The Experience of a Sore Mouth and Associated Symptoms in Patients With Cancer Receiving Outpatient Chemotherapy

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Abstract:

This study aimed to describe sore mouth (SM) severity and distress, associated symptoms, and consequences in cancer chemotherapy outpatients. Secondary analysis was used in this study. A total of 223 patients in 4 treatment centers participated in the study. Data from an intervention study using a computer-based telephone communication system to assess patients' daily symptom experience were analyzed to obtain highest, average, and lowest ratings of severity and distress for SM, fatigue, trouble sleeping, feeling down/blue, and feeling anxious. Consequence data included oral intake, time spent lying down, ability to work, and daily activity. Approximately 51% reported SM, with a mean highest, average, and lowest severity score of 3.1 in cycle 2 and 3.09 in cycle 3. Sore mouth severity was correlated with severity of fatigue, feeling down/blue, feeling anxious, and trouble sleeping. Sore mouth distress was correlated with the same symptoms. Sore mouth severity was correlated with the number of 8-oz glasses of liquid consumed, effect on daily activity, time spent lying down, but not with ability to work. Half of patients experienced SM, which was associated with several other symptoms and led to specific consequences. Understanding the complex symptom experience of patients with SM, including consequences, will assist nurses in developing more comprehensive clinical assessments and interventions. In addition, the association of multiple symptoms with SM will provide a foundation for further research investigation in oral mucositis.

Article:

Oral mucositis (OM) can be a debilitating condition associated with cancer therapy. Comprised of the hallmark signs of erythema and ulceration, OM is typically accompanied by acute oral pain, often expressed by patients as a "sore mouth" (SM), which is due to damage of the affected oral mucosa.1,2 Patients may also experience a variety of physical sequelae such as difficulty swallowing, difficulty speaking, decreased oral intake, mood disturbances (including anxiety and depression), sleep disturbances, and fatigue.3 Significant nutritional shortfalls are also common and can be manifested as anorexia, dehydration, malnutrition, and weight loss.

Although OM is best evaluated through a systematic oral examination, there is clearly a subjective component to the experience.4 This subjective component is an SM, reported by patients as altered sensations that can be measured both by intensity and distress. The use of such self-reports is the best way to evaluate the experience when patients are not available for an oral examination, as typically occurs in patients receiving chemotherapy in the outpatient setting. This report applies Armstrong's Symptoms Experience Model (SEM)5 to examine the experience of SM in relation to antecedents, co-occurring self-reported symptoms, and consequences of SM as self-reported by patients receiving chemotherapy on a daily basis (Figure 1).

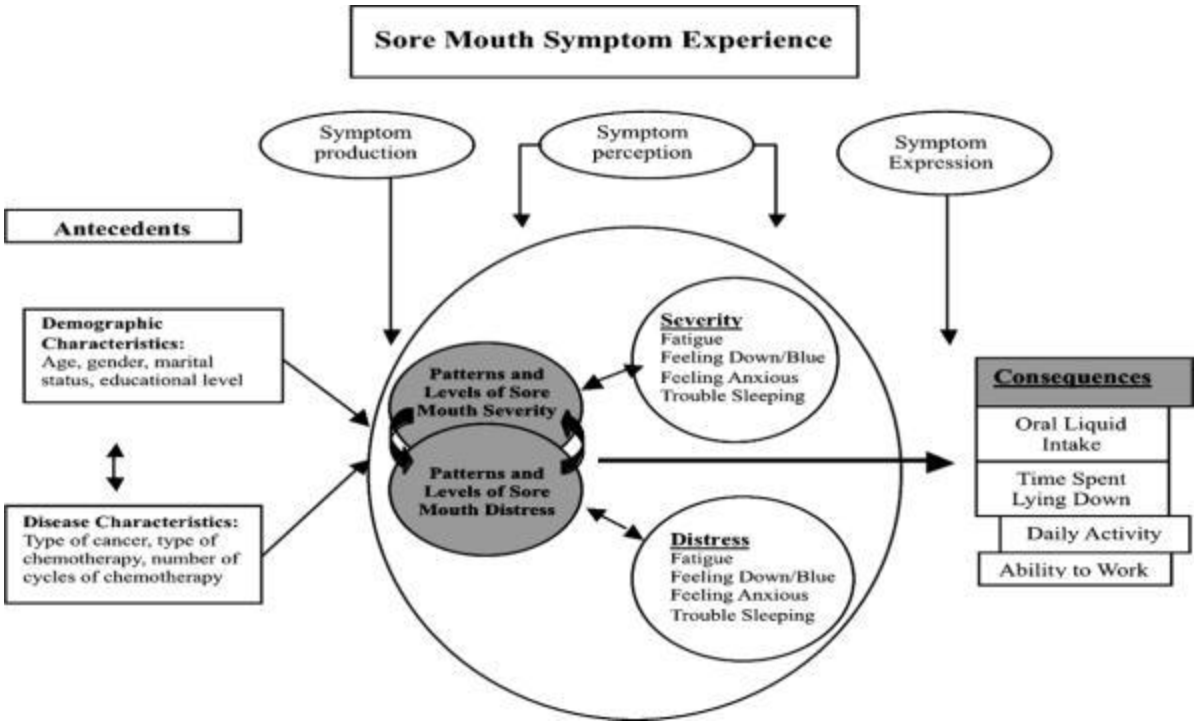

Figure 1 Armstrong's Symptom Experience Model 5 adapted for the purpose of this study.

