

Addressing Pain in Oral Mucositis: Narrative Review of Current Practices and Emerging Treatments

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Objective: Oral mucositis (OM) is a debilitating complication of cancer therapies, affecting up to 85% of patients undergoing bone marrow transplantation and nearly all receiving head and neck radiotherapy. Characterized by mucosal inflammation, ulceration, and severe pain, OM significantly impairs oral intake, speech, and quality of life. These disruptions, compounded by complications such as infection, bleeding, and increased healthcare costs, often necessitate treatment delays or modifications, negatively impacting cancer prognosis. Recent insights into nociceptive and neuropathic mechanisms of OM-related pain have led to the development of innovative management strategies. Given the debilitating nature of OM in cancer patients and the critical need for effective pain control, this review aims to examine pharmacological advancements targeting the complex nature of OM-related pain, including agents such as lidocaine, doxepin, benzydamine, methylene blue, opioids, gabapentin, palifermin, caphosol, and ketamine.

Methods: A literature search was conducted in the PUBMED, COCHRANE, and MEDLINE databases, covering studies from 2000 to 2024. Studies focusing on OM pathogenesis and pain management strategies were screened. Inclusion criteria encompassed randomized controlled trials, meta-analyses, and systematic reviews involving adult patients treated with lidocaine, doxepin, benzydamine, methylene blue, opioids, gabapentin, palifermin, caphosol, or ketamine for OM-associated pain.

Conclusion: OM pain arises from nociceptive and neuropathic pathways involving inflammatory cytokines and neuropeptides. Current interventions, including topical and systemic agents, have shown promise, yet variability in treatment protocols and limited high-quality evidence hinder standardized practices. This review highlights the clinical applicability of emerging therapies, such as avasopasem manganese, which has demonstrated efficacy in mitigating OM progression. Ongoing clinical trials targeting novel pathways that modulate mucosal inflammatory response and limit disease severity offer hope for improved pain relief. Addressing the multifaceted nature of OM-associated pain is essential for enhancing quality of life and optimizing cancer treatment outcomes. Further research is needed to establish robust, evidence-based guidelines for OM pain management.

Keywords: oral pain, head and neck cancer, mucosal ulceration, pain management, mouth washes, oral mucositis

Introduction

Oral Mucositis (OM) is a condition characterized by mucosal damage that can range from mild inflammation to deep ulceration of the oral mucosa.¹ OM can develop because of radiotherapy, chemotherapy, combined radio/chemotherapy, or stem cell transplantation.² OM-related pain is frequently reported among the most common and distressing symptoms experienced by patients during cancer therapy.³ It significantly impacts quality of life and affects up to 40% of patients receiving chemotherapy, up to 85% of patients undergoing bone marrow transplantation, and nearly all patients receiving head and neck radiotherapy.^{3,4} OM-related pain arises primarily from direct cytotoxic injury to the oral mucosa and the subsequent activation of inflammatory pathways. This damage leads to the release of pro-inflammatory cytokines and mediators, which sensitize peripheral nociceptors and contribute to neuroplastic changes that perpetuate pain symptoms. Consequently, current treatment strategies focus on targeting both inflammatory and neuromodulatory pathways to effectively alleviate pain.⁵

Patients with poor oral hygiene, concomitant chemotherapy, obesity, smoking, and drinking history are at higher risk for developing radiation-induced OM.⁶ The severity of OM is influenced by both the type and dosage of antineoplastic therapy. For example, severe OM is frequently observed following myeloablative conditioning regimens for hematopoietic stem cell transplantation (HSCT). Approximately 70% of patients receiving cyclophosphamide-based regimens in combination with total body irradiation (TBI) develop severe OM. Similarly, more than one-third of patients undergoing BEAM (carmustine, etoposide, cytarabine, melphalan) conditioning therapy experience heightened OM severity.⁷ Certain chemotherapeutic agents also carry differing risks: the antimetabolite 5-fluorouracil (5-FU) is associated with a higher incidence of OM compared to the fluoropyrimidine S-1.⁸ In patients receiving head and neck radiation therapy, OM severity is determined by factors such as the cumulative radiation dose, the specific area irradiated, and the use of concurrent chemotherapy. Total radiation doses exceeding 39 grays (Gy) to the oral cavity are linked to prolonged OM duration, and cumulative doses greater than 60 Gy in patients with head and neck cancer are associated with a higher incidence of severe OM.^{9,10} However, advanced techniques such as intensity-modulated radiation therapy (IMRT) have been shown to reduce the progression and severity of OM compared to traditional three-dimensional conformal radiation therapy (3D-CRT).¹¹

In addition to pain, OM can cause significant difficulties with eating and swallowing, often necessitating enteral or parenteral nutritional support.¹² The onset of OM is characterized by oral mucosal erythema accompanied by burning and numbness. However, as OM progresses, the clinical presentation can vary significantly among patients, with most developing deep ulcerations in areas such as the floor of the mouth, soft palate, and lateral aspects of the tongue. The severity and nature of pain can differ depending on the extent and location of mucosal involvement.^{13,14}

More importantly, severe OM can result in delays, interruptions, or modifications to planned cancer treatment regimens, potentially impacting the overall prognosis of cancer.¹⁵

Severe pain associated with OM can have profound consequences, potentially disrupting a patient's cancer treatment course. Studies show that approximately 30% of patients with advanced mucositis are forced to discontinue their treatment regimens due to the debilitating pain and other associated conditions such as bacteremia (particularly in neutropenic patients) and bleeding. The additional hospital costs for patients diagnosed with high-grade oral mucositis in the context of HSCT are estimated to be \$42,000.⁵ In patients with solid tumors who receive myelosuppressive chemotherapy, cost increments range from \$2,500 for mild mucositis to \$5,500 for severe mucositis per chemotherapy cycle.¹⁶ These costs stem from the need for supplementary nutritional support, increased analgesic prescriptions, and extended hospitalizations, further compounding the financial and emotional burden on patients. Mucositis, therefore, not only leads to prolonged hospital stays but also places a significant financial strain on both patients and healthcare systems.

OM presents a significant challenge in pain management, particularly as its severity progresses. While various interventions, such as oral rinses or mucosal agents containing topical anesthetics and analgesics, may offer some relief in mild cases, they often fail to provide sufficient pain control as the condition intensifies. Currently, there is no curative treatment for OM; thus, ongoing research and the development of novel therapies are critically important. Consequently, systemic analgesics—including opioids, antidepressants, anticonvulsants, and others—have been investigated for their effectiveness in achieving adequate pain relief. This review focuses on the pharmacological management of OM-associated pain, discusses the challenges inherent in its treatment and highlights promising advancements aimed at enhancing pain control for this patient population.

Methodology

We aimed to investigate the therapies used for treating OM-related pain in patients undergoing antineoplastic treatment. We conducted a literature review using the electronic databases PUBMED, COCHRANE, and MEDLINE, covering publications from 2000 to 2024. The review included randomized controlled trials, retrospective studies, meta-analyses, and systematic reviews. The search strategy utilized keywords and MeSH terms such as: (“oral mucositis” OR “stomatitis” OR “mucositis”) AND (“radiotherapy” OR “chemotherapy” OR “antineoplastic agents” OR “chemoradiotherapy”) AND (“lidocaine” OR “doxepin” OR “benzylamine” OR “methylene blue” OR “opioids” OR “gabapentin” OR “palifermin” OR “caphosol” OR “ketamine”). The initial database search yielded 1018 articles. Duplicates (n=520) were removed. Two independent reviewers screened the titles and abstracts (n=498), and disagreements, if present, were

resolved by a third reviewer. Subsequently, 252 articles were retrieved for full-text review. Studies with limited methodological rigor or investigating herbal compounds were excluded from further analysis. Articles were selected based on the following criteria: (a) studies were published in English, (b) studies involved adult participants, (c) the administration of lidocaine, doxepin, benzydamine, methylene blue, opioids, gabapentin, caphosol or ketamine targeted patients with cancer, and (d) the studies evaluated the effects of these medications on OM-related pain. Additionally, relevant studies cited in the reviewed articles were included in the analysis.

