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Effectiveness of Amitriptyline Versus Cough Suppressants in the Treatment of Chronic Cough Resulting From Postviral Vagal Neuropathy

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Objective: **The objective of this prospective, randomized, controlled study (N = 28) was to evaluate the effectiveness of amitriptyline versus cough suppressants in the treatment of chronic cough resulting from postviral vagal neuropathy.** ***Methods:*** **Patients were selected based on a clinical history consistent with postviral vagal neuropathy and a history of an antecedent upper respiratory tract infection. All patients had been tried on antireflux medication (proton pump inhibitors) and had a negative chest x-ray before presentation. All were nonsmokers without a history of asthma. Patients on angiotensin-converting enzyme inhibitors were excluded from the study. All patients completed a pretreatment, validated cough-specific quality-of-life (QOL) survey. Patients were randomized by chart numbers to either 10 mg amitriptyline at bedtime or 10 to 100 mg/5 mL, 10 mL codeine/guaifenesin every 6 hours standing dose while awake. Both groups were instructed to complete 10 days of therapy and then asked to subjectively rate the reduction in the frequency and severity of their cough by 100%, 75%, 50%, 25%, or 0% as well as completing the posttreatment cough QOL questionnaire. Those patients experiencing a 75% to 100% reduction were recorded as having a complete response, 25% to 50% a partial response, and 0% as having no response. Final results and the cough QOL survey were recorded and used for statistical analysis.** ***Results:*** **A majority of patients in the amitriptyline group achieved a complete response on the initial dose of 10 mg. None of the codeine/guaifenesin group achieved a complete response. The data were analyzed using a logistic regression model, and amitriptyline was found to be a highly significant predictor of a greater than 50% response when compared with codeine/guaifenesin (P = .0007). The same data were analyzed using a proportional odds model and similar results were noted.** ***Conclusions:*** **Chronic cough can have a profound impact on the psychosocial function of patients. The most common causes of a persisting cough in the absence of infection or chronic smoking are laryngopharyngeal reflux, asthma, particularly the cough variant, allergy, rhinosinusitis, bronchitis, and medications, in particular angiotensin-converting enzyme inhibitors. Currently, there are few effective treatments for cough with an acceptable therapeutic ratio and more selective drugs with a more favorable side effect profile are needed. This is this first prospective, randomized, controlled study comparing the effectiveness of amitriptyline versus codeine/guaifenesin for select cases of chronic cough resulting from suspected postviral vagal neuropathy.**
Key Words: **Chronic cough, postvagal viral neuropathy, amitriptyline, cough suppressants.**
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INTRODUCTION

Despite considerable advance in the understanding of cough, the effective management of patients with a chronic cough can be difficult. For the patient, a persistent cough can be associated with considerable distress and an impaired quality of life.[1] The key to successful management is to establish a diagnosis and to treat the cause of cough. The most common causes of a persisting cough in the absence of infection or chronic smoking are laryngopharyngeal reflux, asthma, particularly the cough variant, allergy (of which asthma and "postnasal drip" may be considered subsets of), rhinosinusitis, bronchitis, and medications, in particular angiotensin-converting enzyme inhibitors.[2]

Truly idiopathic cough is rare and misdiagnoses are common. Failure to obtain a treatment response may lead

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to the mistaken belief that the cough is functional or psychogenic, frequently overlooking a number of reasons why a cough may be difficult to treat. In some cases, treatment failure may reflect an inadequate approach to diagnostic evaluation or a failure to appreciate pulmonary and extrapulmonary causes for chronic cough.[3] However, an alternate explanation is that a distinct diagnostic entity exists, namely cough secondary to postviral vagal neuropathy (PVVN).[4]

Cranial nerves are known to be affected by inflammatory neuropathic processes. Bell's palsy, trigeminal neuralgia, and glossopharyngeal neuralgia are examples of such cranial neuropathies. These represent isolated nerve injuries that result in motor or sensory dysfunction (e.g., paralysis, pain) depending on the nerves affected. Other cranial neuropathies have also been described. Of particular interest to the otolaryngologist is the existence of vagal neuropathy. Postviral vagal neuropathic cough is not usually included as a standard origin for chronic cough. It must be pointed out that confirmatory evidence of a viral etiology of PVVN is not available or feasible today. There is no standard of care for PVVN cough. Conversely, cough secondary to the acute, direct effects of a viral upper respiratory tract infection may be palliated with guaifenesin with codeine by thinning the mucus or phlegm in the lungs and helping suppress the cough (U.S. Food and Drug Administration-approved). In the study done by Woo et al.,[2] patients with a negative workup for reflux, asthma, or "postnasal drip" were treated with gabapentin at 100 to 900 mg per day. Symptomatic relief was achieved in 68% of the patients. Establishment of PVVN was not specifically noted.