Purpose

This study was designed to describe the experience of SM, with a focus on severity and distress, associated symptoms, and consequences in patients with cancer receiving cycles 2 and 3 of outpatient chemotherapy. The data were obtained from a larger intervention study in which patients reported their SMs and other symptoms daily (see Methods below).

The specific aims were to (1) evaluate demographic and clinical factors associated with the occurrence of SM, (2) examine associations among SM severity and SM distress and the severity and distress of 4 self-reported symptoms (feeling down/blue, feeling anxious, trouble sleeping, and fatigue) over cycles 2and 3 of chemotherapy, and (3) explore the consequences of the experience of SM.

Background

The incidence, duration, and severity of OM are often dose limiting, and patterns of mucositis vary.6 Oral mucositis can influence survival, including potential for remission and cure rates. Unfortunately, there are few effective interventions to prevent or treat OM at this time.7,8

Approximately 1.2 million American patients receive antineoplastic treatment each year as a treatment for cancer,7 and approximately 400,000 will develop OM as a consequence.9 The incidence of OM varies related to the respective treatment; for example, approximately 75% of patients undergoing intensive high-dose chemotherapy during hematopoietic stem cell transplantation (HSCT) experience OM.2,10 Nearly 40% of all patients receiving chemotherapy develop OM, and of these, about 50% experience lesions so severe that their chemotherapy regimen must be modified.11

Oral mucositis has been studied extensively for more than 20 years, usually in hospitalized patients receiving high-dose chemotherapy (eg, before stem cell transplantation). There has been only limited research on OM in patients receiving outpatient chemotherapy.1 This research has been limited by methods to assess OM when patients are not available for an oral examination. In the United States, the overwhelming majority of patients are receiving chemotherapy on an outpatient basis, estimated at approximately 90% in outpatient settings nationwide.12 Considering these numbers, the experience of OM in the outpatient population warrants careful attention, specifically the occurrence of OM. Although the occurrence of OM has been described in the literature retrospectively,13 to date, there has been no research that prospectively describes OM in the literature using reliable and valid instruments for measurement.

Symptoms Related to SM

Patients receiving cancer treatment typically experience and require treatment of multiple symptoms simultaneously.14,15 Until recently, symptom research has usually focused on a single symptom such as pain, nausea, constipation, or anxiety.16 Although this approach has led to advances in the understanding and management of a particular symptom, patients rarely present with just 1 symptom.14,17 Studies have demonstrated relationships among the symptoms of pain, anxiety, fatigue, depression, and insomnia in patients with cancer, but only a limited number of studies have investigated symptoms associated with OM 2,16,18-21 and none have investigated symptoms associated with SM. Thus, further investigation is warranted because understanding the complex symptom experience of patients with SM will lead to enhanced knowledge on this experience and identification of directions for prospective research and OM in chemotherapy outpatients and potential new avenues for clinical interventions. The current study addresses the association of symptoms in a given chemotherapy population, and such descriptive work is the foundation of future, more targeted work in symptom management.

Epidemiology and Scope

Mucositis is one of the most common problems seen in patients treated with high-dose chemotherapy and/or head and neck radiation 22 and is a common dose-limiting factor in patients receiving chemotherapy. Mucositis is a common toxicity of high-dose chemotherapy that can compromise the entire gastrointestinal (GI) tract from the mouth to the anus including the mucosa of the stomach, small and large intestine, and rectum.23 Generally referred to as alimentary mucositis, it can be further classified by specific anatomic location (eg, OM, GI mucositis).

Clinical expression of OM varies by type of cancer treatment.22 Elting et al 13 reported OM in 22% of cycles of myelosuppressive chemotherapy, GI mucositis in 7% of cycles, and both oral and GI mucositis in 8% of cycles. In patients receiving high-dose radiation for head and neck cancer, the incidence of OM is virtually 100%.24

Oral mucositis is highly prevalent in patients receiving high-dose chemotherapy as a conditioning regimen for HSCT.25 McGuire et al 2 reported that approximately 86% of patients receiving either an allogeneic or autologous transplant experienced OM.

Patient-specific characteristics (eg, sex, age) may influence prevalence and severity of OM. In one study of patients receiving chemotherapy, females reported a higher incidence of OM than men.26 Zalcberg and collegues 27 identified female gender as an independent risk factor for OM. In contrast, Chiara and colleagues 28 reported a significantly higher incidence in OM in males. Patients older than 50 years developed more severe and longer lasting OM in one study, leading researchers to hypothesize that a decline in renal function may be

causative.29 Sonis and colleagues 30 reported higher prevalence in children than in adults with the same malignancy.

Oral mucositis incidence is also related to specific chemotherapy agents and regimens. Sonis et al 24 analyzed more than 338 research studies that reported outcomes of chemotherapy and radiation trials and also listed grade III and IV OM. Anthracycline-based regimens were associated with rates of OM of approximately 1% to 10%, including those standard regimens for adjuvant treatment in patients with breast cancer (doxorubicin and cyclophosphamide) and regimens for non-Hodgkin lymphomas (cyclophosphamide, doxorubicin, vincristine, and prednisone). Risk of OM increased when rituximab was added to the regimen. Use of 5-fluorouracil, a common treatment for colon and some breast cancers, resulted in rates of grade III and IV greater than 15%.24

Interestingly, only limited research has been conducted on occurrence of OM in outpatients receiving chemotherapy. In their intervention study comparing chlorhexidine and normal saline mouthwashes in chemotherapy outpatients, Dodd et al 1 reported OM incidence rates of 23% in chlorhexidine and 26% in normal saline groups based on oral cavity assessments at baseline and 3 subsequent cycles of chemotherapy. This figure could be an underestimate, however, because although patients were encouraged to visit the outpatient clinic if they had OM between cycles, it is not known how many of them adhered to this suggestion. In addition, data collection occurred at the end of each cycle, when OM had likely resolved, and it was assessed using the Oral Assessment Guide (OAG),31 which is a global oral assessment tool for oral complications of chemotherapy rather than a measure of mucosal tissue damage.

