Narrative review of the management of oral mucositis during chemoradiation for head and neck cancer

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Abstract: Oral mucositis (OM) can be a significant problem for patients undergoing radiation or chemoradiation for head and neck cancer. In modern clinical trials, grade 3–4 OM can be seen in over 40% of patients and can cause a significant impact on their quality of life (QOL). Despite this fact, strategies for the prevention and treatment of OM vary widely, with options including both lifestyle modifications and pharmaceuticals. Here we evaluate and summarize the current clinical interventions for the management of radiation-induced OM. The majority of the current evidence focuses on reducing OM related pain. These agents are detailed over multiple clinical trials including treatment modalities such as: GC4419, doxepin mouthwash, diphenhydramine-lidocaine-antacid (DLA) mouthwash, gabapentin, and methadone. While several strategies have been employed to prevent radiation-induced OM, there is currently no strong evidence for the routine use of these agents in the clinic. After summarization of these treatments, we offer practical guidance for the treatment of OM in the clinic. We recommend a multiagent approach of pharmacological and non-pharmacological treatments including oral rinses, home humidification, escalating doses of gabapentin, doxepin or DLA mouthwash, over the counter analgesics, and lastly methadone. These interventions are tailored to address the expected increase of severity of symptoms during the course of head and neck radiotherapy.

Keywords: Radiation therapy; Head and Neck Cancer; oral mucositis (OM)

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Introduction

The majority of patients receiving chemoradiotherapy develop oral mucositis (OM), with reports demonstrating grade 3 or higher OM in over 40% of patients despite modern radiotherapy techniques (1-3). OM has several distinct phases of evolution that can result in severe pain (4). Subsequently, OM may cause dysphagia, an increase in aspiration risk, weight loss leading to feeding tube placement, and a decrease in quality of life (QOL), culminating in the potential for an increase in treatment breaks, hospitalizations, and medical care costs (5-13).

As reviewed in Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology (MASCC/ISOO), multi-agent combination oral care protocols have been shown to have efficacy for the prevention of OM during head and neck radiation therapy (14). However, these interventions largely focused on patients treated with radiation alone (15,16). Overall, several interventions for the prevention and treatment of OM, including professional oral care, multi-agent combination oral care protocols, and

