonrandomized Studies

Study	Bias From Confounding	Bias in SPS	Bias in MI	Bias From DII	Bias From Missing Data	Bias in MO	Bias in SRR	Overall Bias
Kalinski et al., 2005	Moderate	Low	Low	Low	Low	Moderate	Low	Low

DII—departures from intended interventions; MI—measurement of interventions; MO—measurement of outcomes; SPS—selection of participants into study; SRR—selection of the reported result

Note. The assessment tool used was a Cochrane Risk of Bias Assessment Tool: For Non-Randomized Studies of Interventions (Sterne et al., 2014).

conducted independently by two reviewers, and almost all studies were found to have low risk of bias. The findings of this review are limited, however, by the lack of analgesic intervention studies. The antimicrobial trials had significant clinical heterogeneity, preventing any quantitative analysis. Some trials, particularly the older trials, were poorly reported, so it was difficult to extract data and perform risk-of-bias assessment with confidence. The risk of bias in the included studies appears low; in those that were poorly reported, it is difficult to be confident in these ratings.

Implications for Nursing

Current recommendations for topical control of malignant wounds are not based on strong evidence. Evidence produced by way of robust, controlled trials of topical opioid and antimicrobial use is warranted with the following caution. In the authors' clinical experience, patients with malignant wounds usually receive care in community-based or palliative settings, which are commonly less research-intensive and research-resourced than acute facilities. Undertaking research in this area without considerable community networking and resource allocation could be difficult.

Conclusion

Significant gaps exist in the literature with respect to topical opioid and antimicrobial treatments for the management of pain, odor, and infection control in malignant wounds. This review found no trials of opioids and no studies on products of common clinical application for reducing odor, such as charcoal. Participant groups were small, predominantly female, and predominantly with a diagnosis of breast cancer. All studies had relatively small sample sizes. There was significant heterogeneity in the interventions to prevent any pooling of data, so no comment can be provided on the overall effect of the interventions.

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