Role of Gabapentin in Managing Mucositis Pain in Patients Undergoing Radiation Therapy to the Head and Neck

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Background: Oral mucositis (OM) is a painful and debilitating side effect that affects 80%–100% of patients undergoing radiation therapy for head and neck cancer. This dose-limiting side effect may potentially lead to pain, dehydration, malnutrition, infection, and treatment breaks. Treatment breaks can lead to decreased disease control and suboptimal patient outcomes. No primary prevention exists for OM, and management is focused on pain control. Compelling evidence exists that OM pain has somatic and neuropathic components.

Objectives: This article reviews the existing literature on the use of gabapentin (Neurontin®) as a co-analgesic in treating the neuropathic pain in OM.

Methods: A literature search was performed using CINAHL® and PubMed with the search terms gabapentin and oral mucositis. The selected articles were briefly screened for relevance, and three were included in this review.

Findings: No systematic reviews exist on the role of gabapentin for neuropathic pain in radiation-induced OM. Two retrospective studies concluded that gabapentin reduced escalation of opioid doses and unplanned treatment breaks. One retrospective study demonstrated favorable swallowing outcomes. Pain and OM are nursing-sensitive outcomes that can be significantly affected by evidence-based nursing interventions.

Cancers of the head and neck involve several site-specific anatomic areas. These areas include the oral cavity, pharynx (including the nasopharynx, oropharynx, and hypopharynx), larynx, nasal cavity, paranasal sinuses, and salivary glands (National Cancer Institute, 2015) (see Figure 1). Primary management of head and neck cancer may include surgery, radiation therapy (RT), chemotherapy, or a combination. Treatment plans are based on several factors, including the stage of the cancer at diagnosis, location of the tumor, general health status, and presence of comorbidities. RT alone or in combination with chemotherapy or targeted therapies has become accepted standard care for locally advanced head and neck cancer (Pignon, le Maître, & Bourhis, 2007; Takes et al., 2012). Chemotherapy and targeted therapies, like cetuximab (Erbitux®), act as radiosensitizers to cancerous cells and achieve increased cell kill and ideally improve local tumor control (Lambertz et al., 2010; Takes et al., 2012). Patients with locally advanced head and neck cancer treated with chemotherapy and RT have been found to have an absolute survival benefit of 7% at five years when compared to patients who received RT alone (Takes et al., 2012). However, concurrent treatment with chemotherapy and RT increases the incidence and severity of oral mucositis (OM) as much as 100% (Eilers, Harris, Henry, & Johnson, 2014). OM in patients with head and neck cancer undergoing RT with or without chemotherapy has been reported by patients as the most distressing symptom in the treatment course (Eilers &
Million, 2011). High-grade OM (grade 3 or 4) is associated with significant patient morbidity (e.g., pain; inability to chew, swallow, or maintain caloric intake; unplanned hospitalizations; worse quality of life) (Eilers et al., 2014; Trotti et al., 2003).

Mucositis is one of the most common complications in patients undergoing cancer treatment (Silverman, 2007; Sonis, 2004a). The term mucositis refers to the inflammation along the epithelial cells lining the gastrointestinal tract from mouth to rectum. Oral mucositis (OM) is an inflammation of the mucous membranes along the oral cavity, including the gingiva, buccal mucosa, tongue, and lips. OM affects from 80%–100% of patients undergoing RT to the head and neck (Sonis, 2004a). It is often the starting point for a cascade of complications that leads to pain, infection, decreased nutritional intake, diminished quality of life, and unplanned treatment breaks, potentially leading to decreased locoregional disease control and patient survival (Mallick, Benson, & Rath, 2016; Trotti et al., 2003).

The presentation and course of RT-induced OM follows a clinically predictable course. Radiation is typically given in daily doses, referred to as fractions. A common course of RT for treatment of head and neck cancer is about 200 cGy given daily five days per week for an average of five to seven weeks (Kumar, Balan, Sankar, & Bose, 2009; Sonis, 2012). OM is usually clinically evident by the third week of RT or after about 25–30 Gy of radiation have been delivered. Symptoms may persist for more than four weeks after treatment is completed (Sonis, 2012). Early-stage OM often presents as erythema of the oral cavity and is commonly described by patients as a burning or tingling sensation. The lesions can become confluent and friable, with subsequent bacterial and fungal colonization and overgrowth that can worsen pain and lead to systemic infections requiring treatment breaks, hospitalizations for supportive care, and sepsis (Sonis, 2012).

