Protocol for **H-34438** ***DOUBLE-BLIND PLACEBO CONTROLLED TRIAL OF THE TREATMENT OF CHRONIC LARYNGITIS WITH AMITRIPTYLINE***

NCT02552225

Version 4.4 30-APRIL 30, 2017

PI- Pieter Noordzij, MD
Boston Medical Center

Statistical Analysis Plan pages 6-8

H-34438 ***DOUBLE-BLIND PLACEBO CONTROLLED TRIAL OF THE TREATMENT OF CHRONIC LARYNGITIS WITH AMITRIPTYLINE***

Background

Chronic laryngitis can present with a myriad of symptoms including cough, hoarseness, throat clearing, foreign body sensation, throat pain, sensation of excessive phlegm, and difficulty swallowing. This combination is significantly limiting for many patients, who often report impairment of ability to perform their job, embarrassment, discomfort and avoidance of social settings. Many patients present to primary care providers and specialists with these symptoms. Of these, a significant minority have symptoms not amenable to standard therapies. Several causes for this disorder have been identified, including GERD, rhinosinusitis-induced post-nasal drainage, direct allergic effect, smoking, and other environmental causes. Despite treatments already available for these conditions, some patients fail to improve, despite extensive diagnostic testing and a variety of therapeutic regimens. These patients are often desperate for any relief, and may present to otolaryngologists for consultation. Here at BMC, an otolaryngologist may see up to approximately 10 such patients per week, with a more common number between 2 and 4, of whom about half are prescribed amitriptyline (based on data compiled from Logician for a poster presentation, "*RETROSPECTIVE ANALYSIS OF USE OF AMITRIPTYLINE IN CHRONIC LARYNGITIS", H-29997*).

For these cases, some investigators have suggested a neuropathic etiology for idiopathic chronic laryngitis without a clear cause, and have speculated that this may occur as a post-viral complication (1-4). Diagnosis of this condition, also known as chronic laryngeal neuropathy, remains one of exclusion, since there is no diagnostic test for chronic laryngitis at this time. Multiple medications used in other specialties for the treatment of neuropathic disorders have been tried, with significant clinical relief in many patients. As a result, uncontrolled trials of amitriptyline, nortriptyline, gabapentin, and pregabalin were conducted and shown to have some benefit (10), but it is unknown if improvement seen in these studies was due to placebo effect alone. To date, no controlled (prospective, randomized, placebo-controlled) trials have been performed.

As the prescription of amitriptyline for chronic laryngeal neuropathy is an off-label use, there is no standardized dose. Literature review shows that doses from 10-100mg have previously been well tolerated without serious adverse side effects, with improvement noted with doses as low as 10mg daily for 21 days in non-randomized controlled trials (Table 1). Therefore, the amitriptyline dosing regimen as described in this protocol (12.5-50mg nightly) is unlikely to put subjects at risk for either undertreatment or serious adverse side effects. Subjects randomized to placebo, however, will be at potential risk for undertreatment.

Table 1. Prior dosing regimens for amitriptyline in chronic laryngeal neuropathy (Altman (10))

First Author	Study Type	Intervention	Outcome	Side Effect
Bastian (6)	Prospective cohort, 12 consecutive	10 mg amitriptyline daily	10 of 12 patients had ≥ 50%	None noted.

	patients.	for 21 days.	response; 6 of 8 patients had ≥ 50% response >20 days off amitriptyline. One patient had no benefit with amitriptyline but did with subsequent gabapentin.	
Norris (8)	Retrospective case series of 8 patients, consecutive unknown.	25–100 mg amitriptyline, failures treated with gabapentin or pregabalin, unknown duration of treatment.	Six of 8 improved.	Dry mouth in 30% of all enrolled patients.
Jeyakumar (5)	Randomized controlled trial; 15 patients in amitriptyline group, 14 in codeine group. Randomized by chart numbers and presence of nasal allergies.	Amitriptyline 10 mg daily vs. codeine/ guaifenesin 10 mL every 6 hours for 10 days.	Thirteen of 15 in amitriptyline group had ≥ 50% improvement as compared to 1 of 13 in codeine/ guaifenesin group; improved QOL scores associated with amitriptyline.	No mention of adverse effects.
Stein (9)	Retrospective chart review of 66 patients.	All subjects were prescribed 10-mg tablets of amitriptyline, with variable dosing. 53% took 1 or 2 tablets 10 or 20 mg) at night. 42% took 10 mg (1 tablet) of amitriptyline, also at night. 5% had dosage increased to 2 to 4 times a day as needed for greater control. The response rate was not correlated with dosage (Chi-squared test, p = 0.9179).	32% complete response, 24% partial response, 36% no response, 8% response unknown.	Sedation in 23%.

Purpose/Objectives

We wish to study amitriptyline, which has been previously shown to be potentially useful in a non-controlled study (5), in a double-blind placebo controlled trial to ascertain its effectiveness in treating chronic laryngeal neuropathy. Our hypothesis is that it will be significantly superior to placebo for this condition with respect to symptomatic relief of laryngopharyngeal symptoms. We believe that this is a study that presents a reasonable ratio of risk to benefit, since amitriptyline is the most commonly used medication for this condition at both BMC and elsewhere with promising results clinically, and it has a well-established safety profile and characterized side-effects. Furthermore, in clinical experience here at BMC, it has been found to be well-tolerated by patients in the setting of chronic laryngitis, with the symptomatic relief generally outweighing the side-effects. However, it is critical that its effectiveness be established by comparing it to placebo. No trials have compared any treatment for chronic laryngitis to placebo (thus there is no standard to which amitriptyline could be compared), and it is unknown if currently used therapies are truly effective. Potential subjects will be carefully informed that they can get the same medication by prescription without participation in the study, and that there is a 50% chance that they will have their treatment delayed by 8 weeks when enrolling in the study.