Amitriptyline has been used for years in the treatment of neuropathic pain. Neuropathic pain is one of the most inextricable problems encountered in clinics, because few facts are known about its etiology. Amitriptyline was chosen because it has fewer side effects and has shown great success in the treatment of neuropathies. Second, the single-day dosing is favored over the three times a day typically necessary for gabapentin or similar medications. Additionally, low doses of amitriptyline (10–20 mg) have been used for over 10 years as an "off-label" treatment for suspected postviral vagal neuropathic cough; however, there have been minimal formal studies supporting the efficacy of the treatment.

The objective of our study is to evaluate the effectiveness of amitriptyline versus a standard codeine-based cough suppressant in the treatment of chronic cough in patients with a presumptive diagnosis of postviral vagal neuropathy.

METHOD

This is a prospective, randomized, controlled study. Institutional Review Board approval was obtained for this study.

Patients were selected based on a history consistent with postviral vagal neuropathy, which includes a daily dry, nonproductive cough of 6 months duration precipitated by a throat tickle, dry sensation, laughter, or speaking. Most had a history of a readily identifiable antecedent upper respiratory tract infection. All patients received empiric antireflux medication, specifically proton pump inhibitors, at a standard adult prescription dose for at least 2 consecutive months with minimal to no benefit in cough symptoms and had a negative chest x-ray before presentation. All were nonsmokers without a history of asthma or having been tried on inhalers (both steroid and nonsteroid preparations) without benefit. Patients on angiotensin-converting enzyme inhibitors were excluded from the study. Patients with nasal allergies were included. No patients were taking nasal steroids, antibiotics, or antihistamines during the study period. As part of the standard of care workup for chronic cough, all patients had office endoscopy (flexible laryngoscopy and tracheoscopy with topical anesthesia) to exclude other established causes of chronic cough.

Once the patient selection was done, participants were asked to fill a cough quality-of-life (QOL) questionnaire (Table I).[5] The 28-item cough QOL questionnaire validated and reliability shown by French et al. was used in our study. The questionnaire assesses the impact of cough on the quality of life of chronic (and acute) coughers and the efficacy of cough therapies.[5]

Participants were randomized to therapy by chart numbers and allergies (if present). Those with even numbers were placed on 10 mg amitriptyline at bedtime. Odd numbers were placed on 10 to 100 mg/5 mL, 10 mL codeine/guaifenesin every 6 hours standing dose while awake. Half of the patients with allergies were placed on the amitriptyline, whereas the other half was placed on codeine/guaifenesin. Both groups were instructed to complete 10 days of therapy. Subjects returned for a second endoscopy, questioned about compliance, and asked to rate the reduction in the frequency and severity of their cough by 100%, 75%, 50%, 25%, or 0%. Subjects were also asked to complete a posttherapy cough QOL questionnaire. Each item on the QOL is scored on a 4-point Likert-type scale (1, strongly disagree; 2, disagree; 3, agree; 4, strongly agree). The lowest possible achievable total score indicating no adverse effects of cough on QOL is 28 and the highest possible total score is 112.

Those patients experiencing a 75% to 100% cough reduction were recorded as having a complete response, 25% to 50% a partial response, and 0% as having no response. Final results were recorded and used for statistical analysis. Only single data end points at 10 days were considered.

RESULTS

Twenty-eight patients enrolled in the study. Fifteen patients were randomized to the amitriptyline arm and 13 patients to the codeine/guaifenesin arm. Patient demographics are presented in Table II. The raw data are shown in Table III.

