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WWOM PROCEEDINGS

WILEY ORAL DISEASES

World Workshop on Oral Medicine VII: Non-opioid pain management of head and neck chemo/radiation-induced mucositis: A systematic review

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Abstract

Objective: To evaluate the current evidence regarding the effectiveness of non-opioid interventions for the therapeutic management of pain in head and neck cancer patients with oral mucositis resulting from radiotherapy only or chemoradiotherapy.

Materials and Methods: A literature search was conducted which included randomised controlled trials that assessed patient-related outcome of pain in patients with oral mucositis associated with radiation therapy only or chemoradiotherapy. Literature searches were conducted in MEDLINE via Pubmed, Embase, Scopus and CINAHL.

Results: The electronic searches identified 846 articles. Screening revealed that six articles met all eligibility inclusion criteria. Interventions showing statistically significant benefits to reduce oral mucositis associated pain compared to placebo included doxepin ($p < 0.001$, 95% CI −6.7 to −2.1), amitriptyline ($p = 0.04$), diclofenac ($p < 0.01$) and benzydamine ($p = 0.014$).

Conclusions: Non-opioid interventions, including topical doxepin, amitriptyline, diclofenac and benzydamine, were found to provide relief of pain due to mucositis, and when effective may allow for reduction in the use of opioids in pain management.

KEYWORDS

chemoradiotherapy, head and neck cancer, mucositis, non-opioid analgesia, pain management, radiotherapy

1 | INTRODUCTION

Oral mucositis (OM) is seen as a major complication in head and neck cancer radiotherapy and can be associated with considerable pain and other sequelae (Elting, Cooksley, Chambers, & Garden, 2007). The successful management of OM involves pain reduction, positively affecting quality of life and facilitating oral function, aiding in the maintenance of nutrition, oral hygiene, speech and sleep. Management of OM-related pain also limits the need for gastrostomy tube placement, parenteral feeding and alterations in cancer treatment due to delays, dose reduction or even discontinuation of cancer treatment (Kanagalingam et al., 2018).

The mainstay of pharmacologic management of OM pain involves the use of systemic opioids. However, even when opioids are used in comprehensive pain management in cancer centres, patients experience considerable pain in the later stages of cancer treatment and during recovery from acute toxicities. In addition, opioids carry a risk of development of dependence and the side effects of opioids require extensive management (Mirabile et al., 2016). It would greatly benefit patients if management of OM caused by radiotherapy or chemoradiotherapy could be managed by non-opioid analgesics. For some patients with OM whose pain requires opioid use, alternative therapies, in addition to opioids, may potentially allow lower doses and shorter duration of opioid use. Incorporation of effective non-opioid alternatives for pain management into OM management protocols prior to commencing opioid use should be encouraged.

Several mucositis trials have assessed products to manage radiation- and chemoradiation-induced OM without demonstrated effectiveness of the intervention (Kataoka et al., 2016), and other studies have poor trial methodology (Kaushal, Verma, Manocha, Hooda, & Das, 2001). Reviews on this topic have also been undertaken utilising a combination of cancer populations and treatment regimens including chemotherapy or radiation therapy alone, or combined chemoradiotherapy (Worthington et al., 2011).

This systematic review identified evidence on the effectiveness of non-opioid interventions for the management of pain in head and neck cancer patients with OM resulting from radiotherapy alone or combined chemoradiotherapy. Furthermore, this is the only systematic review which focused on studies that assessed the patient-related outcome measure of pain rather than clinical appearance of OM severity and used interventions in a therapeutic only manner rather than a preventive manner.

2 | METHODS

2.1 | Search strategy and study identification

A comprehensive literature search was conducted in PubMed, Embase, Scopus and CINAHL from each database's inception to 19 July 2018. The search attempted to identify relevant studies assessing interventions for the management of OM in head and neck radiotherapy and chemoradiotherapy patients. Sensitive search strategies were developed by members of the research team, in consultation with a research librarian (JSW), for each database using a combination of controlled vocabulary and related text and keyword searches. These searches attempted to identify all relevant trials published in English with no date limitations (Appendix A). Reporting follows closely the PRISMA (preferred reporting items for systematic review and meta-analysis) statement (Moher, Liberati, Tetzlaff, & Altman, 2009).

2.2 | Study selection

We included phase III or IV randomised controlled trials (RCT). Pilot studies, non-blinded clinical trials, reviews, case reports, comments, editorials, notes, brief communications and letters were excluded. An additional exclusion criterion was a preventative intervention (commencement of the intervention from the initiation of radiotherapy) rather than a therapeutic intervention (when signs or symptoms of mucositis were evident). Comparative studies between new interventions were also excluded. Using the Covidence systematic review support program, the titles and abstracts of all reports identified through the searches were screened by two independent reviewers (JC and JK); conflicts were resolved by a third reviewer (LLP). Full texts were obtained for trials appearing to meet the inclusion criteria or for which there was insufficient information in the title and abstract to make a clear decision. The full texts obtained from all the electronic methods of searching, including contacting authors, were assessed independently, in duplicate, by two reviewers (JC and JK) to establish whether the trials met the inclusion criteria. Disagreements were resolved by a third reviewer (LLP). Searches for grey literature were also undertaken, and studies that did not meet the final inclusion criteria were excluded.