Discussion

Pathogenesis of OM

The pathogenesis of OM is complex and involves multiple factors. The current model of its development includes cytotoxic effects from chemotherapy drugs, disruption of epithelial junctional integrity, inflammation, myelosuppression caused by treatment, and alterations in the oral microbiota.

The pathogenesis of OM follows a complex five-phase process: initiation, upregulation, signal amplification, ulceration, and healing^{1,17} (Figure 1).

1. Initiation Phase: This phase begins with cellular and DNA damage induced by radiation and/or chemotherapy, which leads to the release of Reactive Oxygen Species (ROS) and results in the death of basal and submucosal epithelial cells.

2. Upregulation Phase: In this phase, the release of pro-inflammatory cytokines such as tumor necrosis factor α (TNF- α), interleukin-6 (IL-6), and interleukin-1 β (IL-1 β) occurs. These cytokines activate pathways that damage connective tissue, impair tissue oxygenation, and trigger cellular apoptosis.

3. Amplification Phase: Positive feedback mechanisms involving pro-inflammatory cytokines exacerbate tissue damage, further propagating the inflammatory response.

4. Ulceration Phase: Characterized by the formation of submucosal breaks, this phase allows for the invasion of microorganisms, increasing the risk of infection.

5. Healing Phase: The final phase involves re-epithelialization and tissue repair of the oral mucositis ulcerations, aiming to restore the integrity of the effected mucosal tissue.

Pain Perception Pathways

The etiology of OM pain is multifactorial. In oncology patients, OM-associated pain manifests through a combination of nociceptive and neuropathic mechanisms, reflecting both direct tissue injury and aberrant neuronal signaling (Figure 2). This dual pathogenesis highlights the need for analgesic strategies that target various aspects of the pain experience.

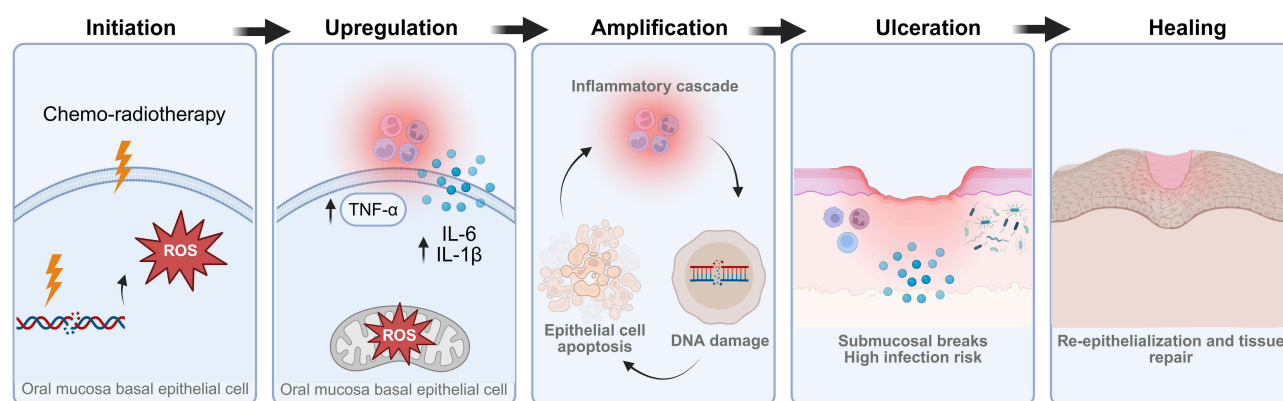


Figure 1 Oral mucositis pathogenesis. Exposure to antineoplastic treatments triggers DNA damage, reactive oxygen species (ROS) generation, and death of basal oral mucosa epithelial cells. Pro-inflammatory cytokine release impairs tissue oxygenation and activates pathways that exacerbate connective tissue damage and cellular apoptosis. The high infection risk can further aggravate mucosal ulceration once the submucosal breaks form in the oral mucosa lining. The final phase involves oral mucosa re-epithelialization and tissue repair. Created in BioRender. Ramirez, (M) (2025) <https://BioRender.com/o32c149>.

