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A Randomized Phase III Trial of Gabapentin versus Standard of Care for Prevention and Treatment of Mucositis in Locally Advanced Head and Neck Cancer Patients Undergoing Primary or Adjuvant Chemoradiation

Derek Smith, DDS, PhD
Deborah Hawkins, RN, NP
Mary S. Dietrich, PhD
Jill Gilbert, MD
Barbara A Murphy, M.D

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1.0 Background

1.1 Head and Neck Cancer

Worldwide, head and neck cancers affect more than 550,000 individuals annually with men accounting for up to two-thirds of reported cases [1]. The relative prevalence of head and neck cancers can be attributed to the regional variation of risk factors such as tobacco use, alcohol consumption and infection from human papillomavirus (HPV) or Epstein-Barr Virus (EBV)[1-4]. Within the United States, nearly 4% or about 42,000 cases of of all malignancies can be attributed to cancer of the oral cavity and nasopharynx [5]. Treatment for patients with and head and neck carcinomas generally include single modal therapy such as chemotherapy or radiation therapy or treatment with multimodal therapy such as induction therapy with concurrent Chemoradiotherapy[6-11]. Treatment is associated with numerous and often severe toxicities.

1.2 Mucositis

Oral mucositis, ulceration of the oral mucosa, is one of the major and frequent complications of radiation and chemotherapy in head and neck cancer patients[12, 13]. A combination of dose-related chemoradiation epithelial damage, micro-vascular injury, elevated release of cytokines such as TNF-α, and oxidative stress with subsequent generation of reactive oxygen species contribute to the development of oral mucositis[12, 14]. Recent data suggests that occurrence of severe oral mucositis occurs in up to 66-85% of patient's [15, 16]. Development of mucositis is accompanied with severe pain [13, 17]. Mucositis associated pain has a mixed pathogenesis which includes both somatic and neuropathic components. The pain symptoms usually begin two to three weeks after the start of chemoradiation therapy and are at its worst at the completion of therapy. Development of mucositis in cancer patients has significant impacts on health, quality of life, and recovery [14, 17]. Associated pain results in dysphagia making it difficult for patients to eat and thus increasing their risk for weight loss and volume contraction dehydration throughout therapy as well precipitates the need for parenteral nutrition[12, 18]. Furthermore, erosive mucositis puts patients at risk for development of secondary infection and sepsis especially in the presence of concurrent neutropenia [14]. Severe mucositis may require a dose reduction during therapy, altering the course of Chemoradiotherapy originally set forth.

Current treatment of mucositis includes symptom management with routine oral care, mucosal coating agents, chlorhexidine, both topical and systemic analgesics, and oral cryotherapy[15, 16, 18]. Systemic analgesics commonly used for treatment include opioids, non-steroidal anti-inflammatory agents, and acetaminophen[15]. Because of issues with dysphagia, oral administration of analgesics may be hampered. Thus, transdermal formulations are frequently utilized. Unfortunately, opioids are associated with well-documented side effects (e.g. addiction, tolerance, and dependence) and are frequently infective for controlling mucositis associated pain [19]. Thus, a search for other pain medications to manage mucositis induced pain is of clinical importance. Since peripheral sensitization is one of the underlying

mechanisms for mucositis associated pain, it may be hypothesized that agents that are effective for neuropathic pain may modulate mucositis associated pain[17, 20]

1.3 Pain

It is estimated that pain affects more than 20% of adults around the world making it one of the most common patient complaints[21]. Pain is often subdivided into two categories – acute and chronic. Acute pain is believed to be an evolutionarily protective mechanism designed to protect the body from harmful stimuli and situations (ie rapidly moving one's hand from the burning stove). Thus acute pain is the body's defense system that produces reflexive actions to prevent severe tissue injury and allow time for healing. Chronic pain is defined as that which lasts beyond the ordinary duration of time that an insult or injury to the body needs to heal. Unlike acute pain, which has a biological role, chronic pain is a pathological process that causes severe impairment even when the insult or injury has healed.

Two types of pain pathways that have been a target of pharmacological therapy include neuropathic pain and nocioceptive pain. Neuropathic pain results from a lesion or disease of the nervous system that causes abnormal neural activity in the neural pathways that signal pain[22]. Patients with neuropathic pain often describe sensations of "burning," "pins and needles," or "electrical stabbing pains." Etiologies of neuropathic pain fall under four broad categories: (1)focal or multifocal lesions of the peripheral nervous system such as entrapment syndromes, postherpetic neuralgia, or diabetic mononeuropathy; (2) polyneuropathies such a vitamin deficiencies, HIV neuropathy, and hypothyroidism; (3) central nervous system lesions such as multiple sclerosis, thalamic infarcts, and syringomyelia; (4) complex neuropathic disorders such as complex regional pain syndromes (reflex sympathetic dystrophy and causalgia.[22]

Alternatively, the nociceptive pain pathway detects noxious mechanical, thermal and chemical stimuli through their specialized free nerve endings (nociceptors) found in the skin, visceral organs, articular surfaces and periosteal surfaces [23]. Receptors responsible for the transduction of nociceptive signals include the Vanilloid Receptor (VR-1) and the Vanilloid-Like Receptor (VRL-1) [24]. Both of these receptors belong to the larger family of transient receptor potential (TRP) channels that resemble voltage-gated ion channels. Once the nociceptors are stimulated, afferent signals travel via the spinothalamic tracts to the brain synapsing in the sensory cortex where the pain signals are processed. Recent research suggests that there are parallel pain pathways that project to secondary brain regions such as the amygdala, hypothalamus, and reticular formation that regulate the sensory discriminative aspects of pain (location, quality, and quantity of the pain) as well as the affective-motivational aspects of pain that are responsible for evoking fear, anxiety, and activation of the autonomic nervous system (the flight or fight response)[25-29]. Thus pain is a full perceptual experience that involves multiple sensory modalities that results in a constellation of systemic symptoms ranging from changes in mood, cognition dysfunction, as well as neurovegetative and somatic complaints.

There are two mechanisms that are thought to facilitate persistent chronic pain and hyperalgesia – peripheral sensitization and central sensitization. Peripheral sensitization is thought to result from the interaction of nociceptors and the "inflammatory soup" of molecules from the injured or inflamed tissue. The release of bradykinin, cytokines, histamine, prostaglandins, growth factors, and extracellular protons create a chemical environment that interacts with nociceptors and pain nerve fibers, augmenting their response to stimuli. Thus

slightly painful stimuli and or otherwise non-painful stimuli are perceived as significantly more painful. Peripheral sensitization explains why medications such as non-steroidal anti-inflammatory drugs (NSAIDS) and anti-histamines that inhibit the production of prostaglandins and histamine respectively are effective in managing pain. [30]

Central sensitization results from an activity-dependent increase in the excitability of dorsal horn neurons of the spinal cord following repeated stimulation from nociceptive afferent signals. Following repeated stimulation, transcriptional changes of ionotropic NMDA receptors in the dorsal horn cells results in removal of the normal voltage-dependent magnesium ion block, increasing the time the channel is open. This is thought to increase the excitability of the dorsal horn cell. Thus, nociceptive afferents that would otherwise be subthreshold become sufficient to depolarize the dorsal horn neurons of the spinal cord pain pathways. Unlike peripheral sensitization, which is restricted to the site of tissue injury, the effects of central sensitization generalize to other inputs that arise from low-threshold mechanoreceptors. Under normal circumstances, these states of heighted pain response return to normal once the insult is removed and tissue healing is complete. [31] However in many pathological pain syndromes, these thresholds are never restored and previously innocuous stimuli result in symptoms of allodynia and hyperalgesia that can spread beyond the site of injury.