With the breach in the oral mucosal membrane, secondary infections may occur, resulting in potentially life-threatening systemic infections and hospitalizations (Eilers et al., 2014). Patients with head and neck cancer who develop severe OM from combined RT and chemotherapy are reported to incur 52% higher costs during treatment when compared to patients who do not develop high-grade OM (Mason, DeRubeis, Foster, Taylor, & Worden, 2013). This finding illustrates the overall financial impact and potential burden of OM on the individual and community.

Unplanned treatment breaks in patients with head and neck cancer are associated with a reduction in local and regional disease control. Clinical studies have demonstrated that malignant tumors accelerate the repopulation process during unplanned radiation treatment breaks (Russo, Haddad, Posner, & Machtay, 2008). OM has been identified as a dose-limiting side effect requiring modification and interruption of the radiation regimen, potentially leading to suboptimal disease control and treatment outcomes (Eilers et al., 2014; Mallick et al., 2016).

This article (a) describes the presentation, pathophysiology, and grading of OM in patients undergoing RT to the head and neck region, as well as the types of pain these patients experience; (b) reviews the novel role of gabapentin (Neurontin®) as a co-analgesic to improve pain management and possibly prevent escalating doses of opioids; and (c) describes the treatment of OM in patients with head and neck cancers receiving RT.

**Pathophysiology of Oral Mucositis**

The pathophysiology of OM has historically been described as a linear “outside-in” process, beginning with damage to the superficial epithelial layer of the oral mucosa. However, research has supported a more complex process. Sonis (2004b) postulated a model that describes the dynamic and complex process of OM where the process actually begins in the submucosal endothelium and connective tissue. This deeper damage results in a cascade of biologic pathways that causes damage to the oral epithelium, ulceration, and the potential for microorganisms to enter the bloodstream, which could lead to systemic infections. The five stages consist of initiation, primary damage response, signal amplification, ulceration, and healing (see Figure 2).

**Grading of Oral Mucositis**

Consistent and uniform reporting of OM is important to compare outcomes of prevention and therapeutic interventions. The use of multiple grading scales made head-to-head comparison of trials unreliable. A variety of grading systems are used worldwide to grade the severity of mucositis, including systems by the Radiation Therapy Oncology Group, the World Health Organization, and the National Cancer Institute (NCI). The NCI (2010) has developed criteria to describe a variety of toxicities, including mucositis. The use of the Common Terminology Criteria for Adverse Events provides a standardized grading system used to describe and document OM (Liu, Zhu, & Guan, 2012) (see Table 1). The use of a uniform standardized system allows for comparisons of multiple studies and can assist in comparing studies and drug trials (Trotti et al., 2003).
Compelling evidence exists that oral hygiene and standard oral care protocols are effective in decreasing severity and delaying onset of OM (Kartin, Tasci, Soyuer, & Elmal, 2014). Professional organizations, including the Oncology Nursing Society, Multinational Association of Supportive Care, and the International Society for Oral Oncology, recommend that patients receive instruction on oral hygiene using a soft-bristle toothbrush, flossing, and use of bland rinses, such as sodium bicarbonate or saline (Kumar et al., 2009). Regular oral assessment before, during, and for several weeks following RT is generally recommended. Symptom management, including pain control, remains a pivotal part of care because no gold-standard evidence exists to reliably prevent the development of OM in this population (Armstrong & McCaffrey, 2006; Eilers et al., 2014).