A prior pilot study H-29925 *DOUBLE-BLIND PLACEBO CONTROLLED TRIAL OF THE TREATMENT OF CHRONIC LARYNGITIS WITH AMITRIPTYLINE* confirmed the safety of the dosing regimens currently used at Boston Medical Center, and provided additional data regarding enrollment and dropout rates to help determine the sample size for this study.

(1) Morrison M, Rammage L, Emami AJ. The irritable larynx syndrome. Journal of Voice. 1999;13:447- 455.
(2) Amin, M R, and J A Koufman. "Vagal Neuropathy After Upper Respiratory Infection: A Viral Etiology?" American journal of otolaryngology 22, no. 4 (2001)
(3) Koufman A. The Visible Voice Newsletter. Voice Institute of New York. ;2 (November 2008)
(4) Rees, Catherine J, Arthur H Henderson, and Peter C Belafsky. "Postviral Vagal Neuropathy." The Annals of otology, rhinology, and laryngology 118, no. 4 (2009): 247-52.
(5) Jeyakumar A, Brickman TM, Haben M. Effectiveness of amitriptyline versus cough suppressants in the treatment of chronic cough resulting from postviral vagal neuropathy. Laryngoscope. 2006;116:2108-2112.
(6) Bastian RW, Vaidya AM, Delsupehe KG. Sensory neuropathic cough: a common and treatable cause of chronic cough. Otolaryngol Head Neck Surg. 2006;135:17-21.
(7) Lee, Bryant, and Peak Woo. "Chronic Cough As a Sign of Laryngeal Sensory Neuropathy: Diagnosis and Treatment." The Annals of otology, rhinology, and laryngology 114, no. 4 (2005): 253-7.
(8) Norris BK, Schweinfurth JM. Management of recurrent laryngeal sensory neuropathic symptoms. Ann Otol Rhinol Laryngol 2010;119:188–191.
(9) Stein DJ, Noordzij JP. Amitriptyline for symptomatic treatment of idiopathic chronic laryngeal irritability. Ann Otol Rhinol Laryngol 2013;122: 20–24.
(10) Altman KW, Noordzij JP, Rosen CA, Cohen S, Sulica L. Neurogenic cough.

Laryngoscope. 2015 Jul;125(7):1675-81.

Study Design

This study will be a randomized, double-blind, placebo-controlled trial to determine whether amitriptyline improves symptoms of chronic laryngeal neuropathy over an 8 week period.

The target of our study is to have 100 subjects complete the study, excluding prior pilot study data. We will run a blinded interim analysis on the primary endpoint when 25 subjects in each arm have completed treatment and follow-up, and a conditional power for detecting a significant treatment effect by the planned end of the study (100 subjects) will be determined. If this conditional power is between 50 and 80%, the sample size will be recalculated to achieve 80% conditional power following the algorithm of Chen and DeMets (2004). Otherwise, the study will continue until 100 patients have completed treatment.

Based on prior pilot study data, we anticipate the study dropout rate to be approximately 30%, from time of initial enrollment to completion of the post-treatment survey. During the prior pilot study, the dropout rate was 50% initially, and dropped to 30% during the last 8 months of enrollment, until the study was closed. Dropout rate was the same in each arm, with 5 subjects in each arm dropping out after starting treatment. Only three subjects cited adverse events (AEs) as a reason for drop out; two subjects on placebo complained of headache and dry mouth, respectively, and one subject on amitriptyline complained of sedation.

Thus, we anticipate a dropout rate during treatment of 30%, and anticipate having to enroll at least 75 subjects in order for 25 patients in each arm to complete the study by the interim analysis.

The physician may elect to discontinue study drug due to serious adverse events (SAEs) or unintended pregnancy. If a subject withdraws from treatment due to adverse events, we will ask that they continue coming in for follow-up visits and finish the remaining parts of the visits off the study drug.

The primary endpoint of the trial will be the total modified RSI at 8 weeks. The Reflux Symptom Index (RSI) has been validated by Belfasky et. al. [Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). Journal of Voice. 2002;16:274-277]. The RSI is a questionnaire consisting of 9 statements to be ranked 0-5. We have added two additional symptoms to be assessed with the RSI, "throat pain or burning" and "pain with swallowing", which we believe are also relevant to chronic laryngeal neuropathy.

The total modified RSI score at 8 weeks will be averaged for each group (amitriptyline vs. placebo) and differences compared between the treatment and placebo arms using analysis of covariance adjusting for baseline severity scale at an overall two-sided 0.05 level of significance across the interim and final analysis (a two-sided significance level

of 0.00306 at the interim and 0.049 at the final analysis). A Wilcoxon Rank Sum test will be used in the case that the data is found to have a non-normal distribution.

A secondary outcome will be improvement in overall symptoms (yes/no), as subjectively assessed by patients. The post treatment survey will ask both the patient and the principal investigator whether they thought the subject was on amitriptyline or placebo.

Additional secondary outcomes will be whether there are changes in scores from baseline on the Voice Handicap Index-10 after treatment [Rosen et. al. Development and Validation of the Voice Handicap Index-10. The Laryngoscope. 2004; 114: 1549-1556] and change in score from baseline on the Cough Severity Index (CSI).[Shembel AC et al.. Development and validation of the cough severity index: a severity index for chronic cough related to the upper airway. Laryngoscope. 2013;123(8):1931-6.] The VHI-10 is a 10-question scale that addresses effects on quality of life from voice disorders while the CSI is a 10-item likert scale that assesses cough symptoms. Furthermore, we will determine whether the severity of each symptom within the modified RSI has improved after treatment. This will account for questions that may be less relevant to laryngitis overall (and more specific to reflux).