1.4 Gabapentin

Gabapentin is a drug structurally similar to GABA that interacts with voltage calcium channels located throughout cortical brain tissue[32, 33]. Although labeled for treatment of partial seizures, Gabapentin's unlabeled indications include treatment of neuropathic pain conditions such as restless leg syndrome, diabetic neuropathy, fibromyalgia and migraines [33-35]. The question has been raised as to whether Gabapentin can decrease radiation-induced acute and chronic oral mucositis pain in head and neck cancer patients. The majority of data looking at Gabapentin in management of acute and chronic pain has taken been done in the setting of post-operative management. A review of Gabapentin in the treatment of acute post-operative pain by Chang et all found that the administration of gabapentin was associated with post-operative reductions of (1) rescue analgesics and pain scores in patients undergoing coronary artery by-pass graft, (2) the requirements of antiemetics in patients undergoing neurological surgery and hysterectomy, and (3) a reduction in pain and narcotic use in patients undergoing lumbar spinal surgery at every time point [36]. A second study by Straube et all found that single 250 mg dose of Gabapentin was associated with 50% reduction in acute pain over 6 hours post-operatively (RB of 2.5 with 95% CI 1.2 to 5.0) in 15% of patients vs only 5% in controls as well as a decreased usage of rescue medications [37]

A study looking at the effects of Pregabalin, a drug structurally similar to Gabapentin, found that Pregabalin is effective at reducing neuropathic and inflammatory orofacial pain in rat models [38]. Gabapentin has also been found to improve dysphagia in patients with oropharyngeal squamous cell carcinoma (OPSCC). A case report of 10 head and neck cancer patients treated with gabapentin after failing other interventions found that three 300 mg doses of gabapentin daily eliminated neuropathic pain in 8 of the 10 patients with partial relief of symptoms in the remaining 2 [39]. A study by Starmer et all found that prophylactic treatment of Gabapentin in patients with OPSCC was associated with delayed onset of PEG use (3.7 vs 2.29 week; P=0.013) and earlier removal of their PEG tubes (7.29 vs 32.56 weeks; P=0.039) than controls [40]. Thus it is plausible that treatment of oral mucositis with Gabapentin can be

hypothesized to improve not only pain but also improve quality of life parameters such as swallowing and nutritional intake.

A retrospective study evaluated this question. Investigators conducted a chart review of 42 patients with head and neck malignancies treated with concurrent chemoradiotherapy using an intensity-modulated radiotherapy technique. Pain outcomes for patients treated with gabapentin for prevention of mucositis associated pain were compared to pain outcomes for patients using standard supportive care. Results found that preventive administration of gabapentin reduced overall pain levels and the total dose of opioids utilized [34]. Although the data is intriguing, there are numerous limitations to this study. First, the study was retrospective. Second, patients were not randomized and third, outcomes were not pre-established. None-the-less, the data would support further investigation of gabapentin as chronic preventive measures for mucositis associated pain in patients undergoing chemoradiation for head and neck cancer

1.6 Study Summary:

The overall goal of this study is to determine whether or not Gabapentin can reduce mucositis associated pain in head and neck cancer patients undergoing chemoradiation. Patients seen in the Oncology Clinic for routine surveillance will be informed about the study and asked if they interested in participation. Interested patients will be asked to sign an informed consent. They will then be randomized into to two arms—standard of care and standard of care plus gabapentin. Prior to chemoradiation therapy, subjects will undergo education on chemoradiation as well as foundations of oral care. Subjects will be asked to complete a demographic survey, the Head and Neck Symptom Survey 2.0 plus the General Symptom Survey (VHNSS v2.0 plus GSS), the Profile of Mood States – short form (POMS-SF), the Neurotoxicity Rating Scale (NRS), the and a Quality of Life (QOL) assessment as outlined below. Subjects will also be requested to maintain a pain diary that will be used throughout the study to assess their pain and their mucositis will be graded weekly during their visits.

Upon completion of therapy, the data will be collected and stored in a secure password protected database and the patient's study participation will end. We anticipate the study duration to be 2 years.

2.0 Specific Aims

Specific Aim 1: To determine whether Gabapentin used as a preventive measure during chemoradiation can reduce radiation-induced mucositis associated pain in head and neck cancer patients as measured by: 1) pain scores on the Vanderbilt Head and Neck Symptom Survey (VHNSS version 2.), and 2) analgesic use.

Hypothesis 1.1: Compared to controls, patients using Gabapentin during radiation-based therapy will have a 1.5 point decreases in self-reported oropharyngeal pain (on a scale of 0 to 10) week six of radiation.

Hypothesis 1.2: Compared to controls, patients using Gabapentin during radiation-based therapy will have a 20% decrease in opioid use (as measured in morphine equivalents) at week six of radiation.

Specific Aim 2: To determine whether pain control is associated with weight loss (in pounds) and duration of use of percutaneous endoscopic gastrostomy utilization (in days).

Hypothesis 2.1 Patients with less pain will have decrease weight loss.

Hypothesis 2.2 Patients with less pain will have a shorter duration of PEG placement.

Specific Aim 3: To assess the safety (grade 3 or 4 adverse events) and tolerability of using gabapentin (discontinuation of drug due to side effects - yes or no).

Specific Aim 4: To correlate pain severity with frequency and severity of general systemic symptoms.

3.0 Inclusion/Exclusion Criteria

Inclusion Criteria

- Histologically proven cancer of the head and neck cancer
- Stage 3 or 4 under the AJCC and IUCC staging System OR patients with Stage 1 or 2 disease who will receive radiation equivalent to patients with Stage 3 or 4 disease
- Planned primary or adjuvant chemoradiation therapy
- Willing and able to provide informed consent
- Age $\geq$ 21 years
- English speaking

Exclusion Criteria

- Currently on gabapentin
- Prior non-tolerance of gabapentin
- History of seizure disorder

4.0 Enrollment/Randomization

A total of 150 patients planned for primary and adjuvant radiation with or without chemotherapy will be recruited. These patients will be identified in the Vanderbilt Oncology Clinic and at head and neck tumor board. Study staff will approach patients to discuss the study and the possibility of patient participation therein. The objectives and requirements of the study will be described to the patients and any questions will be answered. Interested patients will be given consent for to review. If the patient volunteers to participate in the study, the consent will be signed and they will be given a copy for their records. The original copy will be retained in the study files. The patient will be assigned to the usual care or usual care plus gabapentin arm of the study according to the next group assignment specified in the randomization list generated via the use of a computer-generated, permuted block program developed by Co-I Dietrich.

5.0 Study Procedures

5.1 Chemoradiation:

Chemotherapy and radiation will be instituted per standard of care. There will be no alterations in standard of care as a result of participation in this study. Disease treatment related data will be obtained through chart review after the completion of therapy.

5. 2 Study Treatment:

Patients will be randomized to Arm 1 (Usual Care) or Arm 2 – (Usual Care plus Gabapentin).

Arm 1: Usual Care:

Usual care will include the following:

1. Oral health measures including brushing, flossing, and the use of fluoride toothpaste
2. Oral rinsing with baking soda and salt water gargles every 2-3 hours while awake
3. Miracle mouthwash formulated to include topical lidocaine, Benadryl, and Maalox;
4. Nonsteroidal anti-inflammatories around the clock to treat pain and inflammation
5. Opioid analgesics to include a fixed and breakthrough medication.

Patients will undergo an education session at the beginning of treatment to review foundations of oral care and pain management.

Arm 2: Usual Care plus Gabapentin.