2.3 | Quality assessment

The GRADE approach (Guyatt, Oxman, Schünemann, Tugwell, & Knotterus, 2011) was utilised to rate the certainty of the evidence obtained from the included studies. The specific domains for rating down included risk of bias, imprecision, inconsistency, indirectness and publication bias. The GRADE certainty ratings were designated as high, moderate, low and very low.

2.4 | Assessment of risk of bias in included studies

Risk of bias was assessed using the Cochrane risk of bias framework (Higgins & Altman, 2008) which addresses seven specific domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and "any other bias." The validity of each study was assessed as at low, unclear or high risk of bias. A low risk of bias was given when there was a low risk of bias for all key domains assessed, except for any other bias. An unclear risk of bias was designated when there was an unclear risk for one or more domains (except other bias recording), and a high risk of bias

was designated when there was a high risk of bias for one or more key domains. The risk of bias assessment, and subsequent GRADE ratings, was undertaken independently and in duplicate by two review authors (JC and JK) as part of the data extraction process, reaching consensus. The risk of bias assessment aided in the quality assessment of the studies using the GRADE approach (Guyatt et al., 2011).

3 | RESULTS

Electronic searches identified 1,314 articles. After duplicates were removed, 848 articles were screened for eligibility. Of these, 675 articles were excluded during the title and abstract screening phase and an additional 167 were excluded from the full-text phase. Finally, six articles met all eligibility criteria for inclusion (Figure 1): three from USA (Kim, Chu, & Lakshmi, 1986; Leenstra et al., 2014; Meredith et al., 1997) and one each from Czech Republic (Kostrica, Rottenberg, Kvech, Betka, & Jablonicky, 2002), Iran (Kakoei et al., 2018) and Sweden (Franzén, Henriksson, Littbrand, & Zackrisson, 1995). Table 1 summarises the interventions included in this systematic review. Four of the studies recruited participants who underwent radiotherapy only (Franzén et al., 1995; Kim et al., 1986; Kostrica et al., 2002; Meredith et al., 1997), and two studies recruited patients who were undergoing either radiotherapy only or chemoradiotherapy (Kakoei et al., 2018; Leenstra et al., 2014). The radiotherapy doses were 40–66 Gy (1.5–2 Gys/day; Franzén et al., 1995), greater than or equal to 40 Gy (2.39–2.52 Gys/day; Kostrica et al., 2002), (1.8 Gy/day; Meredith et al., 1997), greater than 30 Gy (daily fraction not recorded; Kakoei et al., 2018), minimum of 50 Gy (1.6–2.2 Gys/day; Leenstra et al., 2014) and above 20 Gy (2Gys/day; Kim et al., 1986) to the head and neck region with variation in dose and fractions due to the type of primary cancer. The primary cancers recorded ranged from oropharyngeal, pharyngeal, oral cavity, laryngeal, nasopharyngeal, salivary, hypopharyngeal, oesophageal, salivary gland tumours, lymphomas, bone marrow tumours and others. The type of radiotherapy utilised included 3D conformal and intensity modulated radiotherapy (IMRT; Leenstra et al., 2014), linear accelerators (Franzén et al., 1995), small and large field head and neck radiotherapy (Meredith et al., 1997). The other included studies (Kakoei et al., 2018; Kim et al., 1986; Kostrica et al., 2002) did not identify the radiotherapy method.

Five of the selected trials were placebo controlled and one trial intervention was compared to a standard of care in an identical dispensing container: diclofenac versus placebo (Kostrica et al., 2002), benzydamine HCl versus placebo (Kim et al., 1986), niosomal amitriptyline versus simple amitriptyline versus benzydamine (Kakoei et al., 2018), doxepin versus placebo (Leenstra et al., 2014) and sucralfate versus placebo (Franzén et al., 1995; Meredith et al., 1997). The pain scales utilised included the following: 4-point pain scale (0-absent, 1-slight, 2-moderate, 3-severe; Kostrica et al., 2002), 4-point pain and functional impairment scale (0-no pain, 1-mild, 2-moderate, 3-severe; Franzén et al., 1995), 4-point pain scale and 5-point relief scale (Severity of pain: 1-none, 2-slight, 3-moderate, 4-severe; Relief scores: 1-none, 2-a little, 3-fair, 4-a lot, 5-complete; Kim et al., 1986), visual analogue scale (Kakoei et al., 2018), scale of