Frequencies of AEs for both groups of patients and the rate of discontinuing treatment will be recorded.

The study will be stopped if any patient is permanently disabled, seriously injured, or dies in a manner that could be consistent with the drug usage. The study will be continued if said patient(s) were taking the placebo or the event is demonstrably unrelated to the subject's participation in the trial.

An independent monitor within the otolaryngology department who is not associated with study recruitment or data analysis will also review adverse events for all subjects. The independent monitor will submit a report to the PI, who will then review these events and submit a report to the IRB. Also, if there is a concerning event or group of events, the PI will bring these to the attention of the independent monitor as they occur.

A report will be submitted to the IRB and the PI by the independent monitor at the intervals described in safety monitoring section (see section on Safety monitoring/ reporting for more detail).

Analysis (efficacy and safety)

We will be using the 8 week post-treatment 11-point modified RSI score as our primary outcome. Treatments will be compared using analysis of covariance adjusting for the baseline value using a two-sided 0.05 level of significance.

We thus used the RSI to calculate our sample size. The average starting RSI for subjects with a similar type of laryngitis to what we are studying is 20.9. After treatment, the average was 12.8 (Belfasky et. al. 2002). We estimated a 20% improvement for the

placebo group, using the estimate for continuous indicators from Hróbjartsson et. al. meta-analysis of placebo effects. Thus, we predicted the final mean RSI for the placebo patients to be 16.72. The difference between the means is thus assumed to be 3.92. Dividing this mean difference by the anticipated standard deviation (10.0, using the value from Belfasky et. al. for the final RSI value post-treatment) gives an anticipated standardized effect size of 0.392. Using this for the calculation for a-priori sample size calculations (using two-sided $p < 0.05$ and a desired power level of 0.8) gives a needed sample size of 208.

In prior pilot study data, mean difference in RSI scores was +13 (increase in score post treatment) for the amitriptyline group and +16.4 in the placebo group, with standard deviations of 7.8 and 12.1, respectively. The p-value used to determine significance was 0.5 for a two-tailed unpaired t-test.

Currently, funding is available for 100 subjects to complete this study, not including subjects who completed treatment in the prior pilot study. With a dropout rate of 30%, we expect to enroll 130 subjects in order for 100 to complete treatment. With a standard deviation of 10 as per prior assumptions, we would be able to detect a mean difference of 6 by one-tailed ANOVA analysis.

When 25 subjects in each arm (placebo and amitriptyline) have completed the study and follow-up (i.e. at least 50 subjects total), a blinded interim analysis will be performed, and conditional power for detecting a significant treatment effect by the planned end of the study (100 subjects) will be determined. If this conditional power is between 50 and 80%, the sample size will be recalculated to achieve 80% conditional power following the algorithm of Chen and DeMets (2004). Otherwise, the study will continue until 50 subjects in each arm have completed treatment.

For data analysis, we will be performing both per-protocol and multiple imputation approach analyses. Multiple imputation using the linear regression approach will be used to impute missing data, for subjects who do not complete treatment. Intention-to-treat analysis is not possible, since our outcomes are determined by the 8 week post-treatment survey, and there are no intermediate data points with regards to treatment efficacy outcomes (ie, subjects who drop out will not have any outcomes recorded).

The primary outcome measure will be the pre- and post- treatment difference in scores on the Reflux Symptom Index (RSI), with two additional questions added to assess for symptoms that may be more specific to chronic laryngeal neuropathy.

The RSI is a validated questionnaire consisting of 9 statements to be ranked 0-5. We have added two additional symptoms to be assessed to the RSI, "throat pain or burning" and "pain with swallowing", which we believe may also be relevant to chronic laryngeal neuropathy.

The modified RSI score will be averaged for each group (amitriptyline vs. placebo), and since it is a nearly continuous variable (with an expected normal distribution) and we will

be comparing the mean of the change rather than categorizing the treatment into responder and non-responders, we will also analyze it using an Analysis of Covariance or Wilcoxon Rank Sum test if determined to have a non-normal distribution.

For the modified RSI, we will also conduct a secondary analysis looking at change in severity of each symptom individually. This will account for questions that may be less relevant to laryngitis overall (and more specific to reflux).

Secondary outcome measures will be 1) subjective percent improvement from baseline to after 8 weeks of treatment, 2) subjective report of whether symptoms are better, worse, or same after treatment, and 3) the pre- and post- treatment mean difference in scores on the Voice Handicap Index-10 (VHI-10). 4) the pre- and post- treatment mean difference in scores on the Cough Severity Index.

The VHI-10 is a 10-question scale that addresses effects on quality of life from voice disorders. By asking respondents to score symptoms on the VHQ-10 scale, we expect to gain additional data on the effects of amitriptyline on improvement in voice-related issues.

The Cough Severity Index is a 10-item likert scale. which is a validated questionnaire used to quantify a patient's symptoms associated with upper airway chronic cough, and will allow us to better understand the effect of the amitriptyline intervention for chronic cough.