Patients will receive all measures for Arm 1 **PLUS** Gabapentin. Gabapentin will be dose escalated using a slow escalation schema to minimize the sedating effects of medication and avoid undue toxicities:

Week 1: Gabapentin 100 mg PO 3 times a day
Week 2: Gabapentin 300 mg PO 3 times a day.
Week 3: Gabapentin 600 mg PO 3 times a day.
Week 4 onward: Gabapentin 900 mg PO 3 times a day.

The highest tolerated dose of gabapentin will continue throughout treatment. Missed doses, though regrettable, are part of any patient-administered medication and will not be considered deviations for this study as we are studying practical efficacy. After completion of therapy, mucositis is expected to resolve at a variable rate (1 to 3 months post treatment). Gabapentin will be continued until mucositis resolves **and** pain subsides. Patients will be weaned off opioids prior to initiation of gabapentin de-escalation. Once opioids have been weaned, de-escalation of gabapentin will be initiated. Since the rate at which patients can be weaned of pain medications is variable, de-escalation will be managed by the treating physician. Abrupt discontinuation of gabapentin will be discouraged in order to avoid symptoms related to withdrawal.

5.3 Dose Modifications:

Prior to each dose escalation, patients will be assessed for side effects related to gabapentin.

- Patients who are tolerating the current dosing schedule will undertake an escalation to the next dose level.
- If patients have mild to moderate side effects related to gabapentin, no further dose escalation will be undertaken
- If patients develop severe side effects attributable to gabapentin, gabapentin will be held until the side effects have totally resolved and then restarted at the last known tolerated dose level.
- Although rare, severe mood alterations and suicidal thoughts have been associated with this agent. Should patients experience these symptoms, gabapentin will be permanently discontinued.

5.4 Route of Administration:

Gabapentin is usually taken orally. Gabapentin may also be crushed and given via feeding tube if the patient is unable to swallow the tablet.

5.5 Pain Management:

Pain management for tumor and treatment related toxicities will be at the discretion of the treating physician. Opioid and adjuvant use will be documented for study purposes. At the completion of study, patients on Arm 1 may be started on gabapentin if they have uncontrolled mucositis associated pain. For patients assigned to Arm 1, the treating physician will manage the utilization of gabapentin during the post-treatment phase

5.6 Study Visits:

In order to minimize inconvenience to patients under study, study visits will coincide with scheduled treatment. This may introduce a degree of variability in the timing of weekly visits and follow-up visits which will be considered acceptable accept in cases where explicit visit timing is dictated elsewhere in the protocol. Weekly on treatment visits that are more than 1 week late will be considered missing.

Baseline:

Prior to initiating therapy, patients will undergo education sessions with study staff. The educational intervention will include a discussion of oral health foundations as well as a discussion of pain management. This education is standardly applied to all VUMC patients undergoing radiation therapy for HNC and will not be otherwise documented. In addition, patients will also be given written material to review. Patient will be given a pain diary and instructed on its use. Baseline pain medication use will be documented. Patients will complete the demographic survey. Patients randomized to gabapentin will be given a prescription for gabapentin with dose escalation as noted in the treatment section. Patients who do not have insurance or who are unable to afford gabapentin will be provided with medication from the indigent pharmacy. All baseline assessments must be done within 4 weeks of starting concurrent chemoradiation.

Weekly On Treatment Visits:

Starting with the initiation of concurrent chemoradiation, patients will be evaluated on a weekly basis. The evaluation will include:

1) review of the weekly pain survey
2) for patients on gabapentin (Arm 2) --we will review their compliance log and identify any barriers to compliance and strategies to improve their compliance
3) adjustment of pain regimen
4) completion and review of the Vanderbilt head and neck symptom survey
5) mucositis grading.

End-of-Treatment Visit:

Patients will undergo an evaluation at their final radiotherapy visit or within 2 weeks after. This will include the following:

1) review of the monthly diary survey
2) for patients on gabapentin (Arm 2) --we will review their compliance log and identify any barriers to compliance and strategies to improve their compliance

3) adjustment of pain regimen
4) completion and review of the Vanderbilt head and neck symptom survey
5) mucositis grading.

6.0 Study Measures:

6.1 Mucositis Grading:

Patients will have an oral exam twice a week as part of standard of care. Mucositis will be graded based on the World Health Organization criteria. Mucositis assessments will be done by trained study staff.

6.2 Patient Reported Outcome Measures:

Study Visit: The study nurse will meet with the patient at baseline, weekly during radiation therapy, and at 1, 2 and 3 months post-treatment. At each study visit the study nurse will 1) administer appropriate questionnaires, 2) review the patient's pain diary and compliance diary, 3) document concurrent medications, 4) document toxicities based on CT CAE criteria 4.0, 5) identify and prepare reports for any adverse events, 6) document any dose adjustments in pain medications as recommended by the physician or nurse practitioner, and 7) educate the patient regarding medication dose and schedule.

As these patient reported outcome measures represent outcomes of interest for the study, they will not be altered by study staff due to missingness as changes would threaten the validity of the tool.

Appendix A: *Demographics:*

Includes date of birth, gender, race, education, marital and employment status, area of residence, presence of any co-morbid conditions, medical history, alcohol use, tobacco use, and dietary habits. To be completed by the patient –approximate time for completion is 3 to 5 minutes.

Appendix B: *Vanderbilt Head and Neck Symptom Survey version 2.0 (VHNSS 2.0)*

This 61-item instrument has been developed specifically to measure acute and late symptoms in HNC patients. Items are summed to provide a total score as well as 13 domain scores. Studies have reported good internal consistency for the total VHNSS scale (alpha=0.94) and five subscales (i.e., swallow, nutrition, mucous/dry mouth, pain, voice) (alphas=0.77-0.93), and adequate convergent and divergent validity. Mean scores on each VHNSS subscale can range from 0 (none) to 10 (a lot). Higher scores reflect greater symptom burden. To be completed by the patient – approximate completion time less than 10 minutes.

Appendix C: *Pain Survey:*

Patients will be asked to complete a pain survey that will allow the healthcare providers and study investigators to appropriately assess and monitor the patient's pain throughout the study.

Patients will be asked to mark their **average pain** , **current pain** and their **worst pain** every week on a scale from 1-10, 10 being the worst pain they have ever felt. They will also be asked to document the number of rescue doses used each day.

Appendix D: *Compliance Diary:*

Patients on the gabapentin arm will be asked to maintain a complete a survey to document compliance with gabapentin. The reason for missed doses will be captured.

Appendix E: *Profile of Mood States-Short Form:* The Profile of Moods states is a 37-item scale is composed of six subscales: depression, vigor, confusion, tension, anger and fatigue. Cronbach's alphas ranged from .78 to .91. It correlates will with other measures of mood and physical function, yet is has the benefit of a short administration time.

Appendix F: *Neurotoxicity Rating Scale (NRS):* The NRS is a 37 item instrument whose items reflect symptoms associated with neurotoxicity of medical treatment [41]
Participants rate the severity of all of the 37 item, 5 point Likert-like scale that rates neuropsychiatric symptoms on a scale of "not present" to "extremely severe."

Appendix G: *Quality of Life* QOL will be measured using Cantril's Ladder, a single item self-anchoring scale ([42]; [43]). The measure asks patients to rate their current quality of life on a scale ranging from 0 to 10, with higher scores indicating better overall quality of life. Discriminant validity has been supported by significantly lower scores in patients with rheumatoid arthritis than in healthy controls ([44]). Construct validity has been supported by a positive relationship between scores on to social role retention in survivors of bone marrow transplantation ([45]). A 5 item domain-specific QOL questionnaire will also be used.

Appendix H: *Disease and Treatment Data Form* – Data related to the patient's cancer and treatment including diagnosis date, location, stage of disease, surgical treatment, medical oncology treatment, and radiation oncology treatment will be determined by medical record review at the time of the study visit and will be completed by study nurse or study providers.