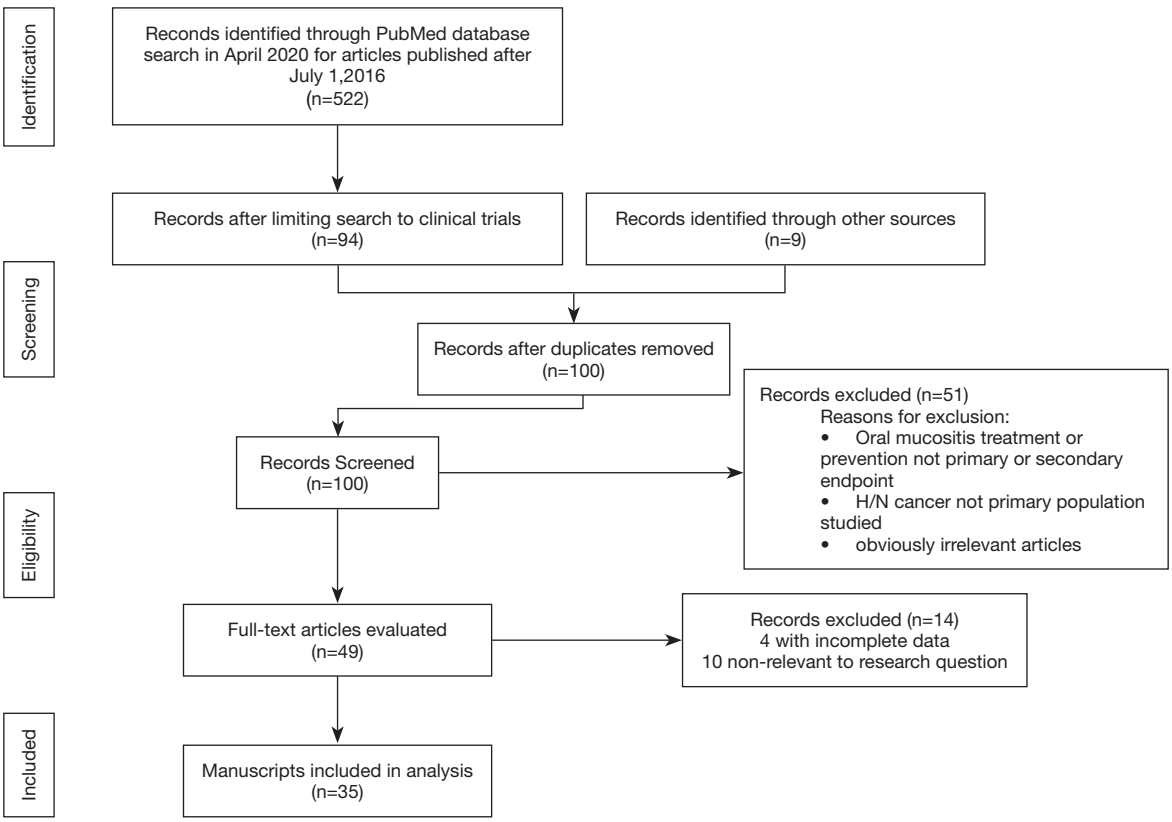

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

various rinses have been described (17).

Despite these overarching reviews, practical guidance on either the particular agent(s) to deploy or when to deploy them during the course of mucositis remains elusive (14,17). Furthermore, several additional treatments for OM during chemoradiation for head and neck cancer, including GC4419 (18), doxepin mouthwash (19), diphenhydramine-lidocaine-antacid (DLA) mouthwash (19), gabapentin (20), and methadone (20), have been published since the MASCC/ISOO review.

We performed this review to evaluate treatment with these newer agents and offer practical guidance on how and when to deploy a therapy. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/atm-20-3931).

Methods

In April 2020, the PubMed database was searched for articles detailing the clinical management of OM in head and neck cancer published after July 1 2016, as prior to that Hong *et al*. detailed interventions for OM. The goal of this search was to identify studies in which OM prevention and/or treatment was a primary or secondary endpoint in head and neck cancer. Author LJ was responsible for the initial search, exclusion, and final assembly of included articles. Keywords utilized for search were "mucositis", "head and neck neoplasms", with the search query defined as ((((“mucositis”[MeSH Terms]) OR “mucositis”[Title/Abstract])) AND (((“head and neck neoplasms”[MeSH Terms])) OR (“head and neck”[Title/Abstract]))) AND (“2016/07/01”[Date - Publication]: “3000”[Date - Publication]), which returned 522 results.

Results

The above search criterion identified 522 studies, of which 94 were human studies (*Figure 1*). In addition, we identified 9 clinical trials from the personal reference library of AS. The results from these databases were combined and 3 duplicates were removed for a total of 100 clinical trials. Of these studies, 51 were excluded because either (I) OM

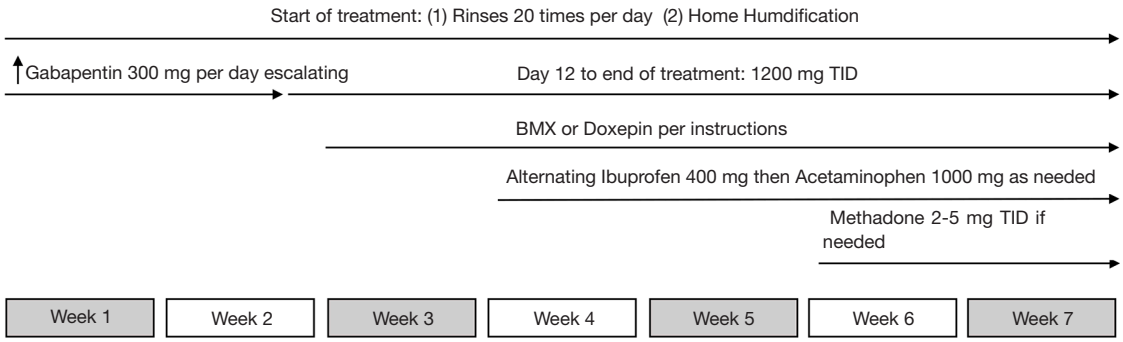

Figure 2 Oral mucositis intervention timeline.

treatment or prevention was not a primary or secondary endpoint, (II) Head and neck cancer was not the primary population studied, or (III) Study was otherwise not relevant to OM. Upon further examination of the full text, 14 additional trials were excluded as ultimately the study was not relevant or there was incomplete data for this review. Ultimately, a total of 35 clinical trials were included in this review.