Statistics

The QOL data correlated strongly with the patients' subjective responses. A logistic regression model was generated for the data (mean ratings) in which we modeled the logit probability of having a response of 50% or more (as opposed to 25% or less) as a function of the type of drug used. A P value of less than .01 was selected as significant. Using the logistic regression model, amitriptyline was found to be a significant predictor of a greater than 50% response when compared with codeine/guaifenesin ($P = .0007$). Several other methods of analysis were performed using the change in the pre- and posttreatment scores established from the cough QOL survey, including analysis of maximum likelihood estimates, proportional odds

TABLE I.
Quality-of-Life Cough Questionnaire.[5]

Question	Not Applicable	Strongly Disagree	Disagree	Agree	Strongly Agree
Family and or close friends cannot tolerate it any more	0	1	2	3	4
I have experienced prolonged absences from important activities such as work, school, or volunteer services	0	1	2	3	4
I have been completely prevented from engaging in important activities such as work, school, or volunteer services	0	1	2	3	4
I have lost my appetite	0	1	2	3	4
I am sick to my stomach and vomit	0	1	2	3	4
I cough and it makes me retch (dry heaves)	0	1	2	3	4
I have a fear that I might have AIDS or tuberculosis	0	1	2	3	4
I have headaches	0	1	2	3	4
I am concerned that I have cancer	0	1	2	3	4
I am dizzy	0	1	2	3	4
I wet my pants	0	1	2	3	4
I soil my pants	0	1	2	3	4
I sweat	0	1	2	3	4
I am hoarse	0	1	2	3	4
It hurts when I breathe	0	1	2	3	4
I broke a rib	0	1	2	3	4
I cannot sleep at night	0	1	2	3	4
I have difficulty speaking on the phone	0	1	2	3	4
I can no longer sing, for instance, in church	0	1	2	3	4
I have stopped going to social activities such as movies, plays, and town meetings	0	1	2	3	4
I have had to change my lifestyle	0	1	2	3	4
I ache all over	0	1	2	3	4
I am exhausted	0	1	2	3	4
I am embarrassed	0	1	2	3	4
I am upset by people thinking that I have something wrong with me	0	1	2	3	4
I want to be reassured that I do not have anything seriously the matter with me	0	1	2	3	4
I am self-conscious	0	1	2	3	4

model, and analysis of the drug by d-response (summarized in Tables IV and V).

A summary of the results is shown in Figure 1.

DISCUSSION

Cough is a protective mechanism and represents the outcome of a complex reflex initiated by activation of irritant receptors in the airway.[6] Chronic cough (CC) is simply defined as a cough persisting beyond a specified period of time that may range from 6 to 8 weeks. Whereas acute cough is considered beneficial to the respiratory system through removing noxious substances and increasing mucociliary clearance, CC is considered to have no benefit to the respiratory system or the body in general.[7]

PVVN is a condition that occurs after an upper respiratory illness, which represents injury (neuropathy) to various branches of the vagus nerve. Vagal neuropathy may involve the motor branches, resulting in paralysis of the recurrent and/or superior laryngeal nerves.[8] Patients with this condition may present with breathy dysphonia, vocal fatigue, effortful phonation, odynophonia, cough, globus, and/or dysphagia lasting long after resolution of the acute viral illness. The sensory divisions may also be affected, resulting in an abnormal sensation triggering a sensory response similar to the burning associated with Zoster or trigeminal neuralgia.[8] In the case of the vagus nerve, this sensation may be perceived as a "tickle," "dry patch," or irritation in the throat, almost invariably located at the cricoid level, which precipitates a coughing "fit," which typically lasts 20 to 30 seconds. In severe cases, laryngospasm may occur with reports of syncope

TABLE II.
Patient Demographics.

N = 28	Amitriptyline (N = 15; 7 female)	Codeine/Guaifenesin (N = 13; 8 female)
Median age	54.6 years	49.7 years
Median duration of cough	15.1 months	11.4 months
History of nasal allergy	2	3

TABLE III.
Raw Data.