Appendix I: Studies to be Done:

	Baseline¥	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6 *	Week 7 *	1,2 3 Months post tx
Study Visit	X	X	X	X	X	X	X	X	X
Chemoradiation Teaching	X								
Foundations of Oral Care	X								
Foundations of Pain Management	X								
Randomization	X								
Gabapentin Arm 2 Only		X	X	X	X	X	X	X	X
Mucositis Grading	X	X	X	X	X	X	X	X	X
Demographic Survey	X								
VHNSS Version 2.0		X	X	X	X	X	X	X	X
Pain Survey		X	X	X	X	X	X	X	X
Compliance Survey Arm 2 Only		X	X	X	X	X	X	X	X
Neurotoxicity Scale	X						X		X (month 3 only)
POMS	X						X		X (month 3 only)
QOL	X						X		X (month 3 only)

Disease and Treatment Form	X								

¥ All baseline assessments must be done within 4 weeks before starting concurrent chemoradiation.
* Weekly assessments will continue until the completion of chemoradiation which may vary between 5 and 7 weeks.

An End of Treatment Visit will be conducted 2 weeks after Chemoradiation therapy

7.0 Risks of Investigational Agents/Devices (side effects)

Gabapentin:

- >10%
  - **Central Nervous System**: Dizziness (IR 17% - 28%, ER 11%), Drowsiness (IR 19%-21%; ER 5%), Ataxia (1% to 13%), Fatigue (11%)
- 1-10%
  - **Cardiovascular**: Peripheral edema (IR: 2% to 8%; ER: 4%), vasodilatation (1%)
  - **Central nervous system**: Hostility (children 5% to 8%), tremor (7%), emotional lability (children 4% to 6%), hyperkinesia (children 3% to 5%), headache (ER: 4%; IR: 3%), abnormality in thinking (2% to 3%; children 2%), abnormal gait (2%), amnesia (2%), depression (2%), nervousness (2%), pain (ER: 1% to 2%), hyperesthesia (1%), lethargy (ER: 1%), twitching (1%), vertigo (ER: 1%)
  - **Dermatologic**: Pruritus (1%), skin rash (1%)
  - **Endocrine & metabolic**: Weight gain (IR: Adults and children 2% to 3%; ER: 2%), hyperglycemia (1%)
  - **Gastrointestinal**: Diarrhea (IR: 6%; ER: 3%), nausea and vomiting (3% to 4%; children 8%), xerostomia (IR: 2% to 5%; ER: 3%), constipation (IR: 1% to 4%; ER: 1%), abdominal pain (3%), dyspepsia (IR: 2%; ER: 1%), dry throat (2%), dental disease (2%), flatulence (2%), increased appetite (1%)
  - **Genitourinary**: Impotence (2%), urinary tract infection (ER: 2%)
  - **Hematologic & oncologic**: Decreased white blood cell count (1%), leukopenia (1%)
  - **Infection**: Infection (5%)
  - **Neuromuscular & skeletal: Weakness** (6%), back pain (IR: 2%; ER: 2%), dysarthria (2%), limb pain (ER: 2%), myalgia (2%), bone fracture (1%)
  - **Ophthalmic**: Nystagmus (8%), diplopia (1% to 6%), blurred vision (3% to 4%), conjunctivitis (1%)
  - **Otic**: Otitis media (1%)
  - **Respiratory**: Rhinitis (4%), bronchitis (children 3%), nasopharyngitis (ER: 3%), respiratory tract infection (children 3%), pharyngitis (1% to 3%), cough (2%)
  - **Miscellaneous**: Fever (children 10%)

8.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

8.1 Safety Monitoring:

Participants will be educated regarding signs and symptoms related to adverse events (AEs) requiring urgent or emergent medical care. All AEs grade 3 or higher will be documented, reviewed by Dr. Murphy. Any contributing factors will be reviewed, and strategies to prevent further complications will be developed and implemented. Dr. Murphy will meet with study staff annually to evaluate any other safety concerns. AEs will be graded using CTCAE criteria 4.0. All unexpected grade 3, 4 or 5 AEs possibly or probably related to study drug will be reported to the IRB.

Data Safety Monitoring Board:

Four experts will be proposed for the DSMB members. The DSMB members must not be co-investigators or consultants, not have been directly involved in protocol development, not have close current or recent affiliations with the study, nor supervise persons who are directly involved in the study. We will make effort to include at least one representative with expertise in biostatistics, clinical trials methodology, and head and neck oncology.

The DSMB will oversee and monitor the activities related to implementing the study to ensure the safety of participants, adherence to the study protocol, overall performance of the trial components, integrity of data, and security of data management. The DSMB will meet annually, at the time of interim analysis and on an as-needed basis if significant issues arise that impact the study participants or any study activities. For each DSMB meeting, progress reports will be prepared and provided to DSMB members by the PI and mentor. The DSMB will prepare an annual safety report, summarizing the efforts and findings through the annual monitoring.

9.0 Study Withdrawal/Discontinuation

Patients may withdraw consent at any time during the study participation without bias or alteration in their ongoing cancer care. The reason for discontinuation or withdrawal will be documented in the study record.

The investigators reserve the right to take patients off of study for failure to comply with study parameters, if patients have undo toxicity secondary to gabapentin, or if the investigators feel it is in the best interest of the patient.

10.0 Statistical Considerations and Sample Size Justification

General evaluation and analysis plan: Statistical software will be used to summarize the data collected and to test study hypotheses. Intent-to-treat principles will be used for all analyses. An interim analysis of the VHNSS pain scores will be conducted when 50% of the participants have been randomized and have completed the 3 month follow-up period. To maintain the final overall alpha of $P < 0.05$, the Haybittle-Peto approach will be used: the trial will be stopped at that point if the symmetric stopping boundaries of $P<0.001$ are met. The interim analysis will only be used for this purpose, i.e. no futility analyses will be conducted.

Management of Missing Data: In-depth investigations of patterns of missing data will be undertaken. Given the longitudinal nature of this study, we expect two types of missing data: 1) randomly missing responses to items within the self-report measures (e.g., VHNSS) and 2) non-randomly missing lost-to-follow up (LTF) assessments. Our proposed sample size accommodates up to 30 LTF (i.e., up to 20% of those randomized) to arrive at a total analysis sample size of 120. Randomly missing item response data will be handled via protocols specified by the instrument developers. When there is no specified protocol, if the participant has completed 75% or more of the items on a particular instrument, prorated scores for that instrument will be generated using available item responses. Non-randomly missing data will be assessed to determine whether it provides clinically important information and implications for generalizability of findings. All efforts as outlined by White et al. (2011) for handling missing outcome data in an RCT-ITT analysis will be conducted.

[2] White IR, Horton NJ, Carpenter J, Pocock SJ. *Strategy for intention to treat analysis in randomised trials with missing outcome data*. BMJ 2011;342:d40

Analyses for study aims. Graphical and descriptive statistical summaries will be generated for all study variables. Evaluation of the key outcome variable data distributions (VHNSS mouth pain scores, opioid dose) will inform the required test distribution (e.g., normal, log-normal). Mixed-level general linear modeling will be used to test study hypotheses. Given that patients will have varying VHNSS pain scores prior to beginning radiated, those baseline values will be included as a covariate in the analyses of outcomes [EOT: VHNSS pain scores (H1.1); opioid use (H1.2); weight loss (H2.1); duration of PEG (H2.2); general symptoms (Aim 4)]. Frequency distributions will summarize the safety and tolerability outcomes (Aim 3). All tests of statistical significance will maintain maximum Type I error of 0.05 ($p < 0.05$).