Discussion

This review summarizes the literature since 2016 for the management of OM in head and neck cancer patients. Moreover, we synthesize the literature into a practical guideline of how to integrate various clinically available therapies to mitigate OM during chemoradiation therapy for head and neck cancer.

A multi-agent approach, in agreement with previous recommendations (14), remains necessary. The rational combination of agents should be designed to optimize both short- and long-term pain relief (*Figure 2*). This is illustrated and explained as a 1-page hand out in Appendix 1.

We recommend initiating home humidification, oral rinses and gabapentin at the beginning of treatment. Macann *et al.* treated patients used humidifiers overnight with additional use throughout the day from the first day of RT for 12 weeks (21). Humidification was found to result in a decrease in the development of functional mucositis. Additionally, treated patients had lower feeding tube use, and a lower risk of being admitted to the hospital. However, patient compliance was an issue. Many patients already have treatment for sleep apnea and their positive pressure devices may achieve some of this effect. Anecdotally, patients also report some benefit with a cool mist humidifier placed by the bed.

The importance of mucosal hydration in ameliorating toxicity is consistent with data showing that in the middle of radiation therapy, patients with worse mucositis pain also have worse dehydration (22). Intravenous fluids during this period can significantly and immediately reduce this pain (Rivers *et al.*, manuscript submitted).

Saline oral rinses in our case are composed of tap water, sodium chloride, and sodium bicarbonate with recommended daily rinses of at least 20 times a day (Appendix 1). Oral care is commonly recommended to reduce the incidence of OM, however this is not based on strong evidence (14). However, they are commonly used, helpful for oral hygiene, and appear to be otherwise harmless. Clinically, while we are quite vigilant about the use of prescription medications, we understand the weakness of the oral care data and only adamantly require its' use in those patients with a large increase in mucus.

Gabapentin, originally developed as an anti-convulsant agent, has been shown to have efficacy in the treatment of neuropathic pain (23). Sharp *et al.* found that gabapentin reduced mucosal neuropathy in two patients who had a received a trial of gefitinib and paclitaxel (24). Gabapentin should be slowly escalated from 300 daily to 1,200 mg three times per day. The use of high dose gabapentin is based on the experience of our on-going current study and Hermann *et al.* who found that high dose gabapentin resulted in a significantly greater percentage of patients never requiring opioids (42% *vs.* 7%, P=0.002) (20) (ClinicalTrials.gov identifier NCT 03547492). Several prospective trials demonstrated that gabapentin can reduce the need for enteric feeding tubes and narcotics, as well as improve QoL despite no significant impact on OM incidence or severity (20,25-27). While gabapentin does require an initial dose escalation, overall it has a favorable

side-effect profile. As such, we recommend the use of prophylactic gabapentin in this setting. Gabapentin is renally excreted and the total dose should be limited in those with a baseline creatinine clearance below 60 milliliters/minute. In practice we have not had any toxicities in those patients taking 3,600 mg daily who were later found to have asymptomatic cisplatin induced acute renal failure; this was treated with intravenous hydration and monitoring without change in the gabapentin dose.

At the development of symptomatic OM, we recommend initiating either doxepin or DLA mouthwash. DLA can be used as a mouth and/or throat wash, or used to treat select sore areas via a sponge stick. Sio *et al*. evaluated the use of doxepin or DLA mouthwashes for the reduction of OM related pain (19). Both interventions were successful at reducing pain at 4 hours without significantly impacting median overall pain scores. The study was not designed to make comparisons between each agent, therefore we recommend either doxepin or DLA mouthwashes for short-term OM-related pain.