Oral Pain and SM

Oral pain is a clinically significant problem in patients with OM, resulting in decreased quality of life among cancer patients.13 Those patients receiving chemotherapy treatment have a 40% to 70% likelihood of also suffering OM pain.32 Patients undergoing HSCT identified OM pain as the most serious adverse effect in the first 100 days of treatment.33 Oral mucositis pain can be so severe that patients receive opioids or other forms of pain medication for symptom relief. Unfortunately, some patients with mucositis experience breaks in their treatment regimen or decreased doses of chemotherapy.34 To date, OM-associated pain has been primarily investigated in the HSCT population and in patients receiving high-dose chemotherapy but not in patients receiving outpatient chemotherapy.

As noted earlier, patients often refer to the erythema and ulceration ("sores") that characterize OM by using the general term sore mouth. Researchers studying OM have used a variety of tools to measure both objective and subjective components of OM, including tissue damage and self-reported symptoms such as oral pain or soreness.1,2,21 These studies reveal that many researchers have used SM as an objective indicator of OM when it is not possible to precisely measure OM.

For example, in a study of 47 patients undergoing either allogeneic or autologous transplantation, 86% reported oral pain, and of these, more than 50% described the pain as "tender," "aching," and "sharp" on the Short-Form McGill Pain Questionnaire.2 Subsequent work in 18 patients receiving high-dose chemotherapy for bone marrow transplantation revealed that 70% experienced mild to moderate oral pain and frequently described it as tender, "irritating," and sore.21 In another example, Dodd and colleagues 1 reported that of 111 chemotherapy outpatients participating in an interview session and completing the OAG, 69% had OM and many described their mouths as having "slight soreness" and "tenderness" and their throats as having "very painful sores."

Several organizations that provide education about cancer symptoms use the phrase sore mouth to describe OM to their patients. For example, both the American Cancer Society 35 and The National Institute of Dental and

Craniofacial Research 36 use the term sore mouth in their materials focusing specifically on OM. Thus, use of sore mouth or similar words (tender) seems common in the context of OM secondary to cancer treatment. Its extensive use by patients, healthcare providers, and organizations clearly validates the authors' exploration of SM as a subjective indicator of OM in the outpatient chemotherapy population.

Association of Symptoms With OM

As noted earlier, McGuire et al 2 found that patients undergoing an allogeneic or autologous transplantation had OM and that 86% reported OM-associated pain. In a subsequent pilot study conducted in preparation for an intervention study of acute oral pain and mucositis in HSCT and leukemia patients (n = 18), McGuire et al 21 reported that mild to moderate OM pain occurred in approximately 70% of participants and noted that patterns of pain, mucositis, and mood disturbances (measured using the 11-item Brief Profile of Mood States 37) were similar in escalation, peaking, and resolution over time.

In a large study (n = 599) of patients receiving chemotherapy for solid tumors, Elting and Shih 21 found that patients with OM were more likely to experience fatigue than those patients without OM (9% vs 5%; P = 0.007). Dodd et al 16 confirmed that outpatients in their study who developed OM had a significant increase in mood disturbances as compared with outpatients who did not have OM (P = 0.03) and also experienced significantly higher levels of depression ($F_{1,75}$ = 13.47, P < .001) and anger ($F_{1,75}$ = 9.47, P = 0.02). In summary, there is initial empirical support for relationships among OM and pain, anxiety, depression, and fatigue in several samples of patients with cancer but little evidence for an association between OM and trouble sleeping. There seem to be no other known studies that investigate the relationship between SM and various symptoms.

CONSEQUENCES OF OM

Patients have reported their experiences with OM to researchers, including consequences.3,4,38 For instance, patients who received radiotherapy (n = 33) for head and neck cancer identified OM as the most troublesome and debilitating of all adverse effects they experienced.3 Consequences of OM in these patients included difficulty eating/drinking (88%), weight loss (83%), depression (38%), difficulty talking (29%), sleep disturbances (25%), and hospitalization (13%).3 Among patients with weight loss, 29% had gastric tube placement to assist with oral intake. In this foundational research on OM, there is no evidence that any researchers have focused on the consequences of patient-reported SM.

Conceptual Framework

Armstrong's SEM 5 served as the conceptual framework for the study. The term symptoms experience is conceptually defined using Armstrong's definition 5 for this study as "the perception of the frequency, intensity, distress, and meaning occurring as symptoms are produced and expressed."5 For this study, symptom experience is operationally defined in 2 ways: (1) severity and distress of individual symptoms (SM and 4 others-fatigue, feeling down/blue, feeling anxious, and trouble sleeping) and (2) a statistically significant association between any 2 symptoms.