Sample size justification. The proposed sample size was based on typical VHNSS pain score values during/end-of-treatment in prior studies (M=4.5, SD=2.8). A total sample size of 120 patients (60 per arm) who complete the protocol will provide 80% statistical power (2-tailed alpha=0.05) to detect a decrease of 1.5 points on the VHNSS pain scale due to the addition of gabapentin to usual care. Given a change of 2.0 points on the scale is proposed to be clinically meaningful, this slightly larger sample size will provide coverage in the case that our sample values are slightly more variable than those observed in our prior studies. A total sample size of 120 will also enable us to detect correlations as small 0.25(6.3% shared variance) with 80% power and 2-tailed alpha=0.05. We expect clinically meaningful associations to be larger than this value.

11.0 Data Management and Safety Monitoring Plan

Data Management: All questionnaires will be completed on line using REDCAP. Hard copy data regarding tumor, treatment, pain diaries and adverse events will be double-entered into a password-protected database. Paper copies will be stored in a locked cabinet in a secure room. All data will be coded without any identifiable information. Only the PI and mentor will maintain a key that links participants to ID number in a password-protected database on a secure server. Paper copies will be destroyed after study completion and publication of results. The PI and/or mentor will monitor all databases at least monthly to ensure data integrity.

12.0 Privacy/Confidentiality Issues

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s). There is no information to be collected that might increase the risk of a breach of confidentiality.

Participant's personal information will remain confidential and will not be used if study information is published or presented at a scientific meeting. Identifying information can be marked as such in REDCap so that it will not be released when the data is downloaded from the database.

13.0 Follow-up and Record Retention

All data will be recorded in the electronic REDCap database, which is a secure, password-protected database. In addition, hard copies of the consent forms, questionnaires, surveys, and digital photographs will be stored in a locking file cabinet. Only the PI and research team have access to the electronic database and the file cabinet. Once the study results have been reported, the database will no longer be accessed and all hard copies will be destroyed.

Sources

1. Jemal, A., et al., *Global cancer statistics.* CA Cancer J Clin, 2011. **61**(2): p. 69-90.
2. Elrefaey, S., et al., *HPV in oropharyngeal cancer: the basics to know in clinical practice.* Acta Otorhinolaryngol Ital, 2014. **34**(5): p. 299-309.
3. Huber, M.A. and B. Tantiwongkosi, *Oral and oropharyngeal cancer.* Med Clin North Am, 2014. **98**(6): p. 1299-321.
4. Khode, S.R., et al., *Exploring the link between human papilloma virus and oral and oropharyngeal cancers.* J Cancer Res Ther, 2014. **10**(3): p. 492-8.
5. Siegel, R., et al., *Cancer statistics, 2014.* CA Cancer J Clin, 2014. **64**(1): p. 9-29.
6. Bar-Ad, V., et al., *Current management of locally advanced head and neck cancer: the combination of chemotherapy with locoregional treatments.* Semin Oncol, 2014. **41**(6): p. 798-806.
7. Gold, K.A., M. Neskey, and W.N. William, Jr., *The role of systemic treatment before, during, and after definitive treatment.* Otolaryngol Clin North Am, 2013. **46**(4): p. 645-56.
8. Gunn, G.B. and S.J. Frank, *Advances in radiation oncology for the management of oropharyngeal tumors.* Otolaryngol Clin North Am, 2013. **46**(4): p. 629-43.
9. Holliday, E.B. and S.J. Frank, *Proton radiation therapy for head and neck cancer: a review of the clinical experience to date.* Int J Radiat Oncol Biol Phys, 2014. **89**(2): p. 292-302.
10. Huang, S.H., et al., *Primary surgery versus (chemo)radiotherapy in oropharyngeal cancer: the radiation oncologist's and medical oncologist's perspectives.* Curr Opin Otolaryngol Head Neck Surg, 2015.
11. Omura, G., et al., *Salvage surgery for local residual or recurrent pharyngeal cancer after radiotherapy or chemoradiotherapy.* Laryngoscope, 2014. **124**(9): p. 2075-80.
12. Sonis, S.T., et al., *Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients.* Cancer, 2004. **100**(9 Suppl): p. 1995-2025.
13. Naidu, M.U., et al., *Chemotherapy-induced and/or radiation therapy-induced oral mucositis--complicating the treatment of cancer.* Neoplasia, 2004. **6**(5): p. 423-31.
14. Sonis, S.T., *The pathobiology of mucositis.* Nat Rev Cancer, 2004. **4**(4): p. 277-84.

15. Lalla, R.V., S.T. Sonis, and D.E. Peterson, *Management of Oral Mucositis in Patients with Cancer.* Dent Clin North Am, 2008. **52**(1): p. 61-viii.
16. Peterson, D.E., et al., *Management of oral and gastrointestinal mucositis: ESMO Clinical Practice Guidelines.* Annals of Oncology, 2011. **22**(suppl 6): p. vi78-vi84.
17. Haverman, T.M., et al., *Oral complications in hematopoietic stem cell recipients: the role of inflammation.* Mediators Inflamm, 2014. **2014**: p. 378281.
18. Keefe, D.M., et al., *Updated clinical practice guidelines for the prevention and treatment of mucositis.* Cancer, 2007. **109**(5): p. 820-31.
19. Baldini, A., M. Von Korff, and E.H. Lin, *A Review of Potential Adverse Effects of Long-Term Opioid Therapy: A Practitioner's Guide.* Prim Care Companion CNS Disord, 2012. **14**(3).
20. Harris, D.J., *Cancer treatment-induced mucositis pain: strategies for assessment and management.* Ther Clin Risk Manag, 2006. **2**(3): p. 251-8.
21. Goldberg, D.S. and S.J. McGee, *Pain as a global public health priority.* BMC Public Health, 2011. **11**: p. 770.
22. Baron, R., *Mechanisms of disease: neuropathic pain--a clinical perspective.* Nat Clin Pract Neurol, 2006. **2**(2): p. 95-106.
23. Dubin, A.E. and A. Patapoutian, *Nociceptors: the sensors of the pain pathway.* J Clin Invest, 2010. **120**(11): p. 3760-72.
24. Ahluwalia, J., H. Rang, and I. Nagy, *The putative role of vanilloid receptor-like protein-1 in mediating high threshold noxious heat-sensitivity in rat cultured primary sensory neurons.* Eur J Neurosci, 2002. **16**(8): p. 1483-9.
25. Ploner, M., et al., *Parallel activation of primary and secondary somatosensory cortices in human pain processing.* J Neurophysiol, 1999. **81**(6): p. 3100-4.
26. Liang, M., A. Mouraux, and G.D. Iannetti, *Parallel processing of nociceptive and non-nociceptive somatosensory information in the human primary and secondary somatosensory cortices: evidence from dynamic causal modeling of functional magnetic resonance imaging data.* J Neurosci, 2011. **31**(24): p. 8976-85.
27. Simons, L.E., et al., *The human amygdala and pain: evidence from neuroimaging.* Hum Brain Mapp, 2014. **35**(2): p. 527-38.
28. Mutso, A.A., *Abnormalities in Hippocampal Functioning with Persistent Pain.* 2012. **32**(17): p. 5747-56.
29. Schlereth, T. and F. Birklein, *The sympathetic nervous system and pain.* Neuromolecular Med, 2008. **10**(3): p. 141-7.
30. Schaible, H.G., A. Ebersberger, and G. Natura, *Update on peripheral mechanisms of pain: beyond prostaglandins and cytokines.* Arthritis Res Ther, 2011. **13**(2): p. 210.
31. Latremoliere, A. and C.J. Woolf, *Central sensitization: a generator of pain hypersensitivity by central neural plasticity.* J Pain, 2009. **10**(9): p. 895-926.
32. Clarke, H., et al., *The prevention of chronic postsurgical pain using gabapentin and pregabalin: a combined systematic review and meta-analysis.* Anesth Analg, 2012. **115**(2): p. 428-42.
33. Todd, R.D., et al., *Gabapentin inhibits catecholamine release from adrenal chromaffin cells.* Anesthesiology, 2012. **116**(5): p. 1013-24.
34. Bar Ad, V., et al., *Gabapentin for the treatment of pain syndrome related to radiation-induced mucositis in patients with head and neck cancer treated with concurrent chemoradiotherapy.* Cancer, 2010. **116**(17): p. 4206-13.