When pain is no longer adequately controlled via this regimen, we recommend introducing alternating doses of ibuprofen and acetaminophen. Patients are instructed to start Ibuprofen 400 mg and 4 hours later, take Acetaminophen 1,000 mg. This can be repeated every 6–8 hours however maximum recommended daily dose of Acetaminophen is 3,000 mg. There is no current guideline regarding the use of over-the-counter analgesics such as ibuprofen or acetaminophen (14). These medications have a well-established role for pain-relief however the role in the treatment of OM is unclear. Nevertheless, given the favorable side-effect profile and potential to relief OM-related pain, it is reasonable to utilize these medications in this setting.

In the last weeks of treatment, many patients have difficulty achieving adequate pain relief and require narcotics. We recommend methadone 2 mg three times a day to supplement the above regimen. In our experience it is rare to require more than 5 mg of methadone three times per day and we have never escalated a patient beyond 10 mg three times per day. Methadone may be more effective for neuropathic pain and unlike other opiates, methadone has a long half-life, therefore providing prolonged pain relief (28). Methadone, when used in conjunction with gabapentin, improves pain control and several QoL/function metrics (20,29). While it is unclear whether high dose gabapentin adds additional benefit to methadone, we recommend the use of methadone for pain relief in patients not well controlled on high dose gabapentin and over-counter-analgesics. Additionally, in order to reduce opioid-constipation, we recommend a stool softener with laxatives as needed to be taken in conjunction with methadone.

Methadone is thought to work in minimizing neuropathic pain due to its action on the N-Methyl-D-Aspartate receptor (20). Methadone also has a long half-life, which provides long acting pain relief (28). Haumann *et al*. ran two RCTs to compare the use of methadone to fentanyl in both nociceptive and neuropathic pain domains in OM. Opioid-naïve patients reported significantly decreased average pain with the use of methadone at 3 weeks of treatment (29). In addition, all measures demonstrated noninferiority of methadone to fentanyl, with no difference in side effect profile. Likewise, in a neuropathic pain focused trial, patients reported significantly decreased average pain with the use of methadone at weeks 1 and 3 of treatment (30). Hermann *et al*. found that use of methadone lowered total narcotic requirements and significantly improved several QOL domains (20).

In terms of OM prevention, there are no well-validated strategies to significantly reduce the development of OM. While modern techniques for radiation therapy have increased capacity for tissue sparing, often a significant dose to the head and neck mucosa is unavoidable due to its proximity to tumor and electively covered regions (31). Another common approach of radioprotection is to mitigate the radiation-induced damage through reduction and/or quenching of reactive-oxygen species. Initial studies of GC4419 have shown a reduction of incidence, duration, and severity of OM (18,32). Results from a phase 3 study, currently underway, are eagerly anticipated. However, this compound requires daily infusions which may limit its use by some patients or physicians.

Reports examining amino acid & amino acid derivatives for OM are either preliminary or have shown no benefit (33-41). Similarly, no recommendation can be made on the use of alternative therapies. Low-level laser therapy (LLLT) has promising limited data which requires additional study; however, LLLT requires technology which is not widely available (42,43). Similarly, the other positive clinical trials reported in *Table 1* merit further consideration and research but are not yet widely clinically applicable.

Additional interventions which are not directly related to OM can still benefit patients. The use of NSAIDs was recently shown to be associated with an improvement in overall survival in head and neck cancer patients (70). As such, we recommend that patients take a low-dose or baby aspirin