Subjects

Inclusion Criteria:

1. Age 18 or older and able to consent for themselves
2. Structural pathology such as tumor previously ruled out using flexible laryngoscopy
3. Able to speak and read the English language
4. Failed a 2 month or longer trial of a proton pump inhibitor for the treatment of gastro-esophageal reflux
5. Women under 55 years of age who may become pregnant must have a negative pregnancy test and agree to barrier or hormonal methods of contraception during the study

Exclusion Criteria:

1. Active, untreated environmental allergies.
2. Smoking within past 5 years
3. Current upper respiratory infections
4. Use of narcotics (e.g. oxycodone, methadone) within the past week
5. History of amitriptyline use or other tricyclic antidepressants, pregabalin, gabapentin, baclofen, or other GABA analogues or inhibitors, for any medical conditions (not limited to chronic laryngitis) with in the past 6 months
6. Use of any other monoamine oxidase inhibitors (MAOIs) other than amitriptyline

within the past 4 weeks (selegiline, phenelzine, tranylcypromine, isocarboxazid, rasagiline, phenelzine sulfate, selegiline hydrochloride, rasagiline mesylate, tranylcypromine sulfate)
7. History of urinary retention
8. History of an acute episode of a major depressive disorder within the past 12 months
9. For women 18-55 years of age without history of menopause: currently nursing or pregnant, plans to become pregnant, or unwillingness to utilize contraception (barrier or hormonal methods)
10. Currently participating in another clinical trial.
11. Active, untreated gastro-esophageal disease

Study Procedures

Patients who present to the Otolaryngology-Head & Neck Surgery clinic at Boston Medical Center with the symptoms of chronic laryngitis will first be evaluated according to the standard clinical procedure. Standard practice includes the following procedures: firstly, the patient's laryngeal symptoms will be documented, as well as related symptoms and past medical history. Consistent with the current standard of care, all other possible etiologies (e.g. untreated laryngopharyngeal reflux, untreated allergies, cancer) will have been ruled out prior to consideration of treatment using neuromodulating medications for chronic laryngitis secondary to presumed neuropathy. For example, subjects will have had a minimum 2 month course of a proton-pump inhibitor to rule out gastroesophageal reflux prior to discussion of study enrollment and had structural lesions (e.g. cancer) ruled out by flexible laryngoscopy. After the physician explains to the subject the possibility that his/her laryngitis may be caused by a neuropathic disorder, the patient will then be asked if he/she wishes to consider treatment for this disorder.

If the patient wishes to pursue treatment, he/she will be explained that there are four medications commonly used to treat this disorder: amitriptyline, nortriptyline, gabapentin and pregabalin. The patient will be presented with the option of receiving one of the standard medical treatments in accordance with standard of care here at BMC, most commonly amitriptyline.

If the patient expresses interest in trying amitriptyline, the physician will first offer to write a prescription for amitriptyline. Based on eligibility for treatment with amitriptyline, the physician will also explain to the patient that he/she is potentially eligible to participate in a study testing the efficacy of this medication. The physician will also clearly explain that the patient is under no obligation to join the trial, and that declining to participate will not in any way change the care provided. It will be explained that since the trial is a placebo-controlled double-blind trial, there is an equal chance that the subject will receive either amitriptyline or a placebo, and that neither the physician nor the subject will know which treatment the subject will be receiving until after completion of the study, which may be years from the initial enrollment date. The physician will further clarify that there is a 50% chance that as a subject, the patient would be delayed in getting treatment for two months. Since the patient will not know which treatment they have received until the study is completed, they will have the option

of starting amitriptyline, or other neuropathic agents such as pregabalin or gabapentin, at the discretion of the principal investigator, at the end of the 8 week study treatment period. In addition, the physician will clarify that even if the subject agrees to participate in the study, it is possible that he/she will not meet all of the inclusion/exclusion criteria and hence may not be eligible to enroll. In that case, the subject would be offered a prescription per standard of care.

The subject will be informed that participating in the study will require additional paperwork and time, but will not add any costs for the subject or his insurer. Subjects will also be informed that they will be contacted every week by telephone by study personnel after receiving their study drug, in order to document dosage and side effects, and address any questions or concerns.

The subject will then be asked to choose whether to enter the trial, receive one of the standard medications outside of the study, or not to receive any medication. Subjects who choose not to receive any medication may elect to participate in the study subsequently provided they are still eligible; those who receive a standard treatment outside the study are ineligible to join the study once they begin treatment.

For women who could potentially be pregnant (55 or younger and have not gone through menopause as determined by a medical provider), the physician will also explain that the effects of amitriptyline on the fetus during pregnancy are unknown, and that the patient cannot take the medication if she is pregnant or is nursing, plans to become pregnant, or is unwilling to use reliable contraception such as barrier or hormonal methods, if sexually active. Subjects known to be pregnant are not eligible to participate (and those who become pregnant will have to discontinue the medication), and all patients under the age of 55 who have not undergone menopause, as verified by a medical provider, will be required to undergo pregnancy testing at the Boston Medical Center patient laboratory before being eligible to receive medication.

If the patient chooses to join the trial, the physician will then discuss in detail all of the requirements of the trial, its potential benefits/risks, and its purpose. If the subject agrees to participate, he/she will be asked to sign and date the consent form. They will also be assigned a subject number. The consent will be signed during a regular clinic visit. Alternatively, patients may take the consent home and mail it back once they have decided to participate. The principle investigator will sign the consent when the subject returns it.

The subject will be informed that he/she will be started on either amitriptyline or placebo tablets taken at bedtime. The subject will then be randomized to amitriptyline or placebo in a 1:1 manner. Randomization of subjects will be managed by Boston Medical Center Investigational Pharmacy Services (IPS).