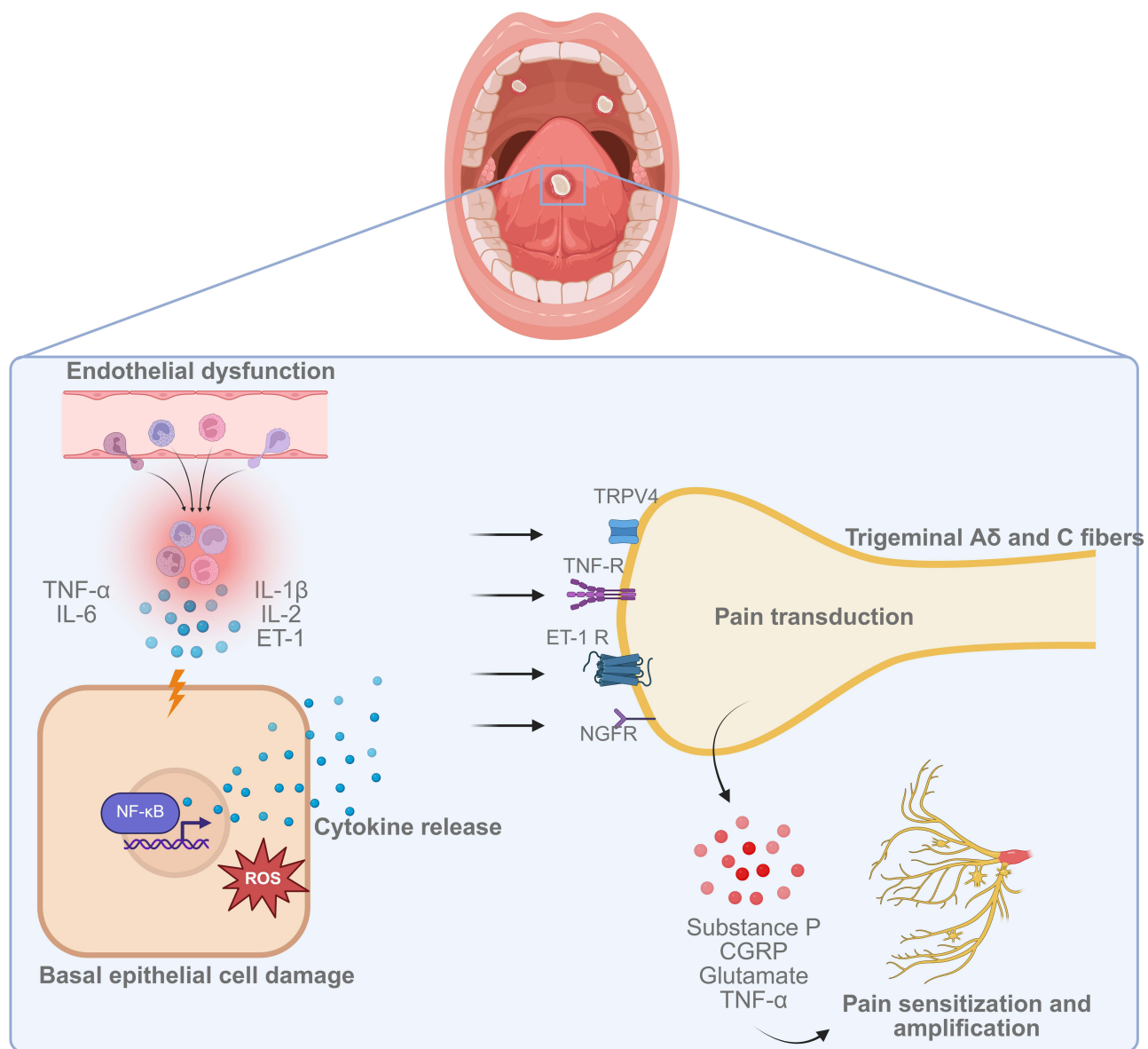


Figure 2 Nociceptive and neuropathic pain perception pathways in oral mucositis. Chemoradiation-induced mucosal injury leads to DNA damage, ROS generation, and proinflammatory cytokine release. TRP, ET-1, and TNF- α receptors in nearby A δ and C fibers initiate the pain transduction process upon cytokine stimuli. Endothelial dysfunction further aggravates the inflammatory cascade by NF- κ B pathway activation, with additional ROS and ET-1 release. The release of substance P, CGRP, glutamate, and proinflammatory cytokines sensitizes neurons and amplifies pain perception. ROS, reactive oxygen species; TRPV4, Transient Receptor Potential V4 channel; TNF-R, Tumor Necrosis Factor Receptor; ET-1, Endothelin-1; ET-1 R, Endothelin 1 receptor; CGRP, Calcitonin Gene-Related Peptide; NGFR, nerve growth factor receptor. Created in BioRender. Ramirez, (M) (2025) <https://BioRender.com/w20d434>.

Both nociceptive and neuropathic pain pathways can be involved in oral mucositis, and evidence suggests they may overlap rather than occur strictly sequentially. Nociceptive pain arises early due to direct tissue injury, inflammation, and ulceration, which expose and sensitize peripheral nerve endings. As the condition progresses, persistent inflammation, repeated tissue damage, and possible infection can lead to neuroplastic changes and nerve injury, resulting in neuropathic pain features such as burning or scalding sensations.¹⁸ Studies indicate that patients with oral mucositis often experience both types of pain simultaneously, especially during the ulceration phase when tissue breakdown and inflammation are most pronounced.¹⁹

Neuropathic pain does not necessarily occur only after nociceptive pain has subsided; rather, chronic inflammation and ongoing tissue injury can induce neuropathic mechanisms while nociceptive pathways remain active. Therefore, the two pain pathways frequently coexist in oral mucositis, contributing to the complex and persistent pain experienced by patients.

Nociceptive Pain

Nociceptive pain arises from actual or threatened damage to non-neural tissue in the oral mucosa. This pain is transmitted through A-delta fibers, and C fibers via the trigeminal system.²⁰ Epithelial cells in the oral mucosa initiate this process by secreting pro-inflammatory cytokines, including IL-1 β , IL-2, IL-6, and TNF α . These cytokines activate various receptors, such as Transient Receptor Potential (TRP) channels, endothelin-1 (ET-1) receptors, TNF α receptors, and Nerve Growth Factor (NGF) receptors. Of particular importance are the TRP channels, especially TRPV4 in the trigeminal ganglion, which contribute to mechanical hyperalgesia in OM. TRPV4 activation triggers the release of ET-1, a potent nociceptive molecule found at elevated levels in cancer patients experiencing pain.^{5,21} Concurrently, endothelial cell damage generates ROS, activating the NF- κ B pathway, which further stimulates ET-1 receptor activation and perpetuates the pain cycle.²²

NF- κ B activation also induces TNF α and cyclooxygenase-2 (COX-2), key components in pain pathways that are upregulated in chemotherapy patients with mucositis.²³ While TNF α blockade has shown promise in reducing pain from chemoradiation-induced OM, clinical trials of COX-2 inhibitors and prostaglandin antagonist oral rinses have not demonstrated significant pain relief.^{20,23,24} Neurotrophic factors like NGF, produced by oral cancer cells, are another potential therapeutic target for relieving nociceptive pain.²⁵

Neuropathic Pain

Persistent nociceptive stimuli in chronic OM-pain, and direct neuronal injury from chemoradiotherapy regimens, can induce neuroplastic changes that amplify neuropathic pain mechanisms.³ At the molecular level, neurogenic inflammation plays a critical role in pain sensitization associated with OM. Key inflammatory mediators include neuropeptides like substance P, Calcitonin Gene-Related Peptide (CGRP), Nerve Growth Factor (NGF), and pro-inflammatory cytokines such as glutamate, TNF-alpha, and interleukins.²⁶ These molecules, primarily released by Trigeminal A-delta (A δ) and C fibers, act as chemical messengers that communicate pain signals and sensitize neurons, amplifying pain perception and creating a self-perpetuating cycle of discomfort.

Pain Management Strategies

The standard approach to managing oral mucositis involves patient education, the use of oral rinses, both topical and systemic pain management, hydration, nutritional support, and infection prevention strategies. Pain management strategies for OM involve a comprehensive approach that targets both nociceptive and neuropathic components. Nociceptive pain, which arises from tissue damage, can be effectively managed with analgesic oral rinses, over-the-counter analgesics like acetaminophen and NSAIDs, as well as opioid medications. However, neuropathic pain often requires alternative therapies. In these cases medications like duloxetine (an antidepressant) and gabapentin (an anticonvulsant) are commonly utilized to address the underlying nerve dysfunction and provide pain relief.⁵

As outlined by the 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 shown efficacy in preventing OM.²⁷ The following section will explore the non-pharmacological and pharmacological treatment options for OM, as well as the latest emerging therapies under investigation to address this highly complex condition.

Non-Pharmacological Interventions

Oral cryotherapy (OC) is an inexpensive intervention with documented evidence on OM prevention. Its effects are mediated by local vasoconstriction, thereby limiting the toxic effects of systemic chemotherapy in the oral mucosa.^{28,29} The current MASCC/ISO guidelines recommend OC 30 minutes prior to a bolus of 5-FU chemotherapy, and as part of conditioning therapy for HSCT, including high-dose melphalan.²⁷ A recent umbrella review demonstrated that cryotherapy reduces the incidence of severe OM.³⁰ Furthermore, in patients undergoing HSCT, OC and photobiomodulation therapy (PBMT) reduced the incidence, severity, pain, and duration of OM.³¹

PBMT is a laser-based treatment with growing evidence for the prevention and management of OM. Preclinical investigations have demonstrated that PBMT influences tissue repair by activating fibroblast activity, thereby promoting extracellular matrix deposition in the injured mucosa. Moreover, PBMT increases ATP production and enhances

a cellular antioxidant state, leading to decreased reactive oxygen species (ROS) generation and tissue repair.^{32,33} The light-emitting diode (LED) beams are frequently administered intraorally for 30 to 60 seconds per point, with a wavelength range between 600–1000 nm.³² A recent systematic review and meta-analysis involving 14 RCTs evaluated the efficacy of PBMT in managing OM in patients with head and neck cancer. The authors demonstrated that PBMT significantly alleviated pain and decreased the incidence and disease severity of OM.³⁴

Overall, OC and PBMT decrease disease severity in patients with OM and are recommended by the MASCC/ISO guidelines for OM prevention in cancer patients undergoing HSCT. More clinical trials are needed to determine the extent of pain relief of these interventions among patients with HNC and different chemotherapeutic regimens.