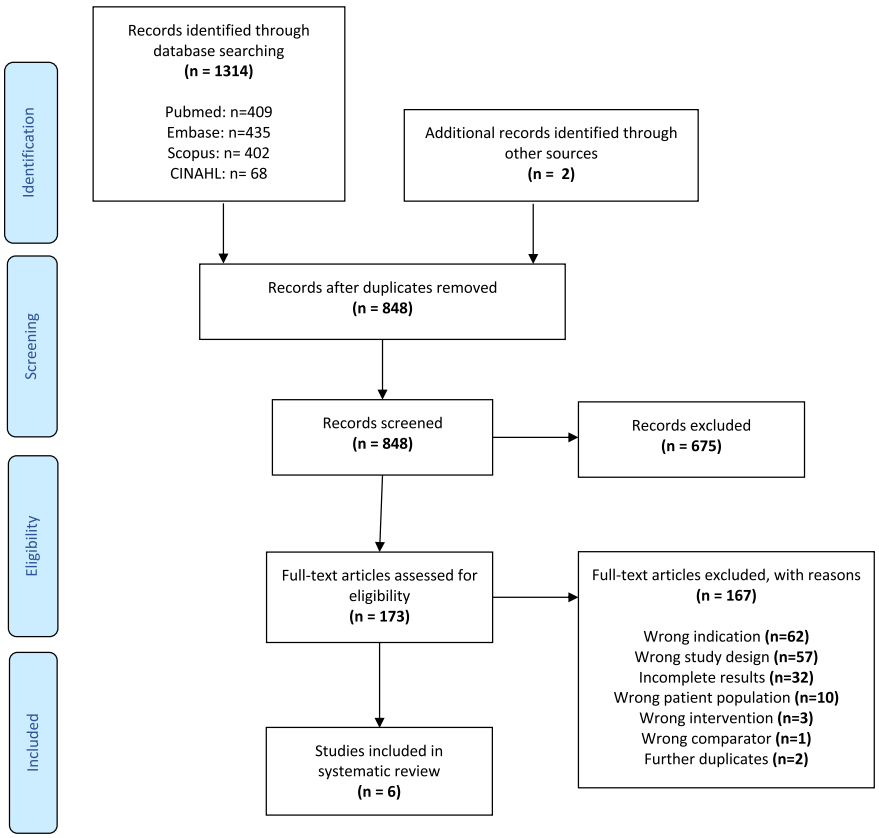


FIGURE 1 PRISMA diagram

0 to 20 (0 indicating no soreness, whereas the upper limit value of 20 indicated such severe inability to swallow that the patients could not handle all of their own secretions; Meredith et al., 1997) and 11-point numerical analogue pain scale (0 to 10 scores; Leenstra et al., 2014).

The time points of assessment and recording of patient pain report varied between studies: three out of the six studies utilised the self-identified presence of pain (Kim et al., 1986; Leenstra et al., 2014; Meredith et al., 1997), whilst the other studies used a fixed time point after commencement of radiotherapy (Franzén et al., 1995) or when OM was diagnosed (Kakoei et al., 2018; Kostrica et al., 2002).

3.1 | Effects of interventions

For the six trials, 441 patients were randomised and provided data for this review. The number of patients ranged from 20 to 69 per treatment or control group. Interventions showing statistically significant benefits for the active intervention to reduce OM-associated pain compared to placebo included doxepin mouthrinse (Leenstra et al., 2014), amitriptyline mouthrinse (Kakoei et al., 2018), diclofenac mouthrinse (Kostrica et al., 2002) and benzydamine mouthrinse (Kim et al., 1986). Comparisons were not made between interventions, except with amitriptyline and benzydamine (Kakoei et al., 2018), where amitriptyline was seen to be more effective than benzydamine. No significant difference was seen with the use of sucralfate compared to placebo (Franzén et al., 1995; Meredith et al., 1997).

3.2 | Quality assessment

The interventions were downgraded one level to reflect the inability to assess the consistency of results due to no comparative studies. Furthermore, confidence intervals were not provided in the studies, (Franzén et al., 1995; Kakoei et al., 2018; Kim et al., 1986; Kostrica et al., 2002; Meredith et al., 1997) to enable accurate assessment of data precision. Overall, the evidence for the effectiveness of doxepin (Leenstra et al., 2014) was judged to be of moderate quality, which means that the true effect is probably close to the estimated effect. Amitriptyline (Kakoei et al., 2018) and diclofenac (Kostrica et al., 2002) trials were of low quality; that is, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Sucralfate was shown to not have a clinical effect in either study (Franzén et al., 1995; Meredith et al., 1997), and these studies were judged to be of moderate quality and hence likely close to the estimated effect.

3.3 | Risk of bias

One study was rated as at low risk of bias (Leenstra et al., 2014), four as unclear risk of bias (Franzén et al., 1995; Kakoei et al., 2018; Kostrica et al., 2002; Meredith et al., 1997) and one at high risk of bias (Kim et al., 1986; Figure 2).