The starting dose will be 12.5mg nightly at bedtime. The dose may subsequently be increased by an additional 12.5mg tablet nightly every week if symptoms have not completely resolved, until either further increase is limited by side effects or a maximum

of 50mg nightly is reached. If the dose is increased and results in side effects such as intolerable dry mouth or fatigue, the patient will be counseled to decrease the dose to the most recent one that was well tolerated. Each patient will be given a "diary" that will specify both the recommended dose escalation schedule and space for the patient to record on a daily basis the dose that was actually taken. All patients will be asked to bring back all remaining capsules at the end of the 8 week treatment period, or return remaining capsules via a prepaid mailer, to further corroborate the dosing diary. At the conclusion of the 8 weeks of treatment, the patients may discontinue the medication without any additional tapering. However, if they choose to start a new prescription of amitriptyline before conclusion of the entire study period, they will be counseled that they will need to re-titrate gradually increase the dosage as needed, at the prescribing clinician's discretion.

At the first study visit, if they meet eligibility criteria, he/she will be asked to complete a pre-treatment questionnaire, which will include the Voice Handicap Index-10 (VHI-10), Cough Severity Index, and a modified Reflux Symptom Index (RSI) scales to assess the baseline severity of symptoms. The RSI will be modified to assess two additional symptoms which are commonly seen with chronic laryngitis, "throat pain or burning" and "pain with swallowing". After these forms have been collected, coded data will be added to a secure database, and the original forms will be kept in a secure locked location. All information in the database will be input under the subject's assigned study number. A separate secure database will be kept correlating the subject's assigned study number to personal identifying information, such as contact information, which will be accessed only as needed to assess for trial safety and to contact subjects. Randomization data will be kept separately, accessible only to BMC Investigational Pharmacy Services (IPS) until study completion, except in case of emergency.

If the subject meets all inclusion criteria they will be assigned a randomization number and receive the assigned study drug according to the Treatment Assignment Table prepared by BMC IPS. The drug may be given to the subject in person or mailed to the subject's address.

The treatment assignment will not be available to the clinical staff that will administer the study questionnaires and analyze resulting data while subjects are receiving the study drug or placebo, except in case of severe adverse side effect or other emergency requiring urgent unblinding. If emergency unblinding is required as noted by the PI or study staff, they will contact the IPS on-call personnel who will have access to the randomization table.

On Days 7, 14, 21, 28, 35, 42, 49, and 56 of the study the subject will be contacted by phone by a blinded study coordinator. The subject will be asked about side-effects and concerns, and confirm the dose they are taking that week. The study coordinator will relay any medical concerns to the primary investigator for consideration and follow-up, or to the nearest emergency department if the issue is too urgent to wait. The study staff will instruct the subject to remain at the same dose, increase the dose by 1 capsule or discontinue the study drug in accordance with the protocol. The subject will also be encouraged to contact the study coordinator both before and after the scheduled phone

calls and initial visits if they experience any adverse events or have additional concerns.

The subject will be instructed to discontinue taking all capsules after 8 weeks, regardless of the number of capsules remaining or any improvement experienced on the capsules. No tapering is required prior to stopping treatment.

At the time of enrollment, at the initial study visit, the subject will also be scheduled for an in-office follow-up 8 weeks after starting the capsules (as is standard of care for the treatment of chronic laryngitis). At this visit the subject will be asked to fill out a post-treatment questionnaire including a repeat modified RSI, CSI, VHI-10, and reported overall subjective percentage improvement from baseline. The latter will serve as a separate independent variable, given that neither the RSI, CSI, nor VHI-10 were specifically designed to evaluate chronic laryngeal neuropathy. Any questions the subject might have regarding the questionnaires are answered by the PI.

The subject will be given the option to receive a prescription for amitriptyline post-study (if clinically appropriate). For subjects who do not wish to take amitriptyline, the physician will discuss the other options for treatment according to the standard of care for chronic laryngitis, and other prescriptions may be provided if the subject wishes to continue pursuing treatment with the physician.

Overall, study participation will be 10 weeks for each subject. After completion of the 8 week course of treatment, weekly phone calls will continue for 2 additional weeks to ensure no adverse effects are being experienced after cessation of treatment, although this is not expected. Any recurrence of symptoms after prior improvement on treatment will also be documented. Alternatively, if the patient desires to start amitriptyline treatment, the weekly phone calls will also serve to document any change in symptoms or side effects after starting new regimen. If an adverse event is noted, it will be followed up until its resolution. For most patients no further follow up will be needed after 10 weeks, since any possible side effects should be noted within the first 4 weeks of starting the initial study treatment, and if the patient is starting treatment after conclusion of the study, further follow up will be arranged accordingly outside of the study. If there is concern for amitriptyline exposure during pregnancy, the patient will be followed up until delivery.

The initial office visit, including flexible fiberoptic laryngoscopy, will be billed to the subject's health insurance provider, not to the study, since it is an evaluation visit part of the standard of care for individuals being treated for presumed neuropathic laryngitis using medications such as amitriptyline.

During the 8 week treatment period, previously unplanned office visits due to medication side effects or procedures done strictly for the purpose of the study will not be billed to the insurer, while other tests/procedures related/unrelated to the treatment for chronic laryngitis will be billed to the insurance. If a pregnancy test is ordered to determine eligibility for the study, this will not be billed to the patient’s insurance.

The final study visit, after 8 weeks of treatment, will be conducted at no charge to the insurer, and will consist of the post-study paperwork and the discussion of post-study therapy. All visits after the final study visit at 8 weeks after initiating treatment or placebo will be billed to the insurance, unless the visit is to follow up a study related adverse event.