Mouthwash Solutions

Lidocaine 2%

Lidocaine is a local anesthetic commonly used in clinical practice. Its principal mode of action involves the inhibition of sodium channels in neuronal fibers, which disrupts neural conduction and provides analgesia.³⁵ Lidocaine-based mouth rinses are frequently combined with other pharmacological agents, including anticholinergics, antacids/coating agents, antimicrobials, and antifungals, resulting in the formulation commonly known as “Magic Mouthwash”. Antacids and coating agents function to protect damaged mucosal surfaces, while anticholinergics such as diphenhydramine contribute an additional anesthetic effect.³⁶ These rinses are primarily employed for the initial symptomatic management of oral mucositis. However, the efficacy of oral rinses is often limited due to dilution in saliva and further shortened by swallowing, which reduces their duration of action.

In a recent longitudinal study of patients with nasopharyngeal cancer undergoing chemoradiotherapy, lidocaine 2% mouthwashes led to better pain control compared to benzydamine, bicarbonate, and nystatin solutions.³⁷ To our knowledge, few randomized controlled trials have assessed lidocaine-diphenhydramine-antacid efficacy in treating OM in cancer patients. The most recent study by Sio et al analyzed overall pain reduction following the use of a doxepin mouthwash or a lidocaine-diphenhydramine-antacid mouthwash compared to placebo in patients with radiotherapy-related mucositis. The lidocaine-diphenhydramine-antacid mouthwash and the doxepin mouthwash resulted in significantly reduced OM-related pain for 4 hours compared to placebo; however, the effect size was not clinically important.^{38,39}

Taken together, lidocaine-based mouth rinses may have a role in alleviating OM pain, but the Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISO) have made no recommendations for its use due to a lack of formula standardization and clinical trials assessing its effectiveness. More research is warranted to compare its effectiveness to placebo and in conjunction with different mouth rinses.

Doxepin

Doxepin is a tricyclic antidepressant widely used in the management of depression and anxiety disorders. Its therapeutic effect is primarily attributed to the inhibition of serotonin and norepinephrine reuptake at the presynaptic level, thereby increasing their availability in the synaptic cleft.⁴⁰ Beyond its antidepressant properties, doxepin has also shown potential anesthetic effects in animal models, believed to result from its sodium channel-blocking activity in nerve terminals.^{41,42} Several clinical studies have investigated doxepin’s effectiveness in treating pain associated with OM (Table 1); however, due to the limitations of these underpowered studies, the most recent MASCC/ISO guidelines did not recommend its routine use in clinical practice.

In a clinical trial involving 275 patients, Sio et al demonstrated that doxepin and lidocaine-diphenhydramine-antacid mouthwashes significantly reduced OM-related pain. However, significant adverse effects, including stinging and burning in the oral cavity and drowsiness, were reported in the doxepin group.³⁸ Overall, doxepin mouthwashes show potential for alleviating OM-related pain due to their local anesthetic properties. Ongoing clinical trials are investigating their efficacy and safety in clinical practice. Further research is needed to better understand the long-term safety profile and overall impact of doxepin in OM management.

Table 1 Clinical Studies Evaluating the Analgesic Effect of Doxepin in Patients with OM

Author	Year	Study Type	Intervention	Conclusion	Reference
Epstein et al,	2001	NRCT	A single dose of Doxepin 0.5% oral rinse and OM pain assessment	Doxepin 0.5% mouth rinse reduced pain by over 50% for more than 3 hours in patients with hematological and solid tumors undergoing chemotherapy and/or radiation therapy	[43]
Epstein et al,	2003	NRCT	A single dose of Doxepin 0.5% oral rinse in healthy volunteers	Doxepin 0.5% oral rinse exhibited significant local anesthetic effects in healthy subjects	[44]
Epstein et al,	2006	NRCT	A single dose of Doxepin 0.5% oral rinse and OM pain assessment	Doxepin 0.5% mouth rinse significantly reduced OM pain in a population of mixed types of cancers (hematological and solid tumors) undergoing chemotherapy and/or radiation therapy. Most patients exhibited pain relief within 15 minutes of oral rinse	[45]
Epstein et al,	2008	NRCT	Doxepin 0.5% mouth rinse 3–6 times daily in a one-week course	In patients with HNC who presented radiation-induced OM, and OM secondary to stem cell transplantation, Doxepin 0.5% oral rinse consistently reduced OM pain intensity over a one-week period of repeated dosing	[42]
Leenstra et al,	2014	Crossover RCT	Single dose Doxepin 0.5% mouth rinse vs Placebo mouth rinse Crossed over to receive the opposite treatment on day two	In patients with HNC undergoing radiation therapy with/without chemotherapy, Doxepin 0.5% oral rinse significantly reduced OM pain	[46]
Sio et al,	2019	RCT	Doxepin 0.5% mouthwash; diphenhydramine-lidocaine-antacid mouthwash; or placebo	Doxepin 0.5% and Diphenhydramine-lidocaine-antacid mouthwashes led to significant pain relief in patients with HNC who presented radiation-induced-OM. The size effect was clinically insignificant	[38]

Abbreviations: RCT, randomized controlled trial; NRCT, non-randomized controlled trial; OM, oral mucositis; HNC, head and neck cancer.

Benzydamine

Benzydamine, an indazole derivative, is a local Non-Steroidal Anti-Inflammatory Drug (NSAID) commonly used topically to treat inflammatory conditions in the mouth and oropharynx, with no systemic effects.⁴⁷ Locally, benzydamine reduces the release of TNF α and IL-1 β from peripheral blood mononuclear cells while preserving anti-inflammatory cytokines.⁴⁸ In vitro studies have shown that benzydamine diminishes neural excitability and inflammatory sensitization, thereby contributing to its anti-inflammatory and analgesic effects.⁴⁹ Additionally, benzydamine exhibits antimicrobial properties and stabilizes the membrane of phagocytes, inhibiting neutrophil respiratory burst, degranulation, and the release of lytic enzymes.⁵⁰

A Phase IV prospective study conducted by Bossi et al in 2024 demonstrated that benzydamine 0.15% mouth rinses, administered 2 to 3 times daily, were a feasible treatment option for oral mucositis secondary to radiotherapy in cancer patients. The authors reported that over 80% of patients adhered to the prescribed treatment regimen during an average 6-week treatment period, with minimal adverse effects. However, the absence of a placebo group limited the ability to directly compare the outcomes and assess the treatment's effectiveness.⁵¹

Several clinical studies support the use of prophylactic benzydamine in patients with head and neck cancer, showing that it reduces the severity of radiotherapy-induced OM (Table 2). However, in a multicenter RCT, benzydamine administration showed no improvement in mucositis severity in patients with high-intensity radiotherapeutic regimens

Table 2 Clinical Studies Evaluating the Analgesic Effect of BZ in Patients with OM

Author	Year	Study Type	Intervention	Conclusion	Reference
Epstein et al	2001	RCT	BZ 0.15% oral rinse vs Placebo oral rinse, administered 4–8 times daily	In patients with HNC and radiation induced-OM, BZ oral rinse showed 30% less erythema and ulceration and had statistically significant delayed use of systemic analgesics compared to placebo	[52]
Kazemian et al	2009	RCT	BZ 0.15% oral rinse vs Placebo oral rinse, administered 4 times daily	BZ 0.15% oral rinse reduced the incidence and severity of radiation induced-OM in patients with HNC	[54]
Roopashri et al	2011	NRCT	BZ 0.15%; Chlorhexidine 0.2%, Povidone-iodine 5%; placebo oral rinse; 4 times daily for 6 weeks	In patients with HNC and radiation induced-OM, BZ 0.15% oral rinse reduced the intensity and duration of oral mucositis during radiation therapy	[55]
Sheibani et al	2015	RCT	BZ 0.15% oral rinse vs Placebo oral rinse; to be used 4–8 times daily	In HNC patients receiving radiation therapy, BZ 0.15% oral rinse showed significantly less OM severity at week 4, continuing through week 7	[56]
Bossi et al	2024	NRCT	BZ 0.15% oral rinse, 2–3 times daily for an average 6 weeks	In HNC patients with radiation-induced OM, BZ 0.15% oral rinses demonstrated good patient tolerability and practical application	[51]

Abbreviations: BZ, Benzylamine; RCT, randomized controlled trial; NRCT, non-randomized controlled trial; OM, oral mucositis; HNC, head and neck cancer.