### Pain Associated With Oral Mucositis

Pain is a common and often undertreated symptom in patients with cancer and is a nursing-sensitive outcome. A nursing-sensitive outcome is within the scope of nursing practice and can be greatly affected by nursing interventions (Aiello-Laws et al., 2009). Pain is reported in as many as 85% of patients with head and neck cancer on presentation and may be the first symptom of head and neck cancer in 20%–50% of patients. Pain in the head and neck region is thought to be multifactorial. Infiltration by the tumor into adjacent tissue and nerves can cause pain. Surgery, chemotherapy, or RT can cause tissue and neural destruction (Epstein, Wilkie, Fischer, Kim, & Villines, 2009). Evidence exists in the literature that patients with head and neck cancer experience a combination of nociceptive and neuropathic pain (Bar Ad, Weinstein, Dutta, Chalian, et al., 2010; Epstein et al., 2009).

Nociceptive pain occurs when somatic or visceral tissue injury results in stimulation of the nociceptive receptors in the skin, connective tissue, viscera, or muscle. The tissue damage can be a result of thermal, chemical, or mechanical injury. This type of pain is typically described as dull, tender, or throbbing. Mild to moderate nociceptive pain may respond to nonsteroidal anti-inflammatory drugs, with opioids being recommended for moderate to severe cancer-related pain (Aiello-Laws et al., 2009; Dy, 2010; Vardy & Agar, 2014).

Neuropathic pain is estimated to be as high as 40% in the general oncology population (Jongen et al., 2013) and is caused by damage to the central or peripheral nervous system. This can be from the direct result of tumor invasion, such as with leptomeningeal disease, nerve plexus invasion, or epidural metastases. Neuropathic pain is often described as aching or burning and is usually poorly relieved with opioids. Evidence supports that a significant percentage of patients with head and neck cancer experience neuropathic pain (Aiello-Laws et al., 2009; Dy, 2010).

Literature on the specific recommendations for the use of systemic analgesics to treat pain from OM is sparse (Ling & Larsson, 2011). The mainstay of OM pain management has been opioid therapy, often leaving the patient open for additional life-altering side effects, including depression, sedation, nausea, vomiting, constipation, pruritus, and respiratory depression. Opioid pain medications have been found to be less effective in neuropathic pain, even with dose escalation (Bar Ad, Weinstein, Dutta, Dosoretz, et al., 2010).

Co-analgesics can play an important role in improving pain management, along with the use of narcotic pain medications (Aiello-Laws et al., 2009). They can assist in preventing dose escalations of opioids and address the often untreated neuropathic components of certain pain syndromes (Bar Ad, Weinstein, Dutta, Dosoretz, et al., 2010). Co-analgesics (also referred to as adjuvants) encompass a category of medications that were not initially developed or officially indicated for pain management. These co-analgesic agents were found to be particularly useful when combined with other categories of pain medications and include medications like antidepressants, topical anesthetics, and anticonvulsants. With many of these agents, the onset of pain relief is delayed, and analgesia may take weeks and require dose escalations until acceptable pain relief is achieved (Aiello-Laws et al., 2009; Ling & Larsson, 2011).

Gabapentin, a co-analgesic agent initially developed as an antiseizure medication, is currently recommended for non–cancer-related pain syndromes, including diabetic neuropathy and generalized anxiety disorders (Dworkin et al., 2007). The exact pharmacologic mechanism is unclear; however, gabapentin has been shown to inhibit calcium influx through voltage-gated ion channels found in the membranes of neurons (Brant, 2010). Gabapentin is not protein-bound in the bloodstream and is excreted though the renal system (Dooley, Taylor, Donevan, & Feltner, 2007). Generally, patients are started on gabapentin with one dose of 100–300 mg at bedtime or daily and are gradually titrated to increasing doses every two to three days until an acceptable level of pain relief is achieved (Dworkin et al., 2007). Patients with impaired

<table>
<thead>
<tr>
<th>Initiation phase:</th>
<th>Message generation phase:</th>
<th>Signaling and amplification phase:</th>
<th>Ulceration phase:</th>
<th>Healing phase:</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA strands break and damage</td>
<td>Activation of transcription factors and increased production of pro-inflammatory cytokines</td>
<td>Tumor necrosis factor alpha activates ceramide and caspase pathways</td>
<td>Breach in the mucosa and secondary bacterial and fungal infections</td>
<td>Cells regenerate and normal microbial flora establishes</td>
</tr>
</tbody>
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**FIGURE 2. A Five-Phase Model Proposed to Characterize Major Steps in Development and Resolution of Oral Mucositis**