All post-study contact regarding clinical treatment outside of the 10-week study period will be conducted according to standard of care by the clinical office staff and the physician. Given the low dose of amitriptyline prescribed in this study, compared to the usual on-label doses used, no significant adverse effects are anticipated with treatment discontinuation, other than return of symptoms. The usual clinical scheduling staff will handle all scheduling. If the subject needs to come in for study purposes only, the subject will be contacted by phone/email/mail, depending on his/her preference, and asked to come in or provide the information over the phone if possible. They will not be compensated for this additional visit. There will be no financial compensation for subjects.

Personal identifying information collected for the study will not be disclosed to any non-study personnel. Any study personnel found to be using such data in an inappropriate manner will be removed from the study. Subjects' names, medical record numbers, and assigned study subject numbers will be stored on a master Excel spreadsheet and kept on a secured server with access limited to study coordinators and the principal investigator. This will be kept separate from each subject's randomization number and assigned treatment arm, which will be managed by IPS. Only the PI and previously approved clinical investigators will have access to outcomes data. No patient names or medical record numbers will be released or published. The data will be kept for 5 years after the publishing of the results or 10 years after beginning of data collection, whichever comes sooner and then deleted from a secured hospital server. All information will be recorded using subject number, and only the master file will link the study subject number to the subject identifiers.

Safety monitoring/reporting

The study is IND exempt based on prior communications with the Boston Medical Center Institutional Review Board.

The PI of the study will have overall responsibility for the monitoring plan. Blinded study coordinators will contact each subject by phone once per week during the study period to monitor for adverse events. Adverse events will be documented and reported to the PI on a weekly basis and classified as per "adverse event definitions" outlined in the supplement section below. Any event that is severe and/or serious will be reported to the PI immediately. If the event is determined to meet the criteria for Unanticipated Problem (UP) it will be reported to the IRB within 2 business days.

The study will be stopped if any patient is permanently disabled, seriously injured, or dies in a manner that could be consistent with the drug usage. The study will be continued if said patient(s) were taking the placebo or the event is demonstrably unrelated to the

subject's participation in the trial.

An independent monitor within the otolaryngology department who is not associated with study recruitment or data analysis will also review adverse events (see appendix for definitions) for all subjects after every 10th subject has completed 8 weeks of treatment. Dr. Michael Platt has agreed to act as this independent monitor. He is not directly supervised by the PI, Dr. J. Pieter Noordzij. His salary is not determined or affected by Dr. Noordzij. The independent monitor will submit a report to the PI, who will then review these events and submit a report to the IRB. Also, if there is a concerning event or group of events, the PI will bring these to the attention of the independent monitor as they occur, within 2 business days, regardless of whether they are thought to be related to treatment or not.

Additionally, reporting to the IRB will be expedited (within 2 business days) for any event that is unexpected, possibly related to treatment and causes risk to subjects or others, or is serious.

We will assess and document all adverse events and will report any adverse event that meets the definition of unanticipated problem, as defined in the Boston Medical Center Data Safety and Monitoring Plan (DSMP).

A report will be submitted to the IRB and the PI by the independent monitor at the above intervals.

Upon enrollment, subjects will be provided with an emergency contact card with a short description of the study drug used and contact information for Investigational Pharmacy services, in case of emergency.

Funding

The study is investigator-initiated and funded by the American Laryngological Association (ALA) ALA - ALVRE RESEARCH GRANT.

There are no other sponsors or industry affiliations.

Patients will receive medication or placebo during the 8-week course and participate in a follow up visit free of charge. Any additional visits during the 8 weeks of treatment due to side effects will also be free of charge. There will be no other compensation provided.

Supplements

Sample screening logs
Enrollment data will be kept in the format below.

Noordzij H-34438 Chronic Laryngitis - Amitriptyline Study Screening Log			
Study ID #	Subject	Date	Eligible for

	Initials	Consented	study? (if excluded, list reasons why)
S-040			
S-041			
S-042			
S-043			
S-044			
S-045			
S-046			
S-047			

Adverse Event Definitions
The following definitions have been adapted from:

- FDA Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA/BE Studies (http://www.fda.gov/downloads/Drugs/.../Guidances/UCM227351.pdf)
- FDA Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance (http://www.fda.gov/downloads/Drugs/Guidances/ucm073122.pdf, Sections 1.2, 1.50, 1.60)

A. Adverse Event
Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

B. Suspected Adverse Reaction
Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of this study, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

The following examples are types of evidence that would suggest a causal relationship between the drug and the adverse event:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group

C. Adverse Reaction
An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

D. Unexpected
An adverse event or suspected adverse reaction is considered "unexpected" if it is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. This means that events not listed for the particular drug under investigation in the study application are considered "unexpected" and those listed are considered "expected."

E. Serious
An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

F. Life-Threatening
An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Drug Profile and Side Effects

Trade Drug Name:	Not applicable
Generic Drug Name:	Amitriptyline
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	
Is the drug supplied at no cost?	Yes
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	Yes
Is an IND necessary	No
IND Number	
Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	The drug being used will be amitriptyline capsules compounded by the Investigational Drug Service at BMC. We believe our use meets the requirements for an IND exemption as per 21 CFR 312.2. As previously mentioned in part D, we believe that the risks of amitriptyline are well-characterized, and not out of proportion to the benefits for patients. Furthermore, this is one of the standard medications used at BMC by otolaryngologists to treat chronic laryngitis felt to be possibly resulting from neuropathy, and has been used successfully for hundreds of patients for this purpose. In a recent analysis of over 50 patients given amitriptyline for this purpose at BMC, over half had significant improvement, and less than 10% had to discontinue use because of side-effects. In addition, this study is not intended to change the indication or marketing for amitriptyline in any way. Nor will the study involve any marketing or commercial activity. Lastly, the study will follow the guidelines set forth in part 50 and 56, as outlined in the applicable sections of this proposal.
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Dose Range:	0-50 mg
Frequency:	qhs
Route of administration:	PO
Will the investigational pharmacy be dispensing?	Yes
If the source is not a FDA licensed facility, provide details regarding the purity, quality,	