(> or = 220 cGy/day).⁵² Moreover, the current evidence is insufficient to recommend benzydamine for preventing OM in patients receiving concurrent radiotherapy and chemotherapy.⁵³ Therefore, the Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISO) recommend benzydamine mouthwashes for preventing OM in patients with head and neck cancer exposed to moderate dose radiotherapy <50 Gy.²⁷

In summary, benzydamine has demonstrated the ability to reduce the severity of OM with minimal adverse effects in patients with head and neck cancer undergoing low to moderate-dose radiotherapy (<50 Gy). However, clinical evidence regarding its efficacy in the context of high-dose radiotherapy (>50 Gy) or OM resulting from concurrent chemoradiotherapy remains limited.

Methylene Blue

Methylene blue is a cationic thiazine dye with an expanding body of evidence supporting its potential benefits in the management of neuropathic pain.⁵⁷ Methylene blue exerts its effects by directly inhibiting Nitric Oxide Synthase (NOS), thereby reducing nitric oxide levels and cyclic Guanosine MonoPhosphate (cGMP), which results in vasoconstriction.⁵⁸ Although the precise analgesic mechanisms are not fully elucidated, the inhibition of monoamine oxidase MAO and its anti-inflammatory properties are believed to play a role in pain modulation. Furthermore, methylene blue appears to decrease neural excitability and may exert neurolytic effects.⁵⁹

In the context of OM, several studies have highlighted the pain-relieving effects of methylene blue mouthwashes in patients undergoing cancer treatment (Table 3). For example, a cohort study found that more than 40% of patients with radiation-induced OM who used methylene blue oral rinse experienced significant pain reduction after just two doses, with the analgesic effect lasting up to 6 hours on average. Additionally, methylene blue appears to be particularly beneficial for patients suffering from intractable OM-related pain.⁶⁰

A RCT involving 60 patients with OM secondary to chemotherapy assessed the efficacy of methylene blue mouth rinses as a topical pain management strategy. The study found that mouthwash concentrations of 0.025%, 0.05%, and 0.1%, when used alongside conventional therapy, significantly reduced pain and improved oral function compared to conventional therapy alone. No significant differences were observed between the different concentrations. Mild adverse effects, including transient teeth discoloration and a burning sensation in the oral cavity were reported in less than 15% of

Table 3 Clinical Studies Evaluating the Analgesic Effect of MB in Patient with OM

Author	Year	Study Type	Intervention	Conclusion	Reference
Roldan et al	2017	Retrospective	MB 0.05% 5-minute mouth rinses every 6 hours	Pain relief >50% at 3 weeks follow-up	[60]
Roldan et al	2021	Retrospective	MB (0.025%; 0.05%, 0.1%) mouth rinse every 6 hours	Irrespective of cancer diagnosis and treatment protocol, significant pain relief was achieved after MB mouth rinse	[61]
Roldan et al	2022	RCT	MB mouth rinse every 6 hours for 48 hours (MB 0.025% + CT; MB 0.05% + CT; MB 0.1% + CT; CT alone)	In chemotherapy induced-OM, SCT, and CAR-T therapy, MB (0.025%, 0.05%, 0.1%) was associated with decreased OM pain	[62]
Roldan et al	2023	Retrospective	MB 0.05% 5 minute mouth rinses every 6 hours + CT	MB was associated with significant pain relief in patients with radiation-induced OM and HNC	[63]

Abbreviations: MB, methylene blue; RCT, randomized controlled trial; NRCT, non-randomized controlled trial; OM, oral mucositis; HNC, head and neck cancer; CAR-T, chimeric antigen receptor T-cell; SCT, stem cell transplantation.

participants, with no adverse effects noted after 30 days.⁶² However, this study did not evaluate the pain-relieving effects of methylene blue in cancer patients undergoing radiation therapy to the head and neck.

Overall methylene blue displays promising pharmacologic properties in treating OM-related pain. It has been shown to provide a rapid analgesic effect after the first dose with minimal adverse effects. Further research is needed to evaluate its impact on opioid consumption and quality of life.

Opioids

Opioids are commonly used to treat moderate to severe cancer-related pain. Their mechanism of action involves interaction with opioid receptors mu (μ), kappa (κ), and delta (δ) in the central and peripheral nervous system.⁶⁴ In a clinical trial involving 52 patients, Haumann et al demonstrated that methadone resulted in greater pain reduction at both 1- and 3-weeks post-administration compared to fentanyl in patients with head and neck cancer experiencing a neuropathic pain component.⁶⁵ Additionally, the same authors showed that methadone was not inferior to fentanyl in managing mucosal nociceptive pain following 1 to 3 weeks of radiation therapy.⁶⁶ However, both studies experienced significant loss to follow-up, and the sample sizes were considered insufficient, highlighting the need for larger, more well-powered clinical trials to validate these findings.

A recent RCT assessed the efficacy of gabapentin and methadone as pain management strategies during chemoradiation therapy for head and neck cancer. In arm 1, patients received high-dose gabapentin (2700 mg daily) along with the standard of care, which included hydrocodone/acetaminophen, titrated to fentanyl for breakthrough pain. In arm 2, patients were administered low-dose gabapentin (900 mg) combined with methadone and oxycodone for breakthrough pain. While no significant difference was found between the two groups regarding adverse events and pain intensity, patients in the methadone group showed statistically significant improvements in insomnia and fatigue, along with better physical functioning and quality of life.⁶⁷

Additionally, a retrospective cohort involving 54 patients who underwent stem cell transplantation and subsequently developed severe OM demonstrated less opioid consumption and pain while swallowing after the implementation of a buprenorphine Patient-Controlled Analgesia (PCA) regimen.⁶⁸ On the other hand, tramadol showed no difference in pain outcomes compared to the NSAID diclofenac in patients with OM.⁶⁹

The efficacy of topical opioids in managing oral pain remains a topic of debate. For instance, 2% topical morphine has demonstrated pain-relieving effects in patients experiencing oral discomfort related to chemotherapy and/or radiotherapy.^{70,71} Additionally, when compared to mouth rinses containing lidocaine, diphenhydramine, and antacid, topical morphine was shown to significantly reduce the severity of mucositis ($p = 0.045$).⁷² However, in a mixed

population of pediatric and adult patients with hematological malignancies or those undergoing hematopoietic stem-cell transplants, topical morphine did not exhibit superior analgesic effects when compared to placebo.⁷³

Clinical studies (depicted in Table 4) suggest that opioids play a key a role in alleviating pain and improving quality of life; however, significant variability in analgesic regimens across studies, along with small sample sizes, limits the generalizability of these findings. Moreover, it remains unclear whether the efficacy of opioids differs depending on whether OM is induced by chemoradiation therapy for head and neck cancer or by chemotherapy during stem cell transplantation. Additionally, due to the limited availability of high-quality studies on the use of opioids specifically for managing OM, the current MASCC/ISO guidelines are restricted to recommending only the use of a 0.2% morphine mouthwash for treatment.