Armstrong's SEM includes the overall symptoms experience, along with antecedents, defining attributes, and consequences of the symptoms and consequences of the overall symptoms experience. Armstrong used symptoms in the plural when discussing an experience. For the purposes of this study, symptom is used in the singular form because all the symptoms combined together are viewed as comprising a symptom experience.

Antecedents that affect the symptom experience fall into 3 major categories: demographic characteristics (age, sex, race), disease characteristics (type and state of disease, treatment, comorbidities), and individual characteristics (health knowledge, values, past experiences).5 In this study, antecedents included age, sex, marital status, type of cancer, and type of chemotherapy. Defining attributes include a symptom's frequency, intensity, distress, and meaning.5 In this study, defining attributes of symptoms were operationally defined as symptom occurrence, severity, and distress, since these were captured in the parent study dataset on a daily basis. Consequences, or negative overall effects of the symptom experience, include specific health outcomes in numerous populations, including those with cancer.5 Examples of consequences within the SEM include adjustment to illness, quality of life, mood, functional status, disease progression, and survival. In this study, the major consequence was impairment in functional status as measured by amount of oral liquid intake, time spent lying down, ability to work, and interference of symptoms with daily activity.

Following the recommendation of Magee et al 39 that a guiding conceptual model will promote a rigorous secondary data analysis and guard against threats to study validity (including external validity [ie, generalizability of findings]), the researchers used SEM 5 as the conceptual framework for analyzing the data for this respective study. Armstrong's SEM also helped organize and classify variables that potentially contributed to (antecedents) SM and its consequences (negative overall effects). Finally, SEM allowed for simultaneous investigation of the effects of severity and distress of SM and other symptoms on the overall SM experience.

Methods

Design

This study was a retrospective descriptive, correlational secondary analysis. Data were used from a prospectively conducted randomized clinical trial entitled "Telephone-Linked Care for Cancer Symptom Monitoring."40 The purpose of the parent study was to assess the efficacy of the telephone-linked care (TLC) chemotherapy alerting system in the symptom management of adults receiving chemotherapy for cancer. The TLC chemotherapy alerting system was a computer-based communication system, using a digitized human voice that recorded and monitored patients' cancer symptom experience through daily, automated telephone "conversations."

Mooney and colleagues 40 described in detail how the TLC script and interview guide were created and tested in pilot work. To assess patients' symptoms, a rating system of 1 to 10 was used with scores increasing as severity increased. An expert panel provided input into the symptom measurement system and drill-down questions if there were any symptoms reported. The script was pilot tested with 27 patients with cancer who reported a high satisfaction with TLC. The technique, TLC voice, and the duration of the calls were acceptable to patients without any difficulty understanding and responding to respective questions.

In consenting to the parent study, participants provided blanket consent for future secondary analyses such as this study. In this secondary analysis, all identifying information (name, social security number, address, etc) was separated from the data. The study was approved by the University of Utah Institutional Review Board. Methods of the TLC parent study, along with specific elements that pertain to this secondary analysis, are discussed below.

Sample and Setting

The original TLC study sample consisted of 223 participants in 4 outpatient chemotherapy treatment centers

across the United States who reported at least one of several targeted symptoms during the first cycle of chemotherapy. In addition, TLC patients needed to have daily access to a touch-tone telephone, understand and speak English, be 18 years or older, have no physical or mental conditions that would have prevented them from participating, and be beginning cycle 2 of cancer chemotherapy with or without biotherapy. Since the 223 participants were screened on all symptoms in the parent study, all of them were used for this secondary analysis, thus allowing an examination of symptom associations in patients who experienced SM and at least one other symptom of interest.

Variables and Measures

In the original TLC parent study,40 the researchers selected common chemotherapy-related symptoms and presented them to participants in everyday language. For example, instead of asking patients whether they were experiencing depression, anxiety, and/or OM, they used the terms feeling down /blue, feeling anxious, having trouble sleeping, and sore mouth. The TLC parent study investigators assumed that these descriptors represented depression, anxiety, insomnia, OM, respectively.

Participants were instructed to call one time per day during cycles 2 and 3 of chemotherapy. They were asked whether they had nausea and vomiting, had trouble sleeping, were experiencing fatigue, were feeling down/blue, were feeling anxious, had SM, had fever and chills, had diarrhea, had constipation, had pain, and had distress about appearance changes. If they answered in the affirmative for any symptom, they were then asked to rate its severity and distress separately using a scale of 1 (minimal) to 10 (worst). Later during the telephone call, the TLC system asked questions about specific consequences of the symptoms in 4 areas. First, patients reported how much their symptoms prevented them from doing their daily activities (on a scale of 0-10, with 0 meaning that the symptoms did not in any way prevent them from doing daily activities and 10 meaning that the symptoms completely prevented them from doing daily activities). Second, they reported the amount of time in hours they had spent lying down in the previous 24 hours. Third, patients who were actively working indicated whether they had worked the last day they were supposed to work. Fourth, they also reported the number of 8-oz glasses of liquid they consumed in 24 hours. In addition to symptom-related data, demographic and clinical data were collected from each patient, specifically age, sex, marital status, ethnical background, educational level, type of cancer, and type of chemotherapy. The number of days in a cycle of chemotherapy ranged from 21 to 28 days.