4 | DISCUSSION

Clinical OM research can involve a variety of patients with very different cancers and undergoing different treatment regimens, each with variable risks of developing OM. This systematic review attempts to identify non-opioid agents shown to have the best evidence for pain management of OM from head and neck radiotherapy or chemoradiotherapy. Many of the systematic reviews in this area have not differentiated between pain management versus prevention of tissue damage (Nagi, Patil, Rakesh, Jain, & Sahu, 2018), whilst others evaluated preventive regimes (Jensen et al., 2013; Saunders et al., 2013; Worthington et al., 2011). Furthermore, some systematic reviews used primary endpoints of the clinically observed severity of OM (Worthington et al., 2011) rather than perceived patient discomfort. This systematic review specifically addresses pain management of OM as an important symptom, given the associated impact on quality of life and function.

Amitriptyline and doxepin are tricyclic antidepressant drugs that were originally developed to aid in the management of depression. Nevertheless, their properties have also been found useful in pain management. Amitriptyline and doxepin block the neuronal reuptake of serotonin (5-HT) and norepinephrine (NE), and the NE blockade is seen to be more effective in analgesia. Also, they may relieve pain due to the blockade of alpha-adrenergic receptors, and they also interfere with depolarisation by blocking of the sodium ion channels. A single study evaluating amitriptyline mouthrinse met the systematic review inclusion criteria (Kakoei et al., 2018). In this study, topical amitriptyline was shown to reduce pain severity in both radiotherapy and chemoradiotherapy patients and was more effective than benzydamine (Kakoei et al., 2018). There have also been a number of studies which utilised doxepin for the management of OM (Epstein, Epstein, Epstein, Oien, & Truelove, 2007, 2008). Nevertheless, only a single study tested doxepin mouthrinse in the head and neck cancer population receiving radiotherapy, which also met our inclusion criteria (Leenstra et al., 2014). In this study, topical doxepin reduced mouth and throat pain in radiotherapy and chemoradiotherapy patients (Leenstra et al., 2014), but more studies need to be undertaken to further evaluate the benefits of doxepin in this population (Miller et al., 2016). Amitriptyline and doxepin are readily available to clinicians and can be simply compounded by a pharmacist into a solution to be used for mouthrinsing. Amitriptyline and doxepin may be effectively used at low doses to reduce opioid use with only mild adverse effects. Nevertheless, caution should be practiced in radiotherapy/chemoradiotherapy patients due to the common complaint of fatigue as a response to cancer treatment. The topical application of medications that may affect neuropathic pain supports the impression that mucositis pain represents both nociceptive and neuropathic components.

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) that acts by inhibiting cyclooxygenase (COX) enzymes which in turn prevents the synthesis of prostaglandins. Diclofenac acts preferentially as a COX-2 inhibitor and may also inhibit the lipoxygenase

TABLE 1 Summary of included studies

Author	Population	Intervention	Comparison
Franzén et al. (1995)	Primary carcinoma or a malignant lymphoma in the head and neck region managed with radiotherapy only. *N* = 50, Dropout = 2	Sucralfate granules dissolved in water	Granules similar in taste, colour and consistency dissolved in water
Kakoei et al. (2018)	Head and neck cancers, consisting of laryngeal and oral cancers, salivary gland tumours and bone marrow tumours treated with either Radiotherapy only or chemoradiotherapy. *N* = 60, Dropout = 0	1. Niosome of amitriptyline—hydration of a thin layer of fat and combination with Brij family and cholesterol. 2. Simple form of amitriptyline—solution with 0.1% consternation of amitriptyline	Benzydamine HCL mouthwash was procured from the pharmaceutical market
Kim et al. (1986)	Head and neck cancers treated with radiotherapy only to the oropharyngeal region. *N* = 67, Dropout = 6. But for subjective patient pain evaluation *N* = 29	Benzydamine chloride rinse/gargle 1.5 mg/ml used every 3 hr during the day	Green control
Kostrica et al. (2002)	Head or neck cancer treated with radiotherapy only with a minimal dose of 40 Gys. *N* = 69, Dropout = 3	Diclofenac (15 ml 3 × day) at 0.074% w/v rinse	Rinse (15 ml gargle 3 × day)
Leenstra et al. (2014)	A head and neck malignancy, undergoing radiotherapy (with or without chemotherapy) to a minimum planned dose of 50 Gy including one-third of the oral cavity mucosa. *N* = 155, Dropout = 15	Doxepin	Ora-Sweet SF is an alcohol-free flavoured sugar- free syrup vehicle that served as the placebo base solution
Meredith et al. (1997)	Patients undergoing radiation therapy only to a volume that included part of the oral cavity, pharynx, or oesophagus. Patients received > 40 Gy. *N* = 111, Dropout = 3–5. (66 patients were specific to the head and neck region.)	A 10 ml suspension prepared with 12 g sucralfate, 150 mg diphenhydramine, 10 ml 2% viscous lidocaine, and antacid suspension consisting of 225 mg aluminium hydroxide + 200 mg magnesium hydroxide per 5 ml qs ad 120 ml	150 mg diphenhydramine 10 ml 2% viscous lidocaine, and antacid suspension qs ad 120 ml