*Note: With permission from Springer Science+Business Media: European Archives of Oto-Rhino-Laryngology, Radiation induced oral mucositis: A review of current literature on prevention and management, 27, 2016, p. 2,286, S. Mallick, R. Benson, & G.K. Rath, Figure 1.*
TABLE 1. Common Terminology Criteria for Adverse Events for Oral Mucositis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No oral lesions or discomfort</td>
</tr>
<tr>
<td>1</td>
<td>Asymptomatic or mild symptoms</td>
</tr>
<tr>
<td>2</td>
<td>Moderate pain; not interfering with oral intake; modified diet indicated</td>
</tr>
<tr>
<td>3</td>
<td>Severe pain; interfering with oral intake</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
</tbody>
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renal function or older adults may require slower titration and a lower total daily dose. The most common side effects include somnolence, dizziness, ataxia, edema, weight gain, dyspepsia, and leukopenia. Older adults may require lower overall dosing or slower titration because they are more likely to have a variety of physiologic changes that can alter absorption and pharmacokinetics. Older adult patients also require particular attention to other medications they may be taking concomitantly with similar side effects because polypharmacy is common in this age group. Patients with renal impairment also require slower titration and lower total daily doses. Several weeks may be required to reach therapeutic levels, and, therefore, patients must have an understanding of the importance of adherence with recommended daily gabapentin dosage and should be encouraged to report side effects to clinicians (Brandt, 2010; Dworkin et al., 2007).

Literature Review

A literature search using CINAHL® and PubMed databases was conducted by a senior reference librarian with search terms gabapentin and oral mucositis in articles published from January 2010 to October 2015. The selected articles and abstracts were briefly screened for relevance. Inclusion criteria were published research studies. Abstracts, posters, and review articles were not included. Other exclusion criteria were nonsystemic use, topical application, or swish or swallow formulations of gabapentin. No systematic reviews were found on the specific use of gabapentin for neuropathic pain in radiation-induced OM. A total of 10 articles met the criteria, and three retrospective studies were included in this review.

Oral Mucositis in Intensity-Modulated Radiation Therapy

A study by Bar Ad, Weinstein, Dutta, Chalian, et al. (2010) examined the role of gabapentin to treat the neuropathic pain syndrome in radiation-induced OM. This retrospective study evaluated the effectiveness of gabapentin as a co-analgesic in patients undergoing intensity-modulated RT to the head and neck. A total of 29 patients were included in the data analysis, but the N value was 30 because one patient underwent two courses of radiation, and both were included in the analysis. All of the patients had undergone surgery for primary or recurrent disease and were treated with radiation postoperatively from 2004–2006. No patients received concurrent or induction chemotherapy. Two patients who received concurrent cetuximab were included in this sample. The patients were started on gabapentin during the second week of treatment at a dose of 600 mg at bedtime and gradually titrated over one week to three daily doses of 900 mg, with a total daily dose of 2,700 mg. Oxycodone (Roxicodone®) was prescribed in addition to the gabapentin in response to patients’ subjective pain scores, and additional narcotic pain medications were added as clinically indicated. The study found that, despite having grade 2 or higher OM during the third (56%) and fourth (73%) weeks of radiation, only 10% required additional narcotic pain medications (15–30 mg oxycodone per day). During the final fifth and sixth weeks of treatment, 35% required additional narcotic pain medications despite the presence of grade 2 or higher OM in 80% of cases. During both of these time periods, 93% of patients were treated with a median dose of 2,700 mg/day of gabapentin. Two patients had interruptions in treatment of greater than three days; however, these interruptions were unrelated to RT toxicity.