Analysis

SPSS version 11.0 (SPSS Inc, Chicago, Illinois) was used to manage and analyze the data. To create measures of severity and distress across multiple daily calls, aggregated scores were computed similar to the method used by Cleeland and Ryan 41 in scoring the Brief Pain Inventory. In this method, the highest, average, and lowest (HAL) ratings of SM severity and distress across all of a given patient's calls were summed and averaged to obtain an SM severity and distress score forboth cycles of chemotherapy. This method captured the variability in individual ratings of all respective symptoms. For the consequence measures (interference of symptoms with daily activities, time spent lying down, and liquid intake), the same method was used to create a HAL score for daily activity, time spent lying down, and liquid intake.

If a patient called into the system and did not report SM, he or she was categorized as a nonresponder in terms of SM, even if at least 1 of the other 9 symptoms was reported. For instance, a patient could report nausea and vomiting and trouble sleeping but no SM. On days when patients did not call into the system at all (ie, missed a call), they were coded as missing. Descriptive statistics, independent t tests, and $[chi]^2$ tests were used to analyze patients' characteristics and SM severity and distress. Analyses of relationships among SM and other variables were conducted using Pearson correlations, tests of differences in correlations, and paired t tests to

examine differences in symptom severity across time.

Findings

Specific Aim 1

Specific aim 1 evaluated the demographic and clinical factors associated with the occurrence of an SM. Of the 223 outpatients in the TLC study, 115 (51%) reported an SM at least once over 2 cycles (cycles 2 and 3) of chemotherapy. Table 1 presents the demographic and clinical characteristics of those patients who did (n = 115) and did not (n = 108) report an SM.

Characteristics	Patients With Sore Mouth n = 115		Patients Without Sore Mouth n = 108		P
	n	%	n	%	
Sex					.87
Male	23	20.5	24	22.0	
Female	89	79.5	84	78.0	
Missing	3	…	…	…	
Marital status					.21
Single	10	9.1	16	15.1	
Married	83	75.5	79	74.5	
Separated	2	1.8	1	0.9	
Divorced	10	9.1	3	2.8	
Widowed	5	4.5	7	6.6	
Missing	5	…	2	…	
Educational level					.54
0–8 y	1	0.9	2	1.9	
1–3 y in high school	1	0.9	5	4.7	
High school graduate	27	24.5	30	28.3	
Some college	34	30.9	25	23.6	
Associates degree	11	10	13	12.3	
Bachelor's degree	21	19.1	19	17.9	
Postgraduate	15	13.6	12	11.3	
Missing	5	…	2	…	
Ethnicity					.83
White	102	94.4	98	91.6	
Black/African American	4	3.7	6	5.6	
Asian	0	0	1	0.9	
Pacific Islander/Hawaiian	1	0.9	1	0.9	
Other	1	0.9	1	0.9	
Missing	7	…	1	…	
Cancer					<.001[a]
Breast	58	53.7	36	33.6	
NHL	14	13.0	3	2.8	
Ovarian	9	8.6	19	17.8	
Lung	6	5.6	14	13.1	
Colon	6	5.6	16	15	
Prostate	2	1.9	2	1.9	
Other	13	12.0	17	15.9	
Missing	7	…	1	…	
Chemotherapy					.01[a]
AC	29	27.4	16	15.2	
CMF	13	12.3	6	5.7	
AC/Taxol	3	2.8	4	3.8	
R-CHOP	8	7.5	2	1.9	
5-Fluorouracil	3	2.8	5	4.8	
Taxol/Carboplatin	13	12.3	21	20.0	
AC/Taxotere	7	6.6	2	1.9	
Other	30	28.3	49	46.7	
Missing	9	…	3	…	
Age, y					
Mean	53.92		57.75		
SD	11.97		12.18		$t = 2.33$, $P = .21$

[a] $P < .001$.

Table 1 Demographic and Clinical Characteristics of the Sample and Subgroups With and Without a Sore Mouth and Differences Between Groups ($[chi]^2$)

Those reporting an SM were younger (53.92 years) than those who did not (57.75 years) (t = 2.33, P = 0.21). Participants with an SM were mostly women (79.5%), were white (94.4%), were married (75.5%), and had some college education (31%). When compared with patients without an SM, those reporting SM were more likely to be diagnosed with breast cancer or Non-Hodgkin's Lymphoma (NHL) ($[chi]^2 = 40.6$, P = .001) and to receive doxorubicin and cyclophosphamide ($[chi]^2 = 9.17$, P = .01) (Table 1).

Table 2 presents the HAL severity scores for SM, trouble sleeping, feeling anxious, feeling down/blue, and fatigue. The mean (SD) HAL SM severity score for cycle 2 was 3.1 (1.50), whereas for cycle 3, it was 3.09 (1.52), and these scores were not significantly different (t_{169} = .38, P = .90). Correlations between HAL SM severity score in cycle 2 and HAL SM severity score in cycle 3 revealed that scores were moderately and significantly correlated (r = .56, P < .001).