[a]GRADE quality assessment approach (Guyatt et al., 2011).

pathway. COX-2 is responsible for the production of inflammatory prostaglandins which cause the dilation of small blood vessels and are responsible for the responses of redness, heat, swelling/oedema and also activate and/or sensitise peripheral nociceptors. Inhibition of the lipoxygenase pathway reduces histamine and prostaglandin production (Gan, 2010). The study by Kostrica et al. (2002) demonstrated that diclofenac mouthrinse reduced patient-reported pain and also reduced the need for other analgesia in head and neck radiotherapy patients. Diclofenac is readily available to clinicians, and a mouthrinse can be simply compounded by a pharmacist. Reported side effects in the study by Kostrica et al. (2002) included burning and vomiting, and this may negatively impact patients undergoing head and neck cancer treatment due to further mucosal irritation and subsequent discomfort. A study (Abo Enin, El Nabarawy, & Elmonem, 2017) reports on the development of a novel double-layer, bi-medicated, prolonged release mucoadhesive buccal film containing diclofenac and lidocaine; clinical trials on the effectiveness of this intervention are required, given that NSAIDs are generally considered ulcerogenic and are associated with an increased risk of adverse cardiovascular events.

Benzydamine is categorised as a NSAID but is considered to be non-ulcerogenic. It predominately acts by inhibiting the synthesis of pro-inflammatory cytokines such as TNF-alpha and IL-1 beta. It is capable of local anaesthetic effects by inhibiting the release of inflammatory mediators like substance P and calcitonic gene-related peptide (CGRP) from sensory nerve endings. Benzydamine mouthrinse has been trialed in multiple studies assessing its effectiveness in OM, although many studies have focused on prevention of OM rather than its effectiveness on pain control (Apaydin, Karadeniz, Ayisigi, & Bilge, 1996; Chitapanarux et al., 2018; Epstein & Stevenson-Moore, 1986; Epstein et al., 2001; Jayachandran & Balaji, 2012; Samaranayake et al., 1988). Benzydamine reduced pain severity in radiotherapy patients during the early stages of cancer treatment (Kim et al., 1986). The benzydamine formulation contains

Timing	Pain scale	Outcome	Adverse effects	GRADE[a] quality analysis
Two weeks after the commencement of radiotherapy	0 to 3-pain and functional impairment scale	No significant difference in pain. ($p > 0.1$)	Low frequency of adverse effects	Moderate
When oral mucositis was diagnosed by a specialist in charge	Visual analogue scale	Decrease in the severity of pain with the use of amitriptyline mouthwash was more than that with benzydamine mouthwash ($p = 0.04$)	None recorded	Low
Commencement of intervention when patient experiences mouth/throat pain	1 to 4 pain scale	The intervention reduced pain severity at day 1. ($p = 0.014$)	Burning and stinging	Low
Commenced from the day of occurrence of mucositis until the completion of radiotherapy	Spontaneous pain and odynophagia used a 4-point scale: (0-absent, 1-slight, 2-moderate, 3-severe)	24% of the diclofenac group required analgesia in comparison to 53% in the placebo group ($p < 0.05$). Diclofenac group had reduced spontaneous pain ($p < 0.01$). Diclofenac had reduced pain on swallowing ($p < 0.05$)	Burning/pain of the throat, vomiting	Low
When mouth pain rated ≥4 on a numerical analogue questionnaire (0, no oral pain; 10, worst oral pain)	0–10 pain scale-area under curve	Mean mouth and throat pain reduction was greater for doxepin compared with placebo ($p < 0.001$, 95% CI −6.7 to −2.1)	Stinging, burning, unpleasant taste, drowsiness. These adverse effects were typically mild	Moderate
Medication was prescribed when the patient became symptomatic	Soreness was graded on a scale of 0–20, with 0 indicating no soreness, whereas the upper limit value of 20 indicated such severe inability to swallow that the patients could not handle all of their own secretions	No significant improvement of pain	Local mouth discomfort immediately after taking the medication	Moderate