35. Moore, R.A., *Gabapentin for chronic neuropathic pain and fibromyalgia in adults.* 2011(3): p. Cd007938.
36. Chang, C.Y., et al., *Gabapentin in Acute Postoperative Pain Management.* Biomed Res Int, 2014. **2014**.
37. Straube, S., *Single dose oral gabapentin for established acute postoperative pain in adults.* 2010(5): p. Cd008183.
38. Hummig, W., C. Machado Kopruszinski, and J.G. Chichorro, *Pregabalin reduces acute inflammatory and persistent pain associated with nerve injury and cancer in rat models of orofacial pain.* J Oral Facial Pain Headache, 2014. **28**(4): p. 350-9.
39. Sist, T.C., et al., *Experience with gabapentin for neuropathic pain in the head and neck: report of ten cases.* Reg Anesth, 1997. **22**(5): p. 473-8.
40. Starmer, H.M., et al., *Effect of gabapentin on swallowing during and after chemoradiation for oropharyngeal squamous cell cancer.* Dysphagia, 2014. **29**(3): p. 396-402.
41. Niiranen, A., et al., *Behavioral assessment of patients treated with alpha-interferon.* Acta Psychiatr Scand, 1988. **78**(5): p. 622-6.
42. Kilpatrick, F.P., Cantril, H. , *Self-Anchoring scalig: A measure of individual's unique reality worlds.* Journal of Individual Psychology, 1960. **16**: p. 158-173.
43. McKuchan, K.M., Cawling, W.R., & Wykle, M.K., *Cantril self-anchoring ladders: Methodological consideration for nursing science.* Nursiing Research Methodology, 1989: p. 285-294.
44. Bekkelund, S.I., G. Husby, and S.I. Mellgren, *Quality of life in rheumatoid arthritis: a case-control study in patients living in northern Norway.* Clin Exp Rheumatol, 1995. **13**(4): p. 471-5.
45. Baker, F., B. Curbow, and J.R. Wingard, *Role retention and quality of life of bone marrow transplant survivors.* Soc Sci Med, 1991. **32**(6): p. 697-704.

Appendix A: Socio-demographic Data Form

Version date: 3-5-2015

Study #_____ ID# _____ Coder #_____

Date_____

Patient Interview;

1. What is your birthdate? ____/____/_____ (month/day/year)

2. Gender:

(1) Female___(2) Male____

(3) Other____(4) Do not care to respond___

3.1 What is your race?

(1) American Indian/Alaskan Native____

(2) Asian____

(3) Native Hawaiian or Other Pacific Islander

_____

(4) Black or African American_____

(5) White_____

(6) Other _____

3.2 What is your ethnicity?

(1) Not Hispanic _____

(2) Hispanic _____

4. What is the highest grade of education you completed? (Please circle)

1 2 3 4 5 6 7 8 9 10 11 12 (high school) 13 14 15 16 (college) 17 18 (master) 19 20 (doctorate)

5. What is your marital status?

(1) Single____

(2) Single, living with partner_____

(3) Married_____

(4) Widowed____

(5) Other____

6. What is your current employment status?

(1) Employed full time____

(2) Employed part time____

(3) Homemaker____

(4) Retired_____

(5) Unemployed_____

(6) Other____

7. What best describes your area of residence?

(1) City___ (2) Country ___ (3) Other___

Version date: 10-15-2014

Study #_____ ID# _____ Coder #_____

Date_____

8. Health Maintenance

8.1 Have you ever used or smoked tobacco?

(1) No ___

(2) Yes ___

What type of tobacco have you used (check all that apply)?

Cigarettes ___, Cigars ___, Pipe ___, Dip ___, Plugs/Chaw ___, Other ___

8.2 Have you quit smoking tobacco?

No ___

Yes ___; When_____

8.3. Have you ever used or smoked Marijuana?

No ___

Yes ___

Do not care to respond ___

marijuana uses per day ____

Age started using marijuana ___

Years using marijuana ___

8.4. Have you quit using marijuana?

No _____

Yes _____; Marijuana quit date ___

Do not care to respond _____

8.5 Drinking Alcohol

(1) No ____

(2) Yes ____

_____years _____ times per week

(3) Quit _____When_____

(4) Not Quit _____

_____ times per week (Current)

9. What is your insurance coverage?

(1) Medicare____ (2) Medicaid____

(3) TennCare____ (4) Private Insurance____

(5) HMO____ (6) None_____

(7) Other_____

10. Do you have any medical problems?

(1) No

(2) Yes (e.g., HBP, DM, Obesity, Injury History) _____

11. What is your yearly household income?
(1) $10,000 or less____
(2) $10,001 to $ 20,000____
(3) $20,001 to $ 30,000____
(4) $30,001-$40,000___
(5) $ 40,001 to $50,000____
(6) $50,001 to $60,000 ____
(7) Over $60,000____
(8) Do not care to respond____

Appendix B: The Vanderbilt Head and Neck Cancer Symptom Survey (version 2.0) Plus General Symptom Survey
Name:_____Date:_____

Directions: Please answer the following questions by checking the appropriate box.

1. **I currently have a feeding tube in place. ⍐ Yes ⍐No**
2. **I have teeth ⍐ Yes ⍐No**
3. **I use dentures ⍐ Yes ⍐No**

Directions: Please read all questions and circle the number that best describes your symptoms over the past week. In general, a "0" indicates the least amount of problems with a particular symptom and "10" indicates the most problems.