Table 4 Clinical Studies Evaluating the Analgesic Effect Opioids in Patients with OM

Author	Year	Study Type	Intervention	Conclusion	Reference
Vayne-Bossert et al	2010	Crossover RCT	2% Morphine mouthwash six times a day vs Placebo	2% Morphine mouthwashes may alleviate OM pain in patients with HNC undergoing chemoradiation therapy	[70]
Sarvzadeh et al	2015	RCT	2% Morphine mouthwash six times a day vs Lidocaine-diphenhydramine-antacid mouthwash	At 6 days of treatment, 2% Morphine mouthwash was associated with reduced OM severity in patients with HNC who underwent chemotherapy and/or radiation therapy	[72]
Haumann et al	2016	RCT	Methadone 2 mg BID vs Fentanyl patch 12 mcg/h	Methadone led to significant pain reduction at 1 and 3 weeks in patients with HNC and radiation induced-OM with a neuropathic pain component	[65]
Haumann et al	2018	RCT	Methadone 2 mg BID vs Fentanyl patch 12 mcg/h	Methadone was not inferior to fentanyl in managing mucosal nociceptive pain following 1 to 3 weeks of radiation therapy in patients with HNC	[66]
Hu et al	2018	NRCT	Oxycodone 10 mg BID (titrated to 30 mg BID if needed) + standardized nursing care	Oxycodone + standardized nursing care improved the quality of life of patients with NPC undergoing chemoradiation therapy and presented moderate pain due to OM	[74]
Hua et al	2019	RCT	Controlled release Oxycodone (started at 20 mg BID) in patients with moderate vs severe OM pain	In patients with nasopharyngeal carcinoma undergoing chemoradiation therapy and have moderate OM pain, controlled-release oxycodone led to faster pain control	[75]
Hermann et al	2020	RCT	High dose (2700 mg) Gabapentin + standard analgesic care vs Low dose Gabapentin (900 mg) + Methadone 5–15 mg BID	No difference in pain outcomes in patients with HNC undergoing chemoradiation therapy. Methadone led to significantly improved quality of life	[67]
Schaller et al	2020	Observational	Pain intensity questionnaires, OM physical examination, pain medication documentation	Opioids were used by 78% of patients with HNC who had radiation induced-OM	[76]
Joshi et al	2021	RCT	Diclofenac 50 mg TID vs. Tramadol 50 mg TID	No difference in pain outcomes in patients with HNC undergoing chemoradiation therapy	[69]
Nielsen et al	2021	RCT	Morphine mouthwash + placebo IV; placebo mouthwash + Morphine IV; placebo mouthwash + placebo IV	In a mixed population of pediatric/adult patients with hematologic malignancies, topical morphine was not different to placebo in pain outcomes	[73]
Meyer et al	2022	Retrospective	Buprenorphine transdermal, sublingual, and intravenous PCA analgesic regimen	In patients who had SCT and severe OM, a buprenorphine based analgesic regimen decreases pain on swallowing and opioid consumption	[68]

Abbreviations: MB, methylene blue; RCT, randomized controlled trial; NRCT, non-randomized controlled trial; OM, oral mucositis; HNC, head and neck cancer; NPC, nasopharyngeal cancer; IV, intravenous; PCA, patient-controlled analgesia; SCT, stem cell transplantation.

Gabapentin

Gabapentin, a commonly used anticonvulsant, is frequently prescribed for the management of chronic neuropathic pain. While its analgesic mechanisms are not entirely understood, it is thought to reduce hyperalgesia and allodynia by antagonizing N-Methyl-D-Aspartate (NMDA) receptors and blocking voltage-dependent calcium channels in the central nervous system.⁷⁷ Despite this theoretical basis, clinical evidence regarding the efficacy of gabapentin for the management of OM pain remains controversial (Table 5). For instance, a RCT by Cook et al investigated the prophylactic use of gabapentin (1800 mg daily) versus placebo over a 6-week period in patients undergoing platinum-based chemotherapy and radiation for locally advanced squamous cell carcinoma of the head and neck. This study found no significant differences in symptom severity or opioid analgesic consumption between the two groups.⁷⁸

A secondary analysis of two clinical trials by Ma et al assessed prophylactic gabapentin doses of 3600 mg, 2700 mg, and 900 mg in SCCHN patients undergoing radiotherapy.^{67,84} They found that the highest dose (3600 mg) was well tolerated, reduced opioid requirements for OM pain management, and had minimal adverse effects.⁸⁶ Furthermore, a retrospective cohort study by Qui et al involving 480 patients revealed that a high-dose regimen of gabapentin (3600 mg) delayed the time to first opioid use and reduced overall opioid requirements when compared to both moderate-dose (300–3200 mg) and non-gabapentin groups, although it did not significantly affect symptom severity.⁸⁵

These studies highlight the variability in outcomes regarding gabapentin's role in OM pain management, suggesting that its efficacy may depend on dosage, patient population, and treatment context.

Table 5 Clinical Studies Evaluating the Analgesic Effect Gabapentin in Patients with OM

Author	Year	Study Type	Intervention	Conclusion	Reference
Bar Ad et al	2010	Retrospective	Gabapentin 2700 mg daily	Gabapentin led to decreased opioid requirements despite important OM severity, in patients with HNC and radiation-induced OM	[79]
Bar Ad et al	2010	Retrospective	Gabapentin 2700 mg daily	In patients with HNC undergoing radiation therapy and concurrent chemotherapy, gabapentin reduced the need for high total opioid doses	[80]
Starmer et al	2014	Observational	Gabapentin 2700 mg daily	Prophylactic gabapentin reduced OM pain intensity and duration and helped to preserve swallow function in patients with HNC undergoing chemoradiation therapy	[81]
Hermann et al	2020	RCT	High dose (2700 mg) Gabapentin + standard analgesic care vs Low dose Gabapentin (900 mg) + Methadone 5–15 mg BID	High-dose gabapentin decreased opioid requirements in patients with HNC undergoing chemoradiation therapy.No difference in pain intensity was found.	[67]
Ala et al	2020	RCT	Gabapentin 5% mouthwashes 3 times a day for 10 days vs Placebo oral rinse	In a mixed population of patients with solid and hematologic tumors and presented chemotherapy induced-OM, gabapentin oral rinse was not different from placebo in pain outcomes	[82]
Smith et al	2020	RCT	Standard therapy + Gabapentin 300 mg daily in week 1 titrated to 2700 mg daily in week 4 vs Standard therapy alone	Gabapentin decreased OM pain, sensitivity and xerostomia in patients with HNC undergoing chemoradiation therapy	[83]
Cook et al	2022	RCT	Gabapentin 900 mg in week 1 titrated to 1800 mg in week 2 vs Placebo	No difference in pain outcomes in patients with HNC undergoing chemoradiation therapy	[78]
Ma et al	2023	RCT	Gabapentin 3600 mg vs Gabapentin 3600 mg + Venlafaxine 150 mg	No difference in pain control and quality of life in patients with HNC undergoing chemoradiation therapy	[84]
Qui et al	2023	Retrospective	High-dose Gabapentin (3600 mg) vs moderate-dose Gabapentin (300–3200 mg) vs No Gabapentin	High-dose Gabapentin decreased overall opioid use and delayed first-time opioid requirement in patients with radiation induced-OM and HNC	[85]

Abbreviations: RCT, randomized controlled trial; OM, oral mucositis; HNC, head and neck cancer.