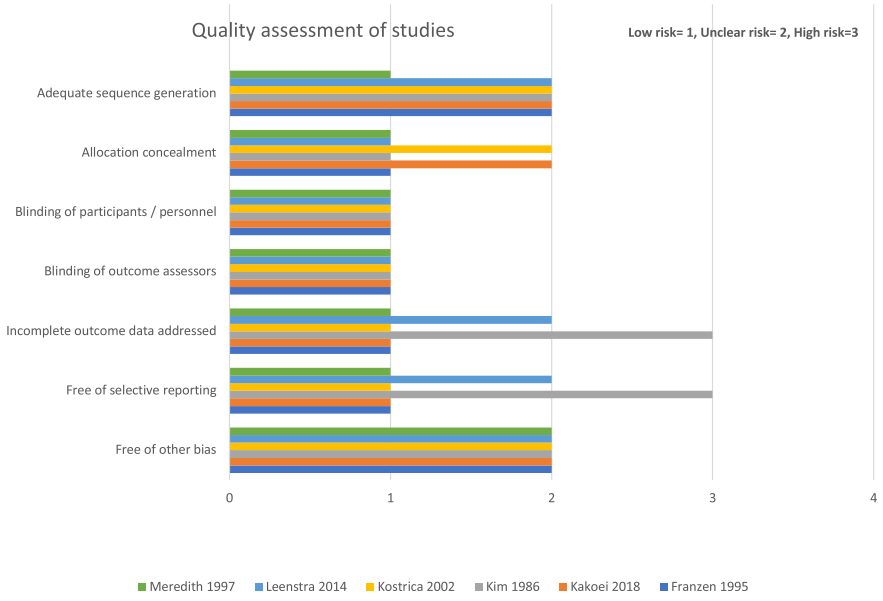


FIGURE 2 Risk of Bias of studies

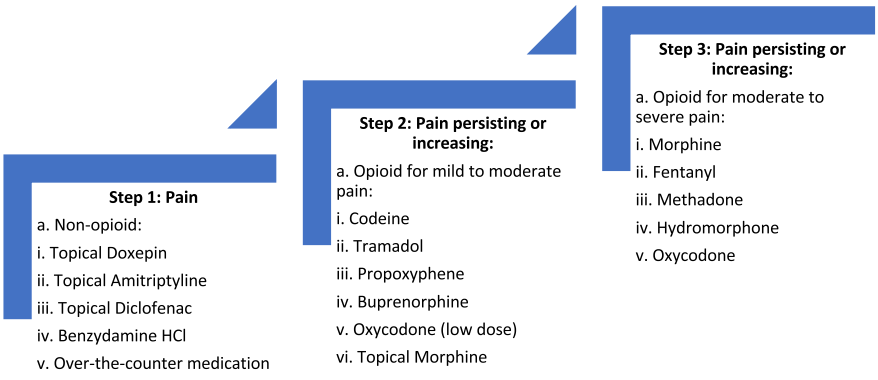
alcohol and can become intolerable to patients as they progress through radiotherapy, with commonly reported side effects of burning and stinging. It is recommended that if oral burning occurs with use, that diluting the rinse with water may allow continuing use. Furthermore, benzydamine is not readily available in the USA.

There are a number of limitations in this systematic review. This review's strict inclusion criteria impacted the selection of papers included in the review, which may have resulted in the omission of studies that support a range of potentially important interventive pain control measures. There are likely other interventions trialed to manage radiation-induced OM which may have positive outcomes, but did not meet this review's strict inclusion criteria. For the six trials in this review, a relatively small number of patients (441) contributed data with 20–69 patients per treatment or control group creating low statistical power to detect effect. The side effects experienced from radiotherapy can greatly be influenced by the modality of radiotherapy administered (Yao et al., 2007). In this review, some of the studies did not comment on the type of modality utilised (Kakoei et al., 2018; Kim et al., 1986; Kostrica et al., 2002), which can add further bias to the results. The comparisons of pain control regimes show a lack of duplication of studies by independent groups investigating the same interventions (Franzén et al., 1995; Meredith et al., 1997) which limits the strength of evidence and generalisability of the results.

The results from this review correspond to the guidelines from the current Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) recommendations (Lalla et al., 2014) in regard to the use of doxepin mouthrinse to treat pain due to oral mucositis and against the use of sucralfate to treat oral mucositis.

There has been a RCT which compared the efficacy of oral opioids to oral amitriptyline and showed that amitriptyline may aid in reducing radiation-induced OM pain (Ehrnrooth, Grau, Zachariae, & Andersen, 2001). Nevertheless, opioids were seen to be more effective and of faster onset. This study was excluded in this review due to lack of blinding (Ehrnrooth et al., 2001). Comparative studies of amitriptyline, doxepin and diclofenac with opioids are required to aid in demonstrating the level of effectiveness of these non-opioid agents. An increase in the number of topical trials for amitriptyline, doxepin and diclofenac is required to ensure that the positive results shown by these interventions in regard to pain management can be replicated. When developing these studies, trial designers need to consider that modifying concentration of the oral rinse with these agents may reduce the risk of severity of side effects. For example, systemic use of tricyclic antidepressant medications is typically conducted beginning at a low dose and increasing dose depending on the therapeutic effect or side effects. It is also known that the side effects of fatigue can decrease with continuing systemic use of tricyclic antidepressants, which may also occur with topical rinse application, and therefore, trial duration should be considered. Additionally, amitriptyline, diclofenac and doxepin can be used systemically; hence, studies evaluating effectiveness in pain management in response to systemic use should also be evaluated.