1. I have been losing weight

0 1 2 3 4 5 6 7 8 9 10
None A lot

2. I have lost my appetite

0 1 2 3 4 5 6 7 8 9 10
Normal No

appetite

3. I have to use liquid supplements (like Ensure® or Boost®) to maintain my weight

0 1 2 3 4 5 6 7 8 9 10
None All liquid

supplements

4. I have trouble maintaining my weight because of swallowing problems

0 1 2 3 4 5 6 7 8 9 10
None A lot

5. I have trouble eating certain solid foods (like hard to chew, crumbly, or sticky foods)

0 1 2 3 4 5 6 7 8 9 10
None A lot

6. I have trouble drinking thin liquids (like water, tea and Ensure®)

0 1 2 3 4 5 6 7 8 9 10
None A lot

7. Food gets stuck in my mouth

0 1 2 3 4 5 6 7 8 9 10
Never Always

8. Food gets stuck in my throat

0 1 2 3 4 5 6 7 8 9 10
Never Always

9. I choke or strangle on liquids

0 1 2 3 4 5 6 7 8 9 10
Never Always

10. I choke or strangle on solid foods

0 1 2 3 4 5 6 7 8 9 10
Never Always

11. I cough after I swallow

0 1 2 3 4 5 6 7 8 9 10
Never Always

12. Swallowing takes great effort

0 1 2 3 4 5 6 7 8 9 10
Never Always

13. It takes me longer to eat because of my swallowing problem

0 1 2 3 4 5 6 7 8 9 10
Never Always

14. I have problems with dry mouth

0 1 2 3 4 5 6 7 8 9 10
Never Severe

15. Problems with dry mouth make chewing and swallowing difficult

0 1 2 3 4 5 6 7 8 9 10
Never Always

16. Problems with dry mouth affect my ability to sleep

0 1 2 3 4 5 6 7 8 9 10
Never Always

17. Problems with dry mouth affect my ability to talk

0 1 2 3 4 5 6 7 8 9 10
Never Always

18. I have thick mucous or phlegm

0 1 2 3 4 5 6 7 8 9 10
Never Always

19. Mucous causes me to choke or gag

0 1 2 3 4 5 6 7 8 9 10
Never Always

20. Mucous causes difficulty swallowing

0 1 2 3 4 5 6 7 8 9 10
Never Always

21. Mucous causes difficulty sleeping

0 1 2 3 4 5 6 7 8 9 10
Never Always

22. I have sores in my mouth or throat that cause pain

0 1 2 3 4 5 6 7 8 9 10
No Pain Severe pain

23. Mouth or throat pain causes difficulty swallowing

0 1 2 3 4 5 6 7 8 9 10
Never Always

24. Mouth or throat pain causes difficulty speaking

0 1 2 3 4 5 6 7 8 9 10
Never Always

25. My average pain level over the last week has been…..

0 1 2 3 4 5 6 7 8 9 10
No pain Severe pain

26. My worst pain level over the last week has been….

0 1 2 3 4 5 6 7 8 9 10
No pain Severe pain

27. The average relief from my pain medication is…. ↑Not Applicable, I am not on pain medications

0 1 2 3 4 5 6 7 8 9 10
No relief Total relief

28. Pain causes difficulty sleeping

0 1 2 3 4 5 6 7 8 9 10
Never Always

29. I have trouble speaking

0 1 2 3 4 5 6 7 8 9 10
Never Always

30. My voice is hoarse

0 1 2 3 4 5 6 7 8 9 10
Not at all Very Hoarse

31. I have trouble being understood because of my speaking or hoarse voice

0 1 2 3 4 5 6 7 8 9 10
Never Always

32. I have trouble with my hearing

0 1 2 3 4 5 6 7 8 9 10
None Severe

33. My taste is altered

0 1 2 3 4 5 6 7 8 9 10
None A lot

34. I have less desire to eat <u>due to taste change</u>

0 1 2 3 4 5 6 7 8 9 10
Never Always

35. My taste changes have altered the foods that I choose to eat

0 1 2 3 4 5 6 7 8 9 10
Never Always

36. My taste changes have caused me to decrease the amount of food I eat

0 1 2 3 4 5 6 7 8 9 10
Never Always

37. My sense of smell has changed

0 1 2 3 4 5 6 7 8 9 10
Not at all Very much

38. I have altered what I eat <u>due to a change in my sense of smell</u>

0 1 2 3 4 5 6 7 8 9 10
Not at all Very much

39. I have difficulty chewing because of my teeth or dentures…↑Not applicable, I do not have teeth or dentures

0 1 2 3 4 5 6 7 8 9 10
None Severe

40. My teeth are sensitive to hot, cold or sweet foods ↑Not applicable, I do not have teeth

0 1 2 3 4 5 6 7 8 9 10
Not at all Very Sensitive

41. My teeth feel looser↑Not applicable, I do not have teeth

0 1 2 3 4 5 6 7 8 9 10
Not at all Very Loose

42. My teeth are cracking or chipping ↑Not applicable, I do not have teeth

0 1 2 3 4 5 6 7 8 9 10
Not at all Severe

43. I have trouble with my dentures↑Not applicable, I do not have dentures

0 1 2 3 4 5 6 7 8 9 10
None A lot

44. I have a burning sensation in the lining of my mouth and throat

0 1 2 3 4 5 6 7 8 9 10
None Very Painful

45. The lining of my mouth and throat is sensitive to spicy, hot or acidic foods

0 1 2 3 4 5 6 7 8 9 10
Not at all Very Sensitive

46. The lining of my mouth and throat is sensitive to dryness

0 1 2 3 4 5 6 7 8 9 10
Not at all Very Sensitive

47. Burning pain in the lining of my mouth and throat changes what I eat

0 1 2 3 4 5 6 7 8 9 10
Never Always

48. Burning pain in the lining of my mouth and throat prevents me from brushing my teeth

0 1 2 3 4 5 6 7 8 9 10
Never Always

49. I have limitations in the ability to open or move my jaw

0 1 2 3 4 5 6 7 8 9 10
Never Severe

50. I have limitations in the ability to move my neck and shoulders

0 1 2 3 4 5 6 7 8 9 10
Never Severe

General Symptom Subscale:

51. I have unexplained fatigue

0 1 2 3 4 5 6 7 8 9 10
Never Always

52. Fatigue limits my day to day activity

0 1 2 3 4 5 6 7 8 9 10
Never Always

53. I have problems falling asleep

0 1 2 3 4 5 6 7 8 9 10
Never Always

54. I have problems staying asleep

0 1 2 3 4 5 6 7 8 9 10
Never Always

55 I have episodes of unexplained sweating

0 1 2 3 4 5 6 7 8 9 10
Never Frequently

56. There are times when I am cold and others around me are not

0 1 2 3 4 5 6 7 8 9 10
Never Always

57. There are times when I am hot and others around me are not

0 1 2 3 4 5 6 7 8 9 10
Never Always

58. I have trouble with my memory or processing my thoughts

0 1 2 3 4 5 6 7 8 9 10
Never Always

59. I have joint pain or muscle aches other than in my neck and shoulders

0 1 2 3 4 5 6 7 8 9 10
Never Always

60. I feel sad or depressed

0 1 2 3 4 5 6 7 8 9 10

Never Always

61. I feel anxious

0 1 2 3 4 5 6 7 8 9 10
Never Always

Appendix C: Pain Diary:

Date:

Please rate the following on a scale of 0-10 with 0 being no pain and 10 being the worst pain you have ever experienced:

1) What is your current pain level?

No Pain Worst Pain

0 1 2 3 4 5 6 7 8 9 10

2) What has been your average pain level this past week?

No Pain Worst Pain

0 1 2 3 4 5 6 7 8 9 10

3) What has been your worst pain level this week?

No Pain Worst Pain

0 1 2 3 4 5 6 7 8 9 10

4) On average, how many breakthrough doses of pain medication have you taken a daily?

5) Do you feel that your current pain regiment is appropriately controlling your pain?

Appendix D Gabapentin Compliance Diary

Date:___

1. Are you currently taking gabapentin for Pain?
    a. Yes
    b. No

IF NO → the patient is not on gabapentin and is no longer required to fill out the remaining questions

IF Yes → have redcap prompt the following questions

2. What is the dosage of each Gabapentin **tablet** you are prescribed to take? (For example, if you are prescribed to take 300 mg tablet 3 times per day, then the dose of each tablet is 300 mg)
    a. 100 mg
    b. 300 mg
    c. 600 mg
    d. 900 mg
    e. Other, please specify: ___

3. How often are you prescribed to take your Gabapentin tablet each day?
    a. 1 times/day
    b. 2 times/day
    c. 3 times/day
    d. Other, please specify: ___

4. Have you missed a dose of your Gabapentin over the last week?
    a. No
    b. Yes

5. If Yes, how many doses have you missed over the last week? (numerical value only) ___

6. For what reason did you miss your dose?
    a. I forgot to take my medicine
    b. I ran out of medicine
    c. I can't swallow my medicine
    d. Other, please specify ___

Appendix E: POMS SF PROFILE OF MOOD STATES-SHORT FORM

Below is a list of words that describe feelings people have. Please read each one carefully. Then circle ONE answer to the right which best describes HOW YOU HAVE BEEN FEELING DURING THE PAST **TWO WEEKS** INCLUDING TODAY.