Table 1 Trials reported for oral mucositis interventions

Intervention	Type	Modality	Indication	Effectiveness						Participants	Key findings	Author, Year
				OM incidence	OM Severity	Duration	Pain severity	Pain duration	Overall QoL			
Amino acids & amino acid derivatives												
D-Methionine	Prospective	CT & RT	Prevention	Y	N					29 treated, 29 control	Lower rate of overall mucositis	Hamstra 2018 (34)
											No difference in amount of grade 3/4 OM	
Dusquetide	Prospective	CT & RT	Prevention			Y				41 treated with 1.5 mg/kg, 3 treated with 3.0 mg/kg, 24 treated with 6.0 mg/kg, 43 control	Reduced duration of OM	Kudrimoti 2016 (35)
Glutamine	Prospective	RT	Prevention		N					31 treated, 33 placebo	No difference in severity of OM	Huang 2019 (44)
HMB/Arg/Gln	Prospective	CT & RT	Prevention	N		Y				35 treated, compared against previous opioid based pain control and oral car programs	No difference in incidence of grade 3 or greater OM	Yokota 2018 (39)
											Reduced duration of OM	
Rebamipide	Prospective	CT & RT	Treatment	Y*						31 treated with 2%, 32 treated with 4%, 31 control	Decreased incidence of grade 3 OM*	Yokota 2017 (40)
Rebamipide	Prospective	CT & RT	Prevention		Y	Y (onset)				30 treated, 30 control	Delay of 3.5 days in the onset of OM	Chaitanya 2017 (33)
											Decreased OM pain score	
Benzydamine HCl	Prospective	CT & RT	Prevention		Y		N			30 treated, 30 control	Lower median OM Assessment Scale score	Chitapanarux 2018 (45)
	Prospective	CT & RT	Prevention	Y**						62 treated (29 RT only, 33 CRT), 58 control (28 RT only, 30 CRT)	Decreased incidence of grade 3 OM in RT only group, no difference in incidence in CRT group**	Rastogi 2017 (46)
Caphosol	Prospective	CT & RT	Prevention	N		N				108 treated, 107 control	No difference in the incidence of severe OM	Wong 2017 (47)
											No difference in duration of severe OM	
Clonidine Mucoadhesive Tablets	Prospective	CT & RT	Treatment	Y*		Y* (onset)	N			56 treated with 50ug, 65 treated with 100ug, 62 control	Decreased incidence*	Giralt 2020 (48)
											Later onset of OM*	
											No difference in mouth or throat soreness	
Doxepin Mouthwash	Prospective	CT & RT	Treatment				Y			92 treated, 92 control	Decreased OM pain score, but not clinically significant	Sio 2019 (19)
Diphenhydramine-Lidocaine-Antacid	Prospective	CT & RT	Treatment				Y			91 treated, 92 control	Decreased OM pain score, but not clinically significant	Sio 2019 (19)
Education Programme	Prospective	CT & RT	Treatment				N		N	51 treated, 45 control	Better physical & social-emotional QoL, no difference on overall QoL	Huang 2018 (49)
											No difference in severity of symptoms of OM	
Gabapentin	Retrospective	RT	Prevention & Treatment				Y			30 treated, median dose 2700 mg	Only 10% of patients used narcotic pain medication during the third and fourth weeks of treatment despite 56% and 73% of patients having grade 2+ OM	Bar Ad 2010 (25)
											Only 35% of patients used narcotic pain medication during the fifth and sixth weeks of treatment despite 80% have grade 2+ OM	
	Retrospective	CT & RT	Prevention & Treatment				Y			42 treated, median dose 2700 mg	Only 33% of patients used narcotic pain medication during the third weeks of treatment despite 71% of patients having grade 2+ OM	Bar Ad 2010 (26)
											Only 55% of patients used narcotic pain medication during the third weeks of treatment despite 86% of patients having grade 2+ OM	
											Only 71% of patients used narcotic pain medication during the fifth and sixth weeks of treatment despite 95% and 100% having grade 2+ OM	

Table 1 (*continued*)