Ketamine

Ketamine is an anesthetic inductor with proven analgesic and anti-neuropathic properties. It exerts its mechanism of action by the noncompetitive inhibition of NMDA receptors in the periphery, dorsal root ganglion, and central nervous system, providing analgesia and dissociative anesthesia.⁸⁷ When used topically in patients with oral mucositis, case reports and retrospective studies have documented its potential benefits in reducing pain intensity in adults.^{88,89} One clinical trial investigated the effects of ketamine mouth rinses in 30 patients with hematologic malignancies who had undergone at least one chemotherapy cycle and were experiencing severe mucositis. In addition to baseline opioid analgesics and lidocaine-based mouth rinses, patients used 5 mL of ketamine mouth rinse (20 mg/5 mL) as part of their treatment. Participants reported significant pain relief at rest ($p = 0.0001$) and during swallowing ($p = 0.0006$). The solution was well tolerated, with no adverse effects attributed to ketamine administration.⁹⁰

In conclusion, ketamine mouthwashes might play a role alleviating OM-related pain in adults. However, current evidence is limited to a single non-randomized clinical trial and a few observational studies. Additionally, the concomitant use of lidocaine-antihistamine-antacid mouthwash solutions in these studies complicates the assessment of ketamine's independent analgesic effects. Therefore, more research is necessary to assess the separate benefits of ketamine and its effects on quality of life.

Caphosol

Caphosol, a supersaturated calcium phosphate rinse, is an FDA-approved adjunct therapy for the treatment of oral mucositis (OM). This concentrated ionic solution is thought to function by penetrating the oral mucosa and activating cellular pathways that mitigate pain and inflammation, thereby promoting tissue healing.⁹¹ Early investigations into Caphosol have demonstrated promising results. A 2003 RCT (Table 6) reported that the use of Caphosol in conjunction

Table 6 Clinical Studies Evaluating the Analgesic Effect Caphosol in Patients with OM

Author	Year	Study Type	Intervention	Conclusion	Reference
Papas et al,	2003	RCT	Caphosol + fluoride rinse vs standard fluoride rinse	Patients undergoing HSCT demonstrated reduced severity, duration, and frequency of OM with Caphosol adjunct therapy	[92]
Wasko-Grabowska et al,	2012	Observational	Caphosol rinse vs palifermin vs historical control group	Patients undergoing HSCT have reduced severity, duration, and frequency of OM with Caphosol rinse vs historical control group	[93]
Younus et al,	2013	Retrospective	Oral mucositis assessment severity before and after Caphosol rinse	Almost all patients showed improvement in chemotherapy-induced OM severity after Caphosol rinse	[94]
Rao et al,	2014	NRCT	Caphosol mouth rinses 4–10 times per day	Caphosol rinse did not significantly reduce WHO grade 2 or higher scores in HNC patients receiving radiotherapy	[95]
Svanberg et al,	2015	RCT	Caphosol rinse with oral cryotherapy vs oral cryotherapy alone	Combining Caphosol with oral cryotherapy had no effect on pain scores and OM grading	[96]
Kiprian et al,	2016	NRCT	Caphosol rinse vs standard OM treatment	Among patients undergoing radiotherapy for HNC, Caphosol rinse reduced OM severity, dysphagia, and xerostomia	[97]
Wong et al,	2017	RCT	Caphosol + standard oral care vs standard oral care	Caphosol rinse failed to reduce the incidence and duration of severe OM in HNC patients receiving radiotherapeutic treatment	[98]
Bhatt et al,	2017	Retrospective	Caphosol vs historic control group	Caphosol showed no benefit in treating or preventing OM in patients undergoing HSCT	[99]
Murdock and Reeves	2020	Retrospective	Oral mucoadhesive hydrogel (MuGard) or Caphosol vs standard topical therapies	Caphosol did not reduce OM pain or improved mucosal recovery in chemotherapy-induced OM compared to standard topical therapy	[100]
Mubaraki et al,	2020	RCT	Standard oral hygiene protocol vs Brushing twice daily group vs Caphosol rinse	Caphosol rinse reduced the severity of OM but has no effect on the incidence of OM among patients undergoing therapy for HSCT	[101]

Abbreviations: RCT, randomized controlled trial; NRCT, non-randomized controlled trial; OM, oral mucositis; HNC, head and neck cancer; HSCT, hematopoietic stem cell transplantation; WHO, world health organization.

with fluoride treatments significantly reduced the incidence and severity of OM, as well as the duration of mucositis symptoms (3.72 vs 7.22 days, $p = 0.001$) and pain (2.86 vs 7.67 days, $p = 0.0001$), compared to fluoride treatment alone.⁹² Additionally, a 2012 study indicated that Caphosol reduced OM severity and pain duration in patients undergoing hematopoietic stem cell transplantation.⁹³ Similarly, Younus et al reported that Caphosol attenuated chemotherapy-induced OM pain.⁹⁴

However, the efficacy of Caphosol for OM in patients undergoing radiation therapy for head and neck cancer (HNC) remains inconclusive. A 2016 study by Kiprian et al found that Caphosol reduced the severity of OM, xerostomia, and dysphagia in patients receiving radiotherapy for HNC.⁹⁷ Conversely, an RCT by Wong et al failed to demonstrate a significant reduction in OM incidence, severity, or associated pain.⁹⁸ These findings were supported by a 2020 Phase II study by Rao et al, which similarly reported no significant reduction in severe OM with Caphosol use in this population.⁹⁵ Given the high prevalence and substantial burden of OM among HNC patients undergoing radiotherapy, further research is warranted to identify effective interventions.

Recent studies evaluating Caphosol in chemotherapy- and hematopoietic stem cell transplantation-associated OM have also yielded mixed results. A retrospective analysis by Murdock and Reeves found no significant differences in symptom duration, pain levels, or opioid consumption between patients using Caphosol and those using conventional topical anesthetic-based mouthwashes for chemotherapy-induced OM.¹⁰⁰ Among hematopoietic stem cell transplant recipients, Mubarak et al (2020) reported that while Caphosol did not reduce OM incidence, it did mitigate OM severity.¹⁰¹ In contrast, Bhatt et al found that supersaturated calcium phosphate was ineffective in preventing or treating OM in this population.⁹⁹ Similarly, Svanberg et al demonstrated that the addition of Caphosol to cryotherapy in stem cell transplant patients did not provide additional benefit in reducing OM grade or pain scores.⁹⁶

Overall, recent interventional and observational studies suggest limited efficacy of Caphosol for cancer therapy-related OM. While no significant adverse effects have been reported, its clinical benefits remain uncertain. Future research should focus on optimizing formulation and delivery methods to enhance its therapeutic potential.

Growth Factor Analogs

Palifermin

Palifermin is a recombinant form of human Keratinocyte Growth Factor (KGF), a protein involved in critical biological processes such as wound healing and tissue repair. Resembling endogenous KGF, palifermin has demonstrated significant benefits in managing chemoradiation-induced OM. Its mechanism of action is primarily mediated through interaction with the Fibroblast Growth Factor Receptor (FGFR), which activates downstream pathways involved in ROS clearance and DNA repair. These processes promote tissue regeneration and exert anti-apoptotic effects on cells, contributing to the repair and protection of the mucosal lining.¹⁰²

In a clinical trial involving 212 patients with hematologic malignancies undergoing high-dose chemotherapy, total-body irradiation, and autologous stem cell transplantation, an intravenous regimen of palifermin (three doses of 60 micrograms per kilogram per day, administered before and after conditioning therapy) significantly reduced the severity and incidence of severe mucositis compared to placebo ($p < 0.001$).^{103,104} Palifermin was well-tolerated with mild to moderate adverse effects such as rash, pruritus, erythema, and paresthesias, none of which led to treatment discontinuation. However, because FGFR are expressed in various epithelial tissues, there is a theoretical concern regarding the potential tumor-promoting effects of palifermin administration.¹⁰⁵

When investigating the efficacy of palifermin for managing OM in patients with solid tumors, Le et al demonstrated that 180 micrograms per kilogram of intravenous palifermin in patients with head and neck cancer improved OM severity compared to placebo. However, no differences were evidenced in opioid analgesic use between treatment arms.¹⁰⁶

A recent meta-analysis by Coutsouvelis et al investigated palifermin efficacy for the management of OM in patients with solid and hematologic malignancies. The study included 10 RCTs and 1388 patients. The authors concluded that palifermin administration led to a lower incidence of severe OM in patients with solid tumors (RR 0.76 [95% CI 0.63–0.92; $p = 0.004$]) and hematologic malignancies (RR 0.63 [95% CI 0.48–0.82; $p = 0.0007$]).¹⁰⁷ Additionally, in prospective studies palifermin administration was associated with better physical well-being after 7 days of treatment in patients undergoing antineoplastic treatment for hematologic cancers.¹⁰⁸

Overall palifermin demonstrates mucosal regenerative properties and has been shown to reduce the severity of OM in patients with hematologic malignancies and head and neck cancer. While tumor proliferation remains a theoretical concern due to the expression of FGFR in various epithelial tissues, no significant evidence of cancer recurrence has been reported in clinical studies. Nevertheless, further research and larger clinical trials are essential to fully assess palifermin's safety profile and its long-term effects in cancer patients.