stability and sterility of the investigational drug/biologic:	
Identify who will be preparing the investigational drug/biologic for administration and describe in detail how it will be prepared:	Amitriptyline 12.5mg and matching placebo capsules will be compounded by IPS at BMC using Avicel as the placebo and inert filler.
Indication(s) under Investigation:	Chronic laryngitis
Where will the drug be stored	IPS at BMC.
Drug Storage Restrictions (including temperature, etc.):	Controlled Room Temperature (15º-30ºC)
Administration Instructions:	The medication will be given in 12.5mg capsules. Patients will take one capsule before bed for one week. The patient may increase dosage by one 12.5mg tablet each week if no improvement and no adverse side effects are noted, up to four 12.5mg capsules every night at bedtime for a maximum dose of 50mg daily. If any adverse side effects are noted, the patient may decrease the dosage to the last well-tolerated dose. Patients are counseled not to completely discontinue treatment without consulting the PI first.
Possible Untoward Effects, Their Symptoms & Treatment:	The most common side effects of amitriptyline are: 1) Feeling lightheaded, sleepy, having blurred vision, or a change in thinking clearly. 2) Feeling dizzy 3) Constipation 4) Dry mouth 5) Change in color of urine to blue or green. All potential side effects include: Cardiovascular: Orthostatic hypotension, tachycardia, ECG changes (nonspecific), AV conduction changes, cardiomyopathy (rare), MI, stroke, heart block, arrhythmia, syncope, hypertension, palpitation Central nervous system: Restlessness, dizziness, insomnia, sedation, fatigue, anxiety, cognitive function impaired, seizure, extrapyramidal symptoms, coma, hallucinations, confusion, disorientation, coordination impaired, ataxia, headache, nightmares, hyperpyrexia Dermatologic: Allergic rash, urticaria, photosensitivity, alopecia Endocrine & metabolic: Syndrome of inappropriate ADH secretion Gastrointestinal: Weight gain, xerostomia, constipation, paralytic ileus, nausea, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue Genitourinary: Urinary retention Hematologic: Bone marrow depression, purpura, eosinophilia Neuromuscular & skeletal: Numbness, paresthesia, peripheral neuropathy, tremor, weakness Ocular: Blurred vision, mydriasis, ocular pressure increased Otic: Tinnitus

Potential or Actual Antidotes for Excessive or Adverse Drug Effect:	Sodium bicarbonate can be used in cases of overdose with cardiac effects.
Contraindications and Interactions, If Known:	Contraindications: Hypersensitivity to amitriptyline or any component of the formulation (cross-sensitivity with other tricyclics may occur); use of MAO inhibitors within past 14 days; acute recovery phase following myocardial infarction; concurrent use of cisapride Interactions: Acetylcholinesterase Inhibitors (Central): Anticholinergics may diminish the therapeutic effect of Acetylcholinesterase Inhibitors (Central). Acetylcholinesterase Inhibitors (Central) may diminish the therapeutic effect of Anticholinergics. If the anticholinergic action is a side effect of the agent, the result may be beneficial. Risk C: Monitor therapy Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). Risk C: Monitor therapy Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. Risk C: Monitor therapy Alpha-/Beta-Agonists (Direct-Acting): Tricyclic Antidepressants may enhance the vasopressor effect of Alpha-/Beta-Agonists (Direct-Acting). Exceptions: Dipivefrin. Risk D: Consider therapy modification Alpha1-Agonists: Tricyclic Antidepressants may enhance the vasopressor effect of Alpha1-Agonists. Risk D: Consider therapy modification Alpha2-Agonists: Tricyclic Antidepressants may diminish the antihypertensive effect of Alpha2-Agonists. Exceptions: Apraclonidine; Brimonidine. Risk D: Consider therapy modification Altretamine: May enhance the orthostatic hypotensive effect of Tricyclic Antidepressants. Risk C: Monitor therapy Amphetamines: Tricyclic Antidepressants may enhance the stimulatory effect of Amphetamines. Tricyclic Antidepressants may also potentiate the cardiovascular effects of Amphetamines. Risk C: Monitor therapy Anticholinergics: May enhance the adverse/toxic effect of other Anticholinergics. Exceptions: Levocabastine (Nasal); Levocabastine (Ophthalmic); Paliperidone. Risk C: Monitor therapy Artemether: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. Risk X: Avoid combination Aspirin: Antidepressants (Tricyclic, Tertiary Amine) may enhance the antiplatelet effect of Aspirin. Risk C: Monitor therapy Barbiturates: May increase the metabolism of Tricyclic Antidepressants. Risk D: Consider therapy modification Beta2-Agonists: Tricyclic Antidepressants may enhance the

adverse/toxic effect of Beta2-Agonists. Risk C: Monitor therapy
BuPROPion: May decrease the metabolism of Tricyclic Antidepressants. Risk C: Monitor therapy

CarBAMazepine: May increase the metabolism of Tricyclic Antidepressants. Risk C: Monitor therapy

Chloroquine: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. Risk C: Monitor therapy

Cimetidine: May decrease the metabolism of Tricyclic Antidepressants. Risk C: Monitor therapy

Cinacalcet: May increase the serum concentration of Tricyclic Antidepressants. Risk C: Monitor therapy

Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. Risk C: Monitor therapy

Ciprofloxacin (Systemic): May enhance the QTc-prolonging effect of QTc-Prolonging Agents. Risk C: Monitor therapy