	HAL Severity Score	HAL Distress Score
	Mean (SD)	Mean (SD)
Sore mouth	3.05 (1.57)	3.01 (1.55)
Trouble sleeping	2.19 (1.37)	4.32 (1.63)
Feeling down/blue	1.57 (1.45)	4.12 (1.67)
Feeling anxious	1.37 (1.36)	1.50 (1.47)
Fatigue	3.20 (1.53)	4.15 (1.53)

Table 2 Mean and SD of Highest, Average, and Lowest (HAL) Severity and Distress Scores for Each Symptom (Possible Range = 1-10)

Specific Aim 2

Specific aim 2 examined relationships among SM severity, SM distress, and the severity and distress of feeling blue, feeling anxious, trouble sleeping, and fatigue over cycles 2 and 3 of chemotherapy (see Table 3). The entire sample of patients (n = 223) were used in these correlations because this allowed examination of associations that included those who may or may not have experienced any of the symptoms of interest. Statistically significant bivariate Pearson correlations (P < .001 with a medium effect size) between SM severity and severity of other symptoms included trouble sleeping, r_{223} = 0.42; fatigue, r_{223} = 0.400; feeling down/blue, r_{223} = 0.36; and feeling anxious, r_{223} = 0.28. Statistically significant (P < .001 with medium or low effect size) bivariate Pearson correlations between SM distress and distress of other symptoms included trouble sleeping, r_{223} = 0.23; fatigue, r_{223} = 0.27; feeling down/blue, r_{223} = 0.16; and feeling anxious, r_{223} = 0.15.

Severity and Distress Measures	SM Severity	SM Distress
Trouble sleeping	0.42[a]	0.23[a]
Feeling down/blue	0.36[a]	0.16[a]
Feeling anxious	0.28[a]	0.15[a]
Fatigue	0.40[a]	0.27[a]

[a]$P < .001$. Correlations represent a match of each severity and distress score by symptom.

Table 3 Correlations of Sore Mouth (SM) Severity and Distress With Severity and Distress of Other Symptoms

Specific Aim 3

Specific aim 3 explored the consequences of the overall experience of SM and other symptoms in outpatients receiving chemotherapy. Table 4 presents descriptive data from patients with and without an SM in relation to amount of daily oral intake daily activity and time spent lying down. To investigate the presumed consequences of an SM, articulated earlier in the discussion of the conceptual model, associations between HAL SM severity scores and HAL scores of amount of daily oral liquid intake, daily activity, and time spent lying down were investigated using bivariate Pearson correlations. There was a significant positive correlation between SM severity and the number of 8-oz glasses of liquid consumed ($r_{223} = 0.85$ [large effect size], P = .001) and between SM severity and interference with daily activity ($r_{223} = 0.31$ [medium effect size], P < .001). As SM severity increased, it seemed that symptoms prevented participants from completing daily activities. There was also a significant positive correlation between SM severity and time spent lying down ($r_{223} = 0.39$ [medium effect size], P = .001). Thus, as SM severity increased, so did a participant's time spent lying down. Finally, for the 57 participants who were actively working, there was no significant correlation between SM severity and percentage of days they worked when they were supposed to have worked, $r_{57} = -0.12$, P = .39 (Table 5).

	Patients With Sore Mouth		Patients Without Sore Mouth	
	Mean	SD	Mean	SD
How much have your symptoms prevented you from doing your daily activities? Range: 0–10	3.58	2.55	3.11	2.59
In the last 24 h, how much time would you say you have spent lying down, resting, or sleeping? Range: 0–24	11.00	4.19	10.66	3.38
In the last 24 h, how many 8-oz glasses of liquid have you been able to drink?	7.47	3.81	NA[a]	NA[a]

[a]Patient who did not have a sore mouth were not asked this question.

Table 4 Consequences in Participants With and Without Sore Mouth

Consequences	Correlation
Liquid intake	0.85[a]
Time spent lying down	0.39[a]
Interference with daily activities	0.31[a]

[a]$P < .001$.

Table 5 Correlations of Sore Mouth (SM) Severity and Consequences

Discussion

The purpose of this study was to describe the experience of SM, with a focus on severity and distress, associated symptoms, and consequences in patients with cancer receiving cycles 2 and 3 of outpatient chemotherapy. The finding in specific aim 1 suggested that approximately half of the patients experienced an SM, which is somewhat higher than that reported by Dodd et al 1 of an incidence rate between 23% and 26%. Patients in the study by Dodd et al 1 who received similar chemotherapy agents (doxorubicin, 5-fluorouracil, paclitaxel, methotrexate) also received an oral care program entitled PRO-SELF, which might have been partially responsible for the lower levels of mucositis in similar patients in addition to factors discussed earlier. Patients in the secondary analysis study reported here did not receive a formal oral care program, nor was prospective evaluation of OM using the OAG or any other tool possible.

In addition, this study's finding of a HAL SM score of approximately 3 on a 0 to 10 scale is new and suggests SM in this sample may not be very severe. Participants with an SM were more likely to have breast cancer and non-Hodgkin lymphoma and to receive chemotherapy treatments of doxorubicin and cyclophosphamide (AC) and rituximab plus cyclophosphamide, oncovin, doxorubicin, and prednisone (R-CHOP). This finding is not surprising given that anthracycline-based regimens such as AC have been associated with higher levels of OM incidence.24 In this study, women (79.5%) were more likely to report an SM when compared with men. This is similar to work conducted by Vokurka and colleagues,26 who reported a higher incidence of chemotherapy-induced OM in female patients.

The finding in specific aim 2 indicating that both SM severity and distress were positively associated with fatigue, trouble sleeping, feeling down/blue, and feeling anxious is interesting. Because the correlations were moderate, it is unclear precisely how these variables are influencing one another. Nevertheless, this information is important because it suggests that having an SM over a period of time may contribute to trouble sleeping and fatigue, which may in turn lead to feeling down/blue and feeling anxious. These findings support clinical observations that patients with OM often report fatigue, trouble sleeping, depression, and anxiety. In addition, the results are supported by, and add to, previous studies demonstrating relationships among pain, anxiety, depression, and insomnia.16,20 Of interest, in the cases of trouble sleeping, feeling down/blue, feeling anxious, and fatigue, the mean HAL scores are higher for distress than they are for severity of a symptom (see Table 2). This finding suggests that patients rate the distress of a particular symptom, such as fatigue for instance, higher (more troublesome) than they do the severity of the same symptom.