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Intervention	Type	Modality	Indication	Effectiveness						Participants	Key findings	Author, Year
				OM incidence	OM Severity	Duration	Pain severity	Pain duration	Overall QoL			
	Retrospective	RT	Prevention & Treatment				Y			31 treated, 33 controls	Less weight loss	Dong 2016 (50)
											Later initiation of narcotic medication	
	Prospective	CT & RT	Prevention & Treatment				Y			2 treated	Reduction in dysesthesia despite OM	Sharp 2008 (24)
	Prospective	CT & RT	Prevention & Treatment				Y	Y	Y	23 treated	Later initiation of PEG tube use	Starmer 2014 (27)
											Earlier cessation of PEG tube use	
											Lower PAS scores	
											Higher FIOS scores	
	Prospective	CT & RT	Prevention & Treatment				Y			31 treated with 2700 mg gabapentin + standard of care, 29 treated with 900 mg dose + methadone	Later initiation of narcotic medication	Hermann 2020 (20)
											Higher number of patients never needing opioids	
	Prospective	CT & RT	Treatment				N	N		11 treated, 11 control	Less weight gain	Kataoka 2016 (51)
											No difference in OM pain score	
											No difference in initiation of opioids	
											No difference in median total dose of opioids	
GC4419	Prospective	CT & RT	Prevention & Treatment	Y	Y	Y				73 treated with 30 mg dose, 76 treated with 90 mg dose, 74 control	90mg dose reduced OM duration, incidence and severity	Anderson 2018 (18)
											40mg dose reduced OM duration, incidence and severity*	
Indomethacin Spray	Prospective	CT & RT	Treatment				Y			35 treated	Decrease in pain score after applying treatment	Momo 2017 (52)
Lactobacillus Brevis CD2	Prospective	CT & RT	Prevention	N					N	32 treated, 36 control	No difference in incidence of severe OM	De Sanctis 2019 (53)
											No difference in QoL or weight loss	
LLLT	Prospective	CT & RT	Prevention	N		Y* (onset)	N		N	42 treated, 41 control	No difference in incidence of grade 3 OM	Legouté 2019 (54)
											Later onset of OM*	
											No difference in overall QoL measures	
											No difference in OM pain scores	
	Prospective	CT & RT	Prevention	Y		Y				11 treated, 15 control	More grade 0 OM during week 1	Marín-Conde 2019 (42)
											Decreased duration of clinical OM	
Methadone	Prospective	CT & RT	Treatment				Y			26 treated, 26 control	Decreased OM pain score at weeks 1, 3 & 5, significant at weeks 1 & 3 compared to Fentanyl	Haumann 2016 (30)
	Prospective	RT	Treatment				Y			42 treated with methadone, 40 treated with fentanyl	Noninferiority of Methadone to Fentanyl for pain reduction at weeks 1 and 3	Haumann 2018 (29)
	Prospective	CT & RT	Treatment				N		Y	29 treated with 900 mg dose + methadone, 31 treated with 2700 mg gabapentin + standard of care	Reduced insomnia	Hermann 2020 (20)
											Reduced fatigue*	

Table 1 (*continued*)

Table 1 (*continued*)