A comparison of the effectiveness between studies could not be undertaken due to the lack of consistency between studies. The pain scales commonly utilised in the evaluated studies were a numerical rating which ranged from (0 to 4) to (0 to 20). Various tools with numerical scales have been validated and can be considered in a model for pain assessment in radiation-induced OM. Such a model includes the Patient-Reported Oral Mucositis Symptom scale (PROMS; Kushner et al., 2008). A study has reported that patient-reported mouth pain was a responsive measure of the patient's clinical course of OM in a study of chemotherapy patients (Cella et al., 2003). Nevertheless, it may be incorrect to extrapolate this finding to radiation-induced OM due to differences in systemic manifestations which may also influence pain. This review utilised subjective patient pain scales rather than clinical OM scoring scales. Studies which commence pain evaluation at the time of onset of the pain may be of increased reliability rather than commencing at the first clinical signs of OM or at a particular time point, since variable awareness of pain is likely to exist between patients (Gussgard, Jokstad, Hope, Wood, & Tenenbaum, 2015). Pain scales with consistent time points for data collection should be used when testing new interventions.



Grading of evidence: Doxepin > Amitriptyline, Diclofenac > Benzydamine HCl

FIGURE 3 WHO analgesic ladder, modified for radiation-induced oral mucositis

The lack of appropriate instruments to assess OM has limited progress in research study data and OM management (Eilers & Epstein, 2004). Agreement is needed on standard tools to assess mucosal damage, and patients' reported outcomes including pain.

All of the interventions which met the inclusion criteria for this systematic review were topically administered. Oral agents such as amitriptyline, doxepin and diclofenac may also have similar effectiveness when administered orally rather than topically. Topical approaches have the potential advantage of local effect for locoregional symptoms and avoiding systemic side effects. Nevertheless, increased systemic absorption of topical agents is expected in erythematous and ulcerated mucosa.

The potential advantage of topical therapies with different mechanisms of action, for example nociceptive and neuropathic mechanisms, may become part of the first step in a ladder of pain management aiming to reduce opioid use that then includes opioid medications if symptoms advance whilst continuing the topical agents. Based on the findings from this systematic review, future randomised, double-blinded, placebo-controlled clinical trials on the utilisation of both topically and systemically administered doxepin or amitriptyline to manage pain in patients with radiation-induced OM should be undertaken. This will allow comparison of results of studies utilising the same intervention to further contribute evidence for or against the use of these interventions. High-quality comparative trials of opioids with doxepin or amitriptyline should also be undertaken. These comparative studies will be required to further answer the question as to whether use of opioids can be reduced or eliminated in the management of pain from radiation OM. Based on the results from this review, an analgesic ladder for radiation-induced OM has been proposed from modifications to the WHO analgesic ladder (Figure 3).

5 | CONCLUSIONS

The broad scope of interventions in the literature indicates the importance of effective OM management to clinicians and the uncertainty of how to manage OM pain optimally. This review showed doxepin mouthrinse, amitriptyline mouthrinse, diclofenac mouthrinse and benzydamine mouthrinse to be of benefit in the management of OM pain. Of these interventions, doxepin mouthrinse was seen to have the highest quality of evidence, but this was still of moderate level. Hence, the use of non-opioid therapies may lead to improved pain management with the potential to reduce dose and duration of opioid medications in OM pain. Given the significant pain that OM causes to a population of patients receiving treatment for cancer, it is important that further RCTs which are of sufficient power and utilise a single validated and preferred OM scoring pain scale are undertaken. These trials should investigate potentially beneficial interventions which have not been adequately performed.

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CONFLICT OF INTEREST

None to declare.

AUTHOR CONTRIBUTIONS

J. Christoforou: Substantial contributions to the formulation of the subject area for review, the conception and design of the project, the screening and review of the studies, acquisition and interpretation of data and discussion of relevant findings. J. Karasneh, L. L. Patton: Substantial contributions to the conception and design of the project, the screening and review of the studies, acquisition and interpretation of data and discussion of relevant findings. M. Manfredi, B. Dave, P. D. Dios: Substantial contributions to the conception and design of the project, the acquisition and interpretation of data and discussion of relevant findings. J. Walker: Substantial contributions to the electronic database search strategies, screening and review of the studies. J. Epstein, N. Kumar, M. Glick, P. B. Lockhart: Substantial contributions to the conception and design of the project, the interpretation of data and discussion of relevant findings. J. Christoforou, J. Karasneh, M. Manfredi, B. Dave, J. Walker, P. D. Dios, P. B. Lockhart, L. L. Patton: Drafting, appraisal and final approval of the manuscript. J. Epstein, N. Kumar, M. Glick: Appraisal and final approval of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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APPENDIX A