The numbers refer to these phrases:

0 = not at all
1 = a little
2 = moderately
3 = quite a bit
4 = extremely

1. Tense	0	1	2	3	4	**20. Discouraged**	0	1	2	3	4
2. Angry	0	1	2	3	4	**21. Resentful**	0	1	2	3	4
3. Worn out	0	1	2	3	4	**22. Nervous**	0	1	2	3	4
4. Unhappy	0	1	2	3	4	**23. Miserable**	0	1	2	3	4
5. Lively	0	1	2	3	4	**24. Cheerful**	0	1	2	3	4
6. Confused	0	1	2	3	4	**25. Bitter**	0	1	2	3	4
7. Peeved	0	1	2	3	4	**26. Exhausted**	0	1	2	3	4
8. Sad	0	1	2	3	4	**27. Anxious**	0	1	2	3	4
9. Active	0	1	2	3	4	**28. Helpless**	0	1	2	3	4
10. On edge	0	1	2	3	4	**29. Weary**	0	1	2	3	4
11. Grouchy	0	1	2	3	4	**30. Bewildered**	0	1	2	3	4
12. Blue	0	1	2	3	4	**31. Furious**	0	1	2	3	4
13. Energetic	0	1	2	3	4	**32. Full of pep**	0	1	2	3	4
14. Hopeless	0	1	2	3	4	**33. Worthless**	0	1	2	3	4
15. Uneasy	0	1	2	3	4	**34. Forgetful**	0	1	2	3	4
16. Restless	0	1	2	3	4	**35. Vigorous**	0	1	2	3	4
17. Unable to concentrate	0	1	2	3	4	**36. Uncertain about things**	0	1	2	3	4
18. Fatigued	0	1	2	3	4	**37. Bushed**	0	1	2	3	4
19. Annoyed	0	1	2	3	4						

Appendix F: Neurotoxicity Rating Scale

Directions: Place an X at the level of severity of each symptom.

	Not present	Mild	Moderate	Severe	Extremely severe
1. Anxiety					
2. Health worries					
3. Sadness/depression					
4. Restlessness					
5. No interest in people					
6. No interest in activities					
7. Difficulty making decisions					
8. Strange thoughts					
9. All-over sick feeling					
10. Difficulty getting to sleep					
11. Diffculty staying asleep					
12. Sleeping too much					
13. Nausea					
14. Vomiting					
15. Loss of appetite					
16. Tiredness/fatigue					
17. Distractibility					
18. Body aches					
19. Joint pain					
20. Other pain					
21. Episodes of confusion					
22. Word-finding problem					
23. Memory problems					

24. Irritability					
25. Decreased motivation					
26. Hallucinations					
27. Lack of emotion					
28. Mood swings					
	Not present	**Mild**	**Moderate**	**Severe**	**Extremely severe**
29. Tension					
30. Slowed movements					
31. Tremor/shakiness					
32. Walking problems					
33. Vision problems					
34. Bowel/blader problems					
35. Loss of interest in sex					
36. Fever					
37. Headaches					

Appendix G: Quality of Life

Name:_____ Date:_____

Directions: Please circle the number (0–10) best reflecting your response to the following that describes your feelings during the past week, including today. A "0" is as bad as it gets while a "10" is a good as it can be.

1. How would you rate your physical well being over the past week?
   This question refers to such things as fatigue, activity, etc.

   0 1 2 3 4 5 6 7 8 9 10

   As bad as it can be As good as it can be

2. How would you rate your emotional well being over the past week?
   This question refers to such things as depression, anxiety, stress, etc.

   0 1 2 3 4 5 6 7 8 9 10

   As bad as it can be As good as it can be

3. How would you rate your spiritual well being over the past week?
   This question refers to such things as a sense of meaning and purpose, relationship with God, etc.

   0 1 2 3 4 5 6 7 8 9 10

   As bad as it can be As good as it can be

4. How would you rate your intellectual well being over the past week?
   This question refers to such things as the ability to think clearly, to concentrate, to remember, etc.

   0 1 2 3 4 5 6 7 8 9 10

   As bad as it can be As good as it can be

5. How would you rate your overall well being over the past week?

   0 1 2 3 4 5 6 7 8 9 10

As bad as it can be As good as it can be

Quality of Life

Here is a picture of a ladder. Suppose we say that the top of the ladder shows the best possible life for you and the bottom shows the worst possible life for you.

10
9
8
7
6
5
4
3
2
1
0

Where on the ladder do you feel you personally are now? Step number _____

Appendix H: Disease and Treatment Data Form

Diagnosis
Date ____/____/_____(mm/dd/year)

Type
(Location/Originating cancerous lesions)
___(1) Nasal cavity
___(2) Paranasal sinuses
___(3) Oral cavity
___(4) Nasopharynx
___(5) Oropharynx
___(6) Hypopharynx
___(7) Larynx
___(8) Salivary gland
___(9) Other_____

Stage: T____N____M____
___X
___0
___I
___IIa
___IIb
___IIIa
___IIIb
___IVa
___IVb
___IVc

Surgery
Date____/___/_____
Type:
___(1) Standard RND (radical neck dissection)
___(2) Bilateral RND
___(3) Modified RND
___(4) Modified neck dissection
___(5) Functional neck dissection
___(6) Selective neck dissection
___(7) Other_____
Number of dissected lymph nodes____
Number of positive lymph nodes____

Radiation Therapy
___None
___Some
Site (1) _____ Dosage_____cGy
Site (2) _____ Dosage_____cGy
Site (3) _____ Dosage_____cGy
Site (4) _____ Dosage_____cGy
Begin date____/____/_____
End date ____/____/_____
Pattern of therapy

Days on to days off ratios_____
Chemotherapy
Induction __ Yes___No
___None
___some
Number of cycles____
Begin date____/____/_____
End date ____/____/_____
Type:
____(1) Taxol
____(2) Carboplatin
(3) Other:_____

ChemoXRT
___None
___Some
Begin date____/____/_____
End date ____/____/_____
Type:
____(1) Taxol
____(2) Carboplatin
(3) Other:_____

Total treatment received
___ (1) Induction+ ChemoXRT
___ (2) ChemoXRT
___ (3) Surgery + ChemoXRT
___ (4) Surgery + Radiotherapy
___ (5) Surgery only
___ (6) Radiotherapy only
___ (7) other (please list)_____
Treatment-related complications_____

Appendix I: Study Procedure Calendar

	Baseline¥	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6 *	Week 7 *	1,2 3 Months post tx
Study Visit	X	X	X	X	X	X	X	X	X
Chemoradiation Teaching	X								
Foundations of Oral Care	X								
Foundations of Pain Management	X								
Randomization	X								
Gabapentin Arm 2 Only		X	X	X	X	X	X	X	X
Mucositis Grading		X	X	X	X	X	X	X	X
Demographic Survey	X								
VHNSS Version 2.0		X	X	X	X	X	X	X	X
Pain Survey		X	X	X	X	X	X	X	X
Compliance Survey Arm 2 Only		X	X	X	X	X	X	X	X
Neurotoxicity Scale	X						X		X (month 3 only)
POMS	X						X		X (month 3 only)
QOL	X						X		X (month 3 only)
Disease and Treatment Form	X								

¥ All baseline assessments must be done within 4 weeks before starting concurrent chemoradiation.
* Weekly assessments will continue until the completion of chemoradiation which may vary between 5 and 7 weeks.