One of the most intriguing elements of these results is the potential insight they may provide into fundamental biological mechanisms underlying interrelated symptoms. There are increased levels of proinflammatory cytokines (especially tumor necrosis factor and interleukin-6) in patients with nonhematologic toxicities that include mucositis.42 Some researchers have theorized that symptom clusters occur as a direct result of massive proinflammatory cytokine production.43 A massive release of cytokines during the ulcerative phase of OM might explain, in part, why patients with OM also experience other symptoms such as fatigue and depression.24 There is recent evidence implicating proinflammatory cytokines as a potential factor in the etiology of anorexia, cachexia, anemia, pain, sleep disturbance, fatigue, and depression.44 Thus, increased release of proinflammatory cytokines occurring as a result of OM may likely contribute to sleep disturbance, fatigue, depression, and anxiety.24 Although exploring this hypothesis is beyond the scope of this study, the relationships found in this secondary analysis provide a foundation for prospective examination of relationships among symptoms, particularly if researchers are able to conduct a prospective study with precise measures of OM. One potentially fruitful area for investigation might involve the identification of symptom clusters involving OM, fatigue, sleep disturbances, depression, and anxiety, coupled with an exploration of possible

etiological mechanisms.18

The finding in specific aim 3 that, as participants experienced increased SM severity, they had decreased daily activities and increased time spent lying down is new but not surprising. What was surprising was that oral intake increased as the severity of participants' SM increased. Clinically, this is counterintuitive since patients often experience an SM that is painful enough to prevent oral intake of both food and liquids. However, because data were collected from the second and third cycles of chemotherapy, it is possible that patients' experiences of SM in cycle 1 taught them that they could tolerate oral intake despite discomfort. In addition, they may have received education from their healthcare providers on the importance of proper oral intake after chemotherapy. Perhaps the most likely explanation is that because of the HAL severity score of approximately 3 (in a range of 1-10), overall SM severity was not significant enough to interfere significantly with oral intake.

The finding that an increase in SM did not significantly affect patients' ability to work suggests that, although they had negative consequences as a result of SM and other symptoms, those consequences did not interfere with their work role. This finding is limited, however, by the fact that only 57 participants were working while receiving outpatient chemotherapy.

Previous research focusing on the consequences of OM has been limited, as noted earlier, with existing research focusing on economic, clinical, and quality of life outcomes using aggregated samples across a variety of disease and treatment types.13,45 Although this work is important, it does not focus on the actual daily consequences related to OM nor to SM. Thus, the unique aspect of this study is that it lays a foundation for future prospective investigation (using precise OM measurement tools) of the impact of OM on important elements of daily life such as nutrition and functional status.

Limitations

Conduct of a secondary analysis study poses certain limitations that must be noted. First, the data analysis is restricted to the data already collected, and these data may not provide all the needed information. For instance, in this study, SM was used as a subjective indicator for OM, thus it is unclear whether the 115 patients reporting SM actually had documented OM, which by definition consists of erythema and ulceration and may or may not include oral pain (SM).24 As a result, the associations among severity and distress of SM (and therefore presumed OM) and other symptoms must be cautiously interpreted. Second, the items used in this secondary analysis were single indicator items assumed to represent the constructs of fatigue, insomnia, depression, and anxiety as opposed to psychometrically sound scales measuring these constructs, thus it cannot be assumed that the single items were valid measures of the constructs of interest.

Several factors prevent generalizing these findings beyond the immediate sample. First, the sample consisted primarily of white women with some college education, who were married and had breast cancer. Second, data were analyzed only for cycles 2 and 3 of chemotherapy. Details of SM and the relationships with other symptoms during the first cycle of chemotherapy (received prior to participating in the TLC study [Table 6]) and all subsequent cycles were not available. Finally, the parent study also investigated nausea and vomiting, distress about changes in appearance, fever and chills, diarrhea, constipation, and pain other than SM, but relationships among SM and these symptoms were not examined as they were beyond the scope of this inquiry. Thus, the possibility that significant relationships may have existed among SM and other symptoms cannot be ruled out.