Search	Query	Results
PubMed		
#1	(stomatitis[mesh] OR stomatitis[tw] OR mucositis[tw] OR Stomatitides[tw] OR Oromucositis[tw] OR mucosa inflammation[tw])	34,800
#2	(Radiotherapy[mesh] OR radiotherapy[tw] OR chemoradiotherapy[mesh] OR chemoradiotherapy[tw] OR chemoradiation[tw] OR radiation[mesh] OR radiation[tw] OR Chemoradiotherapies[tw] OR Radiochemotherapy[tw] OR Radiochemotherapies[tw])	947,715
#3	(pain[tw] OR soreness[tw] OR sore[tw] OR irritation[tw])	658,261
#4	((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])	5,032,449
#5	#1 AND #2 AND #3 AND #4	454
#6	(#1 AND #2 AND #3 AND #4) AND English[Language] NOT (Animals [mesh] NOT Humans [mesh])	409
Embase		
#1	('oral mucositis'/exp OR 'stomatitis'/exp OR 'mucosa inflammation'/exp OR ('oral mucositis' OR stomatitis OR 'mucosa inflammation' OR mucositis OR Stomatitides OR Oromucositis):ab,ti)	84,057
#2	('radiotherapy'/exp OR 'chemoradiotherapy'/exp OR (radiotherapy OR radiation OR chemoradiotherapy OR Chemoradiotherapies OR chemoradiation OR radiochemotherapy OR Radiochemotherapies):ab,ti)	791,996
#3	('pain'/de OR (pain OR soreness OR sore OR irritation):ab,ti)	896,646
#4	'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR (random* OR factorial* OR crossover* OR cross NEXT/1 over* OR placebo* OR doubl* NEAR/1 blind* OR singl* NEAR/1 blind* OR assign* OR allocat* OR volunteer*):de,ab,ti	2,260,305
#5	#1 AND #2 AND #3 AND #4	490
	#1 AND #2 AND #3 AND #4 AND [english]/lim AND [humans]/lim AND [embase]/lim	435
Scopus		
#1	TITLE-ABS-KEY ("oral mucositis" OR stomatitis OR "mucosa inflammation" OR mucositis OR Stomatitides OR Oromucositis)	68,215

(Continues)

APPENDIX A (Continues)

Search	Query	Results
#2	TITLE-ABS-KEY (radiotherapy OR radiation OR chemoradiotherapy OR Chemoradiotherapies OR chemoradiation OR radiochemotherapy OR Radiochemotherapies)	1,739,540
#3	TITLE-ABS-KEY (pain OR soreness OR sore OR irritation)	1,073,501
#4	TITLE-ABS-KEY ("crossover procedure" OR "double-blind" OR "randomi?ed controlled trial" OR "single-blind" OR (random* OR factorial* OR crossover* OR cross W/1 over* OR placebo* OR doubl* W/1 blind* OR singl* W/1 blind* OR assign* OR allocat* OR volunteer*))	781,301
#5	(#1 AND #2 AND #3 AND #4)	416
#6	(#1 AND #2 AND #3 AND #4) AND (LIMIT-TO (LANGUAGE, "English ")	402
CINAHL		
S1	(MH "Stomatitis+") OR TI (Oral Mucositis OR stomatitis OR "mucosa inflammation" OR mucositis OR Stomatitides OR Oromucositis) OR AB(Oral Mucositis OR stomatitis OR "mucosa inflammation" OR mucositis OR Stomatitides OR Oromucositis)	5,103
S2	(MH "Radiotherapy+") OR (MH "Chemoradiotherapy+") OR (MH "Radiation+") OR TI (radiotherapy OR radiation OR chemoradiotherapy OR Chemoradiotherapies OR chemoradiation OR radiochemotherapy OR Radiochemotherapies) OR AB (radiotherapy OR radiation OR chemoradiotherapy OR Chemoradiotherapies OR chemoradiation OR radiochemotherapy OR Radiochemotherapies)	91,048
S3	(MH "pain+") OR TI (pain OR soreness OR sore OR irritation) OR AB (pain OR soreness OR sore OR irritation)	254,070
S4	placebo* OR random* OR "comparative stud*" OR clinical NEAR/3 trial* OR research NEAR/3 design OR evaluat* NEAR/3 stud* OR prospectiv* NEAR/3 stud* OR (singl* OR doubl* OR trebl* OR tripl*) NEAR/3 (blind* OR mask*)	450,892
S5	S1 AND S2 AND S3 AND S4	69
S6	S1 AND S2 AND S3 AND S4 Narrow by Language: - English	68