Future Directions and Ongoing Clinical Trials

Avasopasem Manganese (AVA), also known as "GC4419", is a promising agent currently under investigation for the treatment of cancer-associated Oral Mucositis (OM). AVA is a molecule that rapidly and specifically converts superoxide into hydrogen peroxide, acting as a free-radical scavenger.¹⁰⁹ Given that high levels of ROS and inflammatory cytokines play a central role in the pathogenesis of OM, AVA may help mitigate OM progression by reducing oxidative damage. In a Phase IIb clinical trial, 90 mg of intravenous AVA, compared to placebo, significantly reduced the incidence and severity of OM in patients with oral cavity or oropharynx cancers undergoing chemoradiation therapy.¹¹⁰ These results were further confirmed in the ROMAN Phase III trial where the incidence of severe OM in the AVA group was 54% compared to 64% in the placebo group ($p = 0.045$). Moreover the median duration of severe OM was reduced to 8 days in the AVA group compared to 18 days in the placebo group ($p = 0.002$).¹¹¹

CAM-2028 is a lipid-based formulation primarily developed as a carrier for oral benzydamine preparations. Its mechanism of action occurs upon contact with saliva, where phospholipids and triglycerides self-assemble to form a protective crystalline layer over ulcerated oral mucosa. The bioadhesive properties of CAM-2028 facilitate the controlled release of medications, such as BZ, commonly used in patients with OM. However, in a clinical trial conducted by Hadjieva et al, CAM-2028 alone demonstrated similar pain-relieving effects when compared to a CAM-2028-benzidamine combination. The authors concluded that the pain reduction observed was primarily due to the bioadhesive and protective properties of CAM-2028, with no additional benefit from the release of benzidamine.¹¹²

Gelclair (Polyvinylpyrrolidone-sodium hyaluronate gel) is a viscous oral gel used to treat mucosal lesions in the oral cavity, particularly in cancer patients with OM. It adheres to exposed injured epithelium and nerve terminals, forming a protective barrier that helps alleviate pain.^{113,114} In a clinical trial involving 20 patients with head and neck cancer who developed radiation-induced OM, gelclair mouth rinses were compared to standard therapy (sucralfate and mucaine) as a pain management strategy. Unfortunately, the study found no significant difference in pain outcomes after 24 hours of treatment and no improvement in pain during activities such as speaking, eating, or drinking.¹¹⁵ In alignment with these findings, another clinical study involving 37 patients who underwent stem cell transplantation and developed OM showed no significant differences in pain relief between gelclair and other rinsing solutions (chlorhexidine, benzidamine, and saliva). Nevertheless, gelclair was associated with a longer-lasting effect and significantly reduced the incidence of oral mucosa colonization by *Enterococcus faecalis* and *Candida* species in OM patients.¹¹⁶

Ongoing clinical trials are evaluating various therapies to address pain associated with oral mucositis. One trial is investigating the efficacy of a doxepin solution spray (administered 10 minutes prior to meals) to manage breakthrough pain in patients undergoing radiotherapy (NCT06017895). Another Phase II trial is assessing the synergistic effects of long-acting transdermal buprenorphine combined with oral tramadol in patients receiving radiation therapy (NCT04752384). Among novel topical treatments, Orosol[®], an osmotically active viscous solution (NCT05161091), and Mucopad HA, an antiseptic solution containing ostenidine and sodium hyaluronate polysaccharide (NCT06276270), are currently under investigation. Nutritional supplementation strategies are also gaining attention, with studies focusing on oral vitamin D to mitigate oral inflammation in chemotherapy patients (NCT06016400) and hydrogen-rich water for its potential to alleviate radiotherapy-induced oral mucositis (NCT05278260). Probiotic research is examining the role of Lactobacillus strains, such as Lactobacillus reuteri (NCT06285591) and Lactobacillus rhamnosus (NCT06390176), in the prevention of severe oral mucositis during radiotherapy. Furthermore, a Phase II clinical trial is evaluating BMX-0001, a therapeutic intervention aimed at reducing free radicals and potentially alleviating the symptoms of oral mucositis (NCT06532279). The results of these trials will undoubtedly provide valuable insights and shape future clinical practices. Advancements in oral mucositis therapies have the potential to significantly enhance pain management and improve the quality of life for affected patients.

Conclusion

In conclusion, this review highlights the range of pharmacological and non-pharmacological interventions aimed at alleviating pain in OM. OM remains a significant complication of cancer therapy, with complex pathogenesis and substantial impact on patient quality of life. Enhanced pain management strategies are crucial, as they can reduce treatment delays, minimize dose reductions, and ultimately enhance therapeutic outcomes. Additionally, effective management may lower healthcare costs by decreasing the need for supportive interventions and hospitalizations.

Given the complexity of OM pathogenesis and the diverse inflammatory mediators involved in pain perception, no single intervention has proven sufficient to address OM across its various stages. Effective management often requires a combination of treatments, beginning with topical medications and escalating to systemic therapy. Despite the variety of available options, a well-established gold-standard protocol has yet to be defined.

Assessing the efficacy of mouthwashes for pain management presents challenges due to variations in their composition and concentration across clinical studies. This lack of standardization complicates the application of findings to clinical practice. Certain mouthwashes, such as those containing lidocaine, doxepin, or benzydamine, have demonstrated promising results for pain relief. However, the potential benefits of combining different pain management strategies remain unclear. Further clinical data are needed to determine whether such combinations could enhance pain reduction. Looking ahead, prioritizing research on novel molecular pathways—such as transient receptor potential (TRP) channels and neurotrophic factors—holds promise for the development of more targeted and effective therapies.

Abbreviations

OM, Oral mucositis; IL-1 β , Interleukin 1- β ; IL-6, Interleukin-6; TNF- α , Tumor necrosis factor- α ; TRP, Transient receptor potential; ET-1, Endothelin-1; NGF, Nerve growth factor; TRPV4, Transient receptor potential V4; COX-2, Cyclooxygenase-2; CGRP, Calcitonin gene-related peptide; NOS, Nitric oxide synthase; cGMP, Cyclic guanosine-MonoPhosphate; NMDA, N-Methyl-D-Aspartate; KGF, Keratinocyte Growth Factor; FGFR, Fibroblast Growth Factor Receptor, HNC, Head and neck cancer; SCT, Stem cell transplantation; CAR-T, Chimeric antigen receptor T-cell therapy; BZ, Benzydamine; MB, Methylene blue; AVA, Avasopasem manganese; RCT, Randomized controlled trial; NRCT, Non-randomized controlled trial; HSCT, Hematopoietic stem cell transplantation; WHO, world health organization.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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