Patient No.	Therapy	10-Day Response
1	Amitriptyline	50% improvement
2	Amitriptyline	75% improvement
3	Codeine/guaifenesin	0% improvement
4	Amitriptyline	75% improvement
5	Codeine/guaifenesin	0% improvement
6	Amitriptyline	100% improvement
7	Amitriptyline	75% improvement
8	Codeine/guaifenesin	25% improvement
9	Codeine/guaifenesin	0% improvement
10	Codeine/guaifenesin	0% improvement
11	Codeine/guaifenesin	0% improvement
12	Amitriptyline	75% improvement
13	Codeine/guaifenesin	50% improvement
14	Amitriptyline	50% improvement
15	Amitriptyline	100% improvement
16	Codeine/guaifenesin	0% improvement
17	Amitriptyline	0% improvement
18	Codeine/guaifenesin	0% improvement
19	Codeine/guaifenesin	0% improvement
20	Amitriptyline	100% improvement
21	Amitriptyline	25% improvement
22	Codeine/guaifenesin	0% improvement
23	Amitriptyline	75% improvement
24	Amitriptyline	75% improvement
25	Codeine/guaifenesin	0% improvement
26	Codeine/guaifenesin	25% improvement
27	Amitriptyline	100% improvement
28	Amitriptyline	75% improvement

and secondary head injury possible. The patterns of symptoms and lack of objective findings on examination and endoscopy in this condition are consistent with the hypothesis that viral infection causes or triggers vagal dysfunction.[8,9] PVVN appears to have similarities with other postviral neuropathic disorders such as glossopharyngeal neuralgia and Bell's palsy.[8]

Despite adopting a comprehensive evaluation of patients referred with cough, many groups have reported diagnostic and treatment failure in anything from 12% to 42% of patients.[10] For some, this represents a population with idiopathic cough, which some suggest as reflecting failed management.[11] Specifically, the failure to prescribe sedating antihistamines for postnasal drip syndromes[11]

TABLE IV.
Analysis of Maximum Likelihood Estimates.

Parameter	Estimate	Standard Error	χ^2	Pr > χ^2
Codeine/ guaifenesin	−2.4848	1.0408	5.6998	0.0170
Amitriptyline	4.3566	1.2885	11.4326	0.0007

TABLE V.
Statistics for Table of Drug by d-Response.

Statistic	Value	Probability
χ^2	17.3744	<.0001
Likelihood ratio χ^2	19.9851	<.0001
Continuity adjusted χ^2	14.3590	.0002
Mantel-Haenszel χ^2	16.7538	<.0001
Phi coefficient	0.7877	
Contingency coefficient	0.6188	
Cramer's V	0.7877	

and the inadequate treatment of gastroesophageal reflux disease have been highlighted.[12]

Current guidelines have recommended a combination of diagnostic testing and empiric trials in the management chronic cough.[13] Some authors have reported that the characteristics of a cough confer little diagnostic information, but in practice, prominent symptoms of an upper airway disorder or indigestion should prompt a treatment trial of antirhinitis therapy or antireflux therapy.[13] The question of how much and for how long of a specific treatment has yet to be unequivocally answered.

The human cough reflex consists of an afferent arm comprising cough receptors, afferent pathways, central processing, and an efferent pathway. The cough reflex can be modified at any point along this reflex, and unraveling the mechanisms responsible is key to a more complete understanding of cough pathophysiology and its successful treatment.[14] Although viral infections are a major cause of cough and appear to be frequently reported in patients with idiopathic cough, little is known regarding the effects of viruses on cough sensitivity. The authors theorize that amitriptyline works by raising the threshold of the afferent arm of the cough reflex to the persisting stimuli and/or the erroneous triggers.

The theory of viral illnesses causing neuropathy is not without precedent. Viral infection has been proposed as the possible etiology in Bell's palsy. Similarly, Guillain-Barré syndrome is widely believed to be caused by viral-

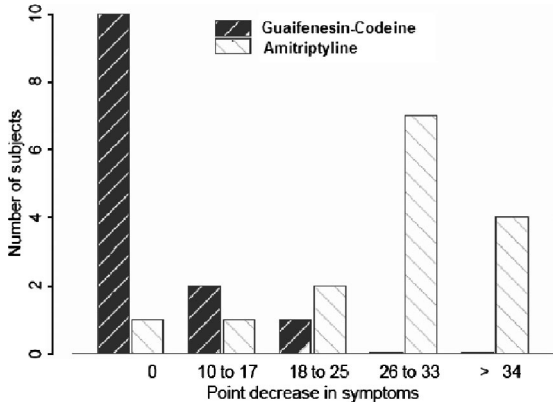

Fig. 1. Bar chart showing the difference in response rates between amitriptyline and codeine/guaifenesin in pre- and posttreatment cough quality of life.