Intervention	Type	Modality	Indication	Effectiveness						Participants	Key findings	Author, Year
				OM incidence	OM Severity	Duration	Pain severity	Pain duration	Overall QoL			
											Less total narcotic use	
											Better physical, social and role functioning at 1 year	
											Better swallowing, fewer speech problems, less trouble with social eating, less trouble opening mouth, less sticky saliva	
N-Acetylcysteine Rinse	Prospective	CT & RT	Treatment				Y*			15 treated, 17 control	Decreased OM pain score	Sio 2019 (55)
Natural Medicine/Alternative Therapies												
Black Mulberry	Prospective	RT	Prevention	Y	Y				Y	38 treated, 42 control	Decreased incidence of OM	Demir Doğan 2017 (56)
											Decreased severity of OM	
Humidification	Prospective	RT	Treatment							20 treated, 19 control	Decrease in functional mucositis	Macann 2017 (21)
Licorice Mucoadhesive Film	Prospective	RT	Treatment				Y			30 treated	Decreased mean OM pain score	Ghalayani 2017 (57)
Melatonin	Prospective	CT & RT	Treatment			Y (onset)				19 treated, 20 control	Later onset of grade 3 OM	Onseng 2017 (58)
											Decreased opioid usage	
Nanomicelle Curcumin	Prospective	RT	Prevention		Y	Y (onset)				16 treated, 16 control	Later onset of grade 1 OM	Delavarian 2019 (59)
											Decreased severity of OM	
											Less weight loss	
Natural Mixture	Prospective	CT & RT	Prevention	N	N		N			53 treated, 51 control	No difference in the incidence of grade 3 OM	Marucci 2017 (60)
											No difference in OM pain scores	
Probiotics	Prospective	CT & RT	Prevention		Y					64 treated, 35 placebo	Decreased incidence of grade 3/4 OM	Jiang 2019 (61)
											Increased number of CD4+, CD8+, and CD3+ T-cells	
Silymarin	Prospective	CT & RT	Prevention		Y	Y (onset)				15 treated, 15 control	Decreased OM grade	Elyasi 2016 (62)
											Later onset of OM	
Thyme Honey	Prospective	CT & RT	Treatment		Y				Y	43 treated, 43 control	Less weight loss	Charalambous 2018 (63)
											Better QoL	
											Lower grades of OM	
Traditional Chinese Medicine (CHIN)	Prospective	CT & RT	Treatment		Y		Y			35 treated, 35 control		Wang 2018 (64)
											Decreased oral pain	
											Decreased OM grade	
											Decreased xerostomia	
Zataria Extract	Prospective	CT & RT	Treatment		Y		Y			31 treated, 33 control		Aghamohammadi 2018 (65)
											Decreased incidence of grade 3/4 OM	
											Decreased OM pain score	
Oral Care	Prospective	CT & RT	Prevention	N						120 treated	No difference in incidence of OM	Yokota 2016 (66)
	Prospective	CT & RT	Prevention	Y**						60 treated (18 RT alone, 42 CRT), 64 control (19 RT alone, 45 CRT)	Decreased incidence in RT only group, no difference in incidence in CRT group	Kawashita 2019 (67)

Table 1 (*continued*)

Table 1 (*continued*)

Intervention	Type	Modality	Indication	Effectiveness						Participants	Key findings	Author, Year
				OM incidence	OM Severity	Duration	Pain severity	Pain duration	Overall QoL			
Platelet Gel Supernatant (PGS)	Prospective	CT & RT	Prevention & Treatment		Y	Y (onset)	Y		Y	16 treated, 64 control	Decreased incidence of grade 3/4 OM	Bonfili 2017 (68)
											Later onset of OM	
											Less weight loss and feeding tube use	
											Decreased opioid usage	
											Higher QoL	
											Decreased mouth and throat soreness	
Transcutaneous Electrical Nerve Stimulation (TENS)	Prospective	RT	Treatment				Y			40, all received one treatment TENS, one placebo TENS and one no TENS control session	Reduced resting pain	Lee 2019 (69)
											Reduced fatigue	
Triamcinolone Mucoadhesive Film	Prospective	RT	Treatment				Y			30 treated	Decreased OM mean pain score	Ghalayani 2017 (57)

*, did not reach statistical significance; **, statistical significance in RT group only, not CT + RT group.

prior to and indefinitely after therapy. Radiation dermatitis is a distinct entity from OM, however it can contribute to the overall pain profile of a patient. Barrier ointments are frequently used to treat radiation dermatitis (71).

There are limitations to this review. We recognize that some of the interventions, namely humidification, saline rinses, and over the counter analgesics, are not based on rigorous studies. Nevertheless, we feel that these recommendations are reasonable based on clinical experience and the relative benign nature of the treatment.

In conclusion, this review highlights a variety of different clinical interventions aimed at alleviating OM in head and neck cancer, favoring a multi-agent approach to this difficult problem. Non-pharmacologic interventions such as humification and saline rinses can be started immediately which may provide symptom relief without potential harm to the patient. Mitigation of OM-related pain can also begin immediately via a tapered increase of Gabapentin. As an adjunct, medicated mouthwashes such as DLA or doxepin can be used for short-term pain relief to aid in eating and drinking. Other strategies to improve pain control during the course of treatment include over the counter analgesics, followed by methadone if OM-related pain continues to be poorly controlled. Future studies include investigating whether other agents for neuropathic pain, such as the selective norepinephrine uptake inhibitors, can be effective in treating OM-related pain. Currently, we are exploring whether the addition of venlafaxine to the gabapentin regimen improves pain control and reduces opioid use in the treatment of head and neck cancer.

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