Oral Mucositis in Patients Undergoing Concurrent Chemotherapy and Radiation Therapy

In another retrospective study conducted by Bar Ad, Weinstein, Dutta, Dosoretz, et al. (2010), patients were followed for seven weeks during concurrent intensity-modulated RT and chemotherapy for head and neck cancers. The sample consisted of 42 patients with head and neck cancer undergoing concurrent chemotherapy and RT from December 2003 to November 2006. Eighteen patients had undergone surgical resection of the primary tumor, with the rest undergoing definitive concurrent chemotherapy and RT. The patients were started on gabapentin with the same titration schedule, with a median dose of 2,700 mg daily in the second week of radiation. Opioid pain medications were added in response to patients’ subjective pain scores and if additional pain medication was clinically indicated. For the purposes of statistical data analysis, specific opioid doses were converted to an oxycodone-equivalent dose. During the fourth week of treatment, a total of 38 patients were maintained on gabapentin 2,700 mg daily, with only 23 patients requiring additional opioid pain medication despite grade 2 or higher OM occurring in 86% of these patients. During the final weeks (weeks six and seven) of treatment, 38 patients were maintained on gabapentin at a median dose of 2,700 mg daily. At this time, 30 patients required opioids for adequate pain control (median dose of 60 mg per day of oxycodone, ranging from 10–180 mg per day) despite the presence of grade 2 or higher OM in 95% (week five) and 100% (week six) of patients. During the study, one patient required a treatment break of greater than three days during treatment because of aspiration pneumonia caused by concurrent chemotherapy and RT.
Based on these studies, many cancer centers have adopted the use of gabapentin to treat radiation-induced OM pain syndrome in patients with head and neck cancer.

**Effect of Gabapentin on Swallowing and Feeding Tube Use**

A study by Starmer et al. (2014) retrospectively examined the impact of gabapentin on swallowing and feeding tube use in patients during concurrent chemotherapy and RT for oropharyngeal squamous cell carcinoma. This was a retrospective study of 23 patients using historic controls matched for cancer stage. The patients underwent prophylactic percutaneous endoscopic gastrostomy (PEG) tube placement as standard of care. Patients were started on gabapentin prophylactically during the first week of RT. Patients treated with gabapentin began using the PEG tubes at a later date (3.7 weeks versus 2.29 weeks) and had the PEG tubes removed earlier (7.29 weeks versus 32.56 weeks). This difference was attributed to improved pain control, allowing patients to maintain normal physiologic swallowing mechanisms for a greater amount of time during and after RT (Starmer et al., 2014).

**Implications for Nursing Practice**

OM and pain are nursing-sensitive outcomes. The use of evidence-based management of symptoms in the population of patients with cancer may improve patient outcomes overall, promote patient and clinician satisfaction, and reduce costs to the healthcare system (Schulmeister & Gobel, 2008).

The identification of mixed neuropathic and nociceptive pain in patients with head and neck cancers and treatment-induced OM has provided additional direction for pain management with the use of co-analgesics. The use of gabapentin shows promise in managing the neuropathic pain component of OM. Further research, including randomized, controlled trials, are warranted to determine the potential role of gabapentin in managing OM neuropathic pain. In particular, nursing research studies may be beneficial because pain and OM are nursing-sensitive outcomes.

Nursing considerations in the use of gabapentin include patient education regarding the titration and side effects, including dizziness, somnolence, ataxia, and leukopenia. Patients with compromised renal function and older adults may require starting gabapentin at lower doses and with slower titration to higher doses. Older adults are particularly at increased risk of polypharmacy and require careful monitoring of all medications.

**Conclusion**

Radiation-induced OM occurs in the majority of patients undergoing radiation to the head and neck region. This dose-limiting side effect can lead to diminished quality of life, disruption in treatment, and potential for suboptimal disease control and patient outcome. Pain from radiation-induced OM appears to be caused by somatic and neuropathic pathways. The use of gabapentin in the early treatment phase appears to be a promising co-analgesic that can address the neuropathic component that otherwise may be left untreated, resulting in escalating opioid doses, which are not as effective for neuropathic pain management. Special attention should be paid to the patient's renal function and risk for side effects, including sedation, ataxia, and interactions with other medications; in these cases, dose reduction may be needed.

**References**


Implications for Practice

- Assess and manage the nociceptive and neuropathic components of oral mucositis pain.
- Suggest the use of gabapentin (Neurontin®), a co-analgesic that has shown promise in preventing escalating doses of opioids for oral mucositis pain.
- Educate patients about gabapentin, a generally well-tolerated drug with few drug—drug interactions, and monitor for side effects, particularly in older adults who are at increased risk for polypharmacy.