Specific Area	Question Number	Question
Trouble sleeping	2	Did you have trouble sleeping last night? Press (1) for yes, (2) for no. If yes, go to questions 36 and 37.
	36	How severe was your trouble sleeping last night? Rate the severity on a scale of 1 to 10.
	37	On a 1 to 10 scale with 1 being not at all distressing and 10 being completely distressing, how distressing has your trouble sleeping been in the last 24 h?
Fatigue	3	Have you experienced fatigue during the last 24 h? Press (1) for yes, (2) for no. If yes, go to questions 59 and 60.
	59	On a scale of 1 to 10, how would you rate the severity of your fatigue?
	60	On a 1 to 10 scale with 1 being not at all distressing and 10 being totally distressing, how distressing has your fatigue been in the last 24 h?
Feeling down/blue	4	During the past 24 h have you felt blue or down? Press (1) for yes, (2) for no. If yes, go to questions 68 and 69.
	68	On a scale of 1 to 10, how would you rate the severity of your feeling down?
	69	On a 1 to 10 scale with 1 being not at all distressing and 10 totally distressing, how distressing has this feeling been in the last 24 h?
Feeling anxious	5	Have you felt nervous or anxious in the past 24 h? Press (1) for yes, (2) for no. If yes, go to questions 79 and 80.
	79	On a scale of 1 to 10, how would you rate the severity of your feeling nervous or anxious?
	80	On a 1 to 10 scale with 1 being not at all distressing and 10 being totally distressing, how distressing has your feeling nervous or anxious been in the last 24 h?
SM	10	Have you had an SM during the last 24 h? Press (1) for yes, (2) for no. If yes, go to questions 135 and 136.
	135	On a scale of 1 to 10, how would you rate the severity of your SM?
	136	On a 1 to 10 scale with 1 being not at all distressing and 10 being totally distressing, how distressing has your SM been in the last 24 h?
	137	In the last 24 h, how many 8-oz glasses (1 cup) of liquid have you been able to drink? Tell me the number of 8-oz glasses or cups you have drunk.
Other questions	12	Take a moment to think about how you have been feeling, overall, during the past 24 h. How much have your symptoms prevented you from doing your daily activities? Please rate your answers on a scale from 0 to 10, with 0 meaning that your symptoms did not in any way prevent you from doing your daily activities and 10 meaning that your symptoms completely prevented you from doing your daily activities.
	13	Were you able to go to work yesterday? Press (1) for yes, (2) for no, and (3) if yesterday was not a work day.
	14	In the last 24 h, how much time would you say you have spent lying down, resting, or sleeping? Enter number of hours from 0 to 24 that corresponds with the number of hours you have spent lying down, resting, or sleeping.

Table 6 Telephone-Linked Care Script of Questions Asked of Participants

Although the HAL method helped capture the variability in individual ratings of symptoms, the researchers acknowledge that there are limitations to this method. The HAL technique and other traditional statistical methods (eg, repeated-measures analysis of variance) are useful when studying mean group differences in change over time,46 but these same methods limit the ability to explore individual symptom trajectories over time. A different technique, known as visual graphical analysis, described recently by several of this manuscript's authors,47 offers a method for investigating individual daily patterns of symptoms over time and might be useful in future prospective work.

Implications and Conclusions

Clinical implications of these results include both assessment and management. As long as outpatients experience OM and associated symptoms as a consequence of chemotherapy, there is a clear need for a better system to assess symptoms. This can be a challenge because these patients are not usually followed in person between cycles of chemotherapy. These assessments should use validated instruments that include visual analog or numerical rating scales 17 to obtain self-reported symptom data if at all possible. Another important implication is identifying better methods to obtain data on OM rather than the subjective indicator of SM in these patients. Teaching patients how to use standard tools for assessing oral complications, such as the OAG,31 is one possible strategy, although the OAG has limitations as a precise measure of OM. Additional work should focus on developing ways to more specifically assess presence, severity, and consequences of OM in chemotherapy outpatients. It is important that an assessment should focus on patients with particular risk

factors and in different age cohorts.48

The association of symptoms with SM and the consequences observed in patients with OM suggest that interventions targeting these symptoms and their sequelae warrant investigation. To date, there have only been a few attempts to develop interventions that target OM and some of its associated symptoms.21 Development of therapeutic interventions that may eliminate or ameliorate SM and related symptoms could focus not only on symptom management but also on improving patients' abilities to reduce negative consequences and improve their functional status and overall quality of life.

There are important educational implications arising from this study. Healthcare providers should be educated on the importance of assessing multiple symptoms in outpatients to alleviate those symptoms, to improve quality of life, and to provide patients with the best opportunity to complete their respective treatment and to cure or control their cancer. Furthermore, appropriate education of healthcare providers should include the important consideration of the consequences and detriments to daily living, such as oral intake and time spent lying down, of SM and associated symptoms. In addition, patients could be educated on ways to eliminate or lessen some of the consequences associated with chemotherapy treatment. For example, education on the importance of proper oral intake of fluids during the treatment regimen is vital to lessen the chances of dehydration.

Research implications of these results are numerous. It is important to conduct prospective longitudinal studies that measure actual OM to identify symptoms associated with OM and to determine whether they include pain, sleep disturbance, fatigue, depression, anxiety, and other symptoms. Learning more about the nature and trajectory of symptom associations throughout treatment and interrelationships of symptoms within clusters over time should be helpful in assessment and management.

This research is in keeping with the newest Oncology Nursing Society Research Priorities wherein mucositis was ranked 20th in overall symptom importance.49

There is also a need for research that develops and tests intervention strategies focused on alleviating or preventing OM and its associated symptoms. In addition, more research is needed that investigates the consequences of OM, especially in the outpatient population where there is limited access to healthcare providers between chemotherapy treatments. Since the data are inconclusive on whether a particular gender experiences more severe OM, future prospective studies could be designed to detect gender specificity in relation to the impact of OM on overall patient quality of life. Finally, there is a need for studies that focus on the biological mechanisms underlying OM, including the role of proinflammatory cytokines and other substances in the development and interrelationships of OM and other symptoms such as fatigue, depression, and insomnia. Enhanced understanding of the pathobiology could ultimately lead to interventions designed to alleviate the burden associated with mucositis and other symptoms.

Finally, this study is one of the initial studies to examine selected consequences of an SM on oral intake, daily activity, time spent lying down, and the ability to work. The findings will hopefully stimulate further clinical research to delineate better assessment and management strategies for patients who have this challenging treatment-related adverse effect.

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