Cisapride: Amitriptyline may enhance the arrhythmogenic effect of Cisapride. Risk X: Avoid combination

CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. Exceptions: Epinastine; Levocabastine (Nasal); Levocabastine (Ophthalmic); Olopatadine; Olopatadine (Ophthalmic). Risk C: Monitor therapy

Conivaptan: May increase the serum concentration of CYP3A4 Substrates. Management: Upon completion/discontinuation of conivaptan, allow at least 7 days before initiating therapy with drugs that are CYP3A4 substrates. Risk D: Consider therapy modification

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. Risk C: Monitor therapy

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. Risk D: Consider therapy modification

Desmopressin: Tricyclic Antidepressants may enhance the adverse/toxic effect of Desmopressin. Risk C: Monitor therapy

Dexmethylphenidate: May enhance the adverse/toxic effect of Tricyclic Antidepressants. Dexmethylphenidate may increase the serum concentration of Tricyclic Antidepressants. Risk C: Monitor therapy

Divalproex: May increase the serum concentration of Tricyclic Antidepressants. Risk C: Monitor therapy

Dronedarone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Dronedarone. Risk X: Avoid combination

DULoxetine: May decrease the metabolism of Tricyclic Antidepressants. Risk C: Monitor therapy

Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. Risk D: Consider therapy modification

Iobenguane I 123: Tricyclic Antidepressants may diminish the therapeutic effect of Iobenguane I 123. Risk X: Avoid combination Lithium: May enhance the neurotoxic effect of Tricyclic Antidepressants. Risk C: Monitor therapy

Lumefantrine: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. Risk X: Avoid combination

MAO Inhibitors: May enhance the serotonergic effect of Tricyclic Antidepressants. This may cause serotonin syndrome. Risk X: Avoid combination

MAO Inhibitors: May enhance the orthostatic hypotensive effect of Orthostatic Hypotension Producing Agents. Risk C: Monitor therapy

Methylphenidate: May enhance the adverse/toxic effect of Tricyclic Antidepressants. Methylphenidate may increase the serum concentration of Tricyclic Antidepressants. Risk C: Monitor therapy

Metoclopramide: May enhance the adverse/toxic effect of Tricyclic Antidepressants. Management: Seek alternatives to this combination when possible. Monitor patients receiving metoclopramide with tricyclic antidepressants for signs of extrapyramidal symptoms, neuroleptic malignant syndrome, and serotonin syndrome. Risk D: Consider therapy modification

Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. Risk X: Avoid combination

NSAID (COX-2 Inhibitor): Antidepressants (Tricyclic, Tertiary Amine) may enhance the antiplatelet effect of NSAID (COX-2 Inhibitor). Risk C: Monitor therapy

NSAID (Nonselective): Antidepressants (Tricyclic, Tertiary Amine) may enhance the antiplatelet effect of NSAID (Nonselective). Risk C: Monitor therapy

Peginterferon Alfa-2b: May decrease the serum concentration of CYP2D6 Substrates. Risk C: Monitor therapy

Pimozide: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Pimozide. Risk X: Avoid combination

Pramlintide: May enhance the anticholinergic effect of Anticholinergics. These effects are specific to the GI tract. Risk D: Consider therapy modification

Propoxyphene: May enhance the CNS depressant effect of Tricyclic Antidepressants. Risk C: Monitor therapy

Protease Inhibitors: May increase the serum concentration of Tricyclic Antidepressants. Risk C: Monitor therapy

QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. Risk D: Consider therapy modification

QuiNIDine: Tricyclic Antidepressants may enhance the QTc-prolonging effect of QuiNIDine. QuiNIDine may increase the

serum concentration of Tricyclic Antidepressants. Risk D: Consider therapy modification

QuiNINE: QTc-Prolonging Agents may enhance the QTc-prolonging effect of QuiNINE. QuiNINE may enhance the QTc-prolonging effect of QTc-Prolonging Agents. Risk X: Avoid combination

Selective Serotonin Reuptake Inhibitors: May decrease the metabolism of Tricyclic Antidepressants. Risk D: Consider therapy modification

Serotonin Modulators: May enhance the adverse/toxic effect of other Serotonin Modulators. The development of serotonin syndrome may occur. Risk D: Consider therapy modification

Sibutramine: May enhance the serotonergic effect of Serotonin Modulators. This may cause serotonin syndrome. Risk X: Avoid combination

St Johns Wort: May increase the metabolism of Tricyclic Antidepressants. The risk of serotonin syndrome may theoretically be increased. Risk D: Consider therapy modification

Sulfonylureas: Cyclic Antidepressants may enhance the hypoglycemic effect of Sulfonylureas. Risk C: Monitor therapy

Terbinafine: May decrease the metabolism of Tricyclic Antidepressants. Risk D: Consider therapy modification

Terbinafine (Systemic): May decrease the metabolism of Tricyclic Antidepressants. Risk D: Consider therapy modification

Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. Risk X: Avoid combination

Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. Risk X: Avoid combination

TraMADol: Tricyclic Antidepressants may enhance the neuroexcitatory and/or seizure-potentiating effect of TraMADol. Risk C: Monitor therapy

Valproic Acid: May increase the serum concentration of Tricyclic Antidepressants. Risk C: Monitor therapy

Vitamin K Antagonists (eg, warfarin): Tricyclic Antidepressants may enhance the anticoagulant effect of Vitamin K Antagonists. Risk C: Monitor therapy

Yohimbine: Tricyclic Antidepressants may increase the serum concentration of Yohimbine. Risk C: Monitor therapy

Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. Risk X: Avoid combination

Investigators Authorized to Prescribe:

Dr. Noordzij