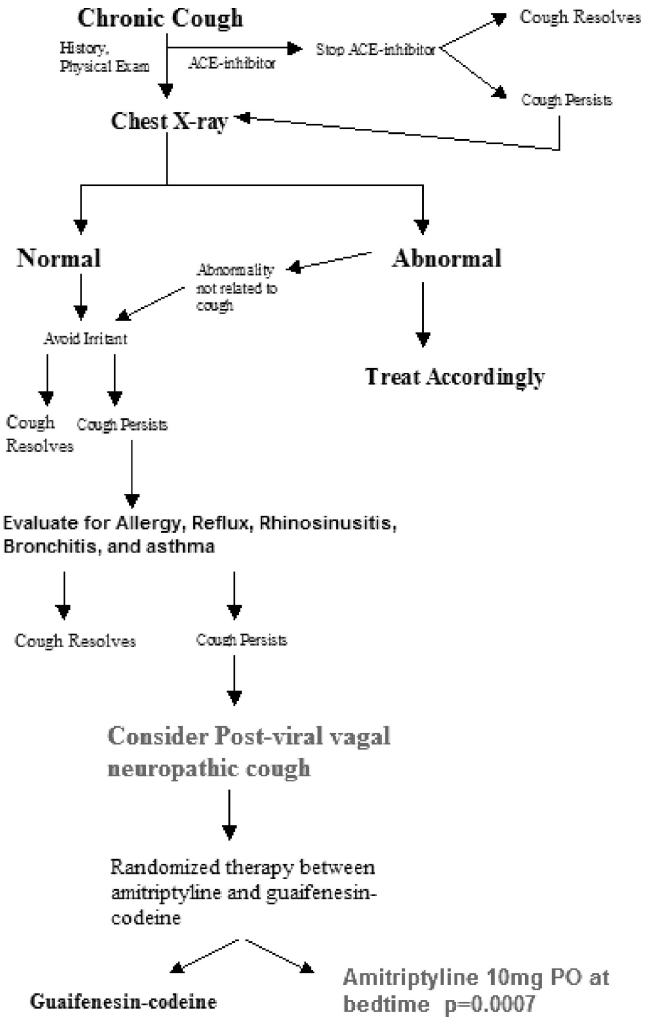

Fig. 2. Anatomic diagnostic protocol for the workup of chronic cough.[7]

induced inflammation.[4] Two mechanisms whereby viral infection may cause neuritis or neuropathy have been proposed: 1) direct infection and inflammation of a nerve or 2) by the induction of a nonspecific inflammatory response that secondarily involves a nerve.[4]

The diagnosis of CC can be made by using the anatomic diagnostic protocol (ADP) (Fig. 2)[7] or by empiric therapy. The ADP is a process for systematically diagnosing the common causes of CC in a particular person such as asthma, allergy (including "postnasal drip"), and (laryngopharyngeal) reflux disease. This protocol, therefore, enables treatment to be directed at the specific underlying cause of the cough. Marchesani et al.[15] found that the success rate of medical therapy improved to 91% when an ADP was used. Cough suppressants are not routinely used in medical assessment or diagnosis of CC and the ADP does not include routine use of such agents.

The literature, i.e., the ADP, has not clearly defined a treatment paradigm in the management of those patients with CC of infectious etiology. Therefore, we have introduced the utilization of amitriptyline as a first-line therapy for the treatment of PVVN cough.

CONCLUSION

Chronic cough can have a profound impact on the psychosocial function of patients.[5] Our understanding of the diagnosis and treatment of chronic cough has undergone a radical change over the past 20 years. The experience of specialty clinics has demonstrated that most chronic cough is treatable provided the characteristic features of the three most common causes of cough—asthma, reflux, and allergy—are recognized in nonsmoking patients with negative medication profiles. Because cough is a vital protective reflex for the airways, the goal of treatment must be the restoration of a normal cough reflex. Although incorrect diagnoses will continue to explain a significant number of patients with what appears to be a refractory chronic cough, an attempt has been made in this article to highlight postviral vagal neurogenic cough as a distinct and treatable clinical entity. Amitriptyline is an effective first-line therapy for select cases of suspected PVVN cough.

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