Review

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State of the Art for Refractory Cough: Multidisciplinary Approach

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Abstract

Chronic cough is a common problem that can be refractory to medical treatment. Nonpharmaceutical management of chronic cough has an important role in well selected patients. This review article outlines the history of chronic cough management, current approaches to speech pathology management of the condition and new modalities of nonpharmaceutical treatment. There is a need for further research into nonpharmaceutical options with well described randomised control trials.

Keywords: Speech Pathology; Nonpharmaceutical; Chronic Cough; Inducible Laryngeal Obstruction; Vocal Cord Dysfunction

Introduction

Chronic cough, defined as a cough lasting longer than 8 weeks, is a common medical condition that can be refractory to medical treatment[1,2]. Chronic cough has numerous physical and psychological side effects, and negatively impacts quality of life[3]. It can last for months or even years, thus perpetuating the impact of these negative side effects[4]. While medical intervention is the mainstay of chronic cough treatment, nonpharmaceutical treatment has an important role to play in the management of chronic cough. This paper outlines current and new developments in nonpharmacological treatment of chronic cough and implications for future research and clinical practice.

History

Traditionally, cough was considered the result of lower airway disease such as chronic bronchitis, or environmental exposure to airborne pollutants[5]. The anatomic diagnostic protocol, was introduced in 1981 to evaluate patients with chronic cough[6,7]. This protocol was based on evaluation of the location of the afferent limb of the cough reflex[7]. It proposed that in non-smokers without lower airway disease, cough was caused by asthma, rhinosinusitis or gastroesophageal reflux disease (GERD), and that systematic assessment and treatment of these underlying diseases would resolve cough. While the anatomic diagnostic protocol was promising and explained many cases of chronic cough, there were challenges with the concept. Treatment based on the anatomic diagnostic protocol, while effective in treating the underlying condition, did not always eliminate cough. Furthermore, these conditions did not universally result in the development of chronic cough, raising questions about the causal relationship between cough and these underlying conditions.

Several new developments in the management of cough have occurred over the last 15 years. Cough hypersensitivity syndrome was proposed as an underlying unifying feature in chronic cough[8]. For chronic cough to develop, patients need to have a trigger, such as exposure or underlying disease, and cough hypersensitivity. Associated conditions such as GERD, asthma or rhinitis act as triggers to cough in an already hypersensitive system[5]. Cough hypersensitivity syndrome explains why some patients with associated diseases will cough and others will not. For example, patients with GERD but without cough hypersensitivity are less likely to develop chronic cough.

Another important development in our understanding of chronic cough relates to the role of the larynx in cough. Laryngeal discomfort and irritation is common in patients with chronic cough, and laryngeal tasks such as speaking and laughing frequently trigger cough[9]. Furthermore, laryngeal disorders such as vocal cord dysfunction/inducible laryngeal obstruction (VCD/ILO) are associated with chronic cough. Ryan and Gibson[10] found that 50% of patients with chronic refractory cough had paradoxical vocal fold movement consistent with VCD/ILO, on laryngoscopy. There is a strong symptom overlap between chronic refractory cough, and VCD/ILO[11]. For example, many patients with chronic cough report breathlessness and dysphonia that is characteristic of VCD/ILO. Conversely, cough frequency in patients with VCD/ILO is as high as those with chronic refractory cough[12]. Therefore, laryngeal dysfunction may be an associated and even causal condition in some patients with chronic cough.

More recent pharmaceutical treatments for chronic cough include centrally acting neuromodulators which reduce cough frequency and severity, and improve cough quality of life[13-15]. P2X3 ligand-gated ion channel 3 (P2X3) inhibitors, which block the P2X3 receptor, are currently in phase three trials. Findings to date suggest that P2X3 inhibitors are associated with reduced cough frequency and improved cough quality of life[16]. Despite the benefits, the treatment effect of neuromodulators may not be sustained once the treatment is withdrawn, and side effects may be intolerable for some patients[13]. For these reasons, nonpharmacological treatment of chronic cough might be a useful adjunct or alternative to drugs such as neuromodulators.

Speech Pathology Treatment for Chronic Cough

1. Treatment description

Speech pathology treatment of chronic cough has been used successfully in many countries over the last 15 years, and utilises therapy techniques adapted from speech pathology treatment of hyperfunctional voice disorders. Speech pathology treatment for chronic cough involves an assessment and approximately four intervention sessions. Candidate patients are those with chronic refractory cough, i.e., those with cough persisting despite medical management. It is essential that a thorough medical investigation has been completed before considering speech pathology treatment. Cough can be due to serious disease, including cardiac disease, lung or laryngeal cancer, or uncontrolled asthma. Symptomatic cough suppression without ruling out serious underlying disease would be detrimental. Further, triggering conditions, such as GERD or rhinosinusitis, may need to be addressed before considering speech pathology treatment.

There are four major components to the speech

Table 1. Components of speech pathology intervention for chronic cough

Component	Description	Examples
Education	Explains the rationale for a behavioural approach Emphasises the capacity for voluntary control	Although the urge to cough is distressing there is no physiological need to cough
Cough suppression techniques	Increase awareness of urge to cough Replace with competing technique	PVFM release breathing, cough control breathing, accent method breathing
Reducing laryngeal irritation	Reduce exposure or behaviours that trigger an urge to cough	Hydration, minimise exposure to irritating substance, reduce phonotraumatic behaviours
Psychoeducational counselling	Facilitate motivation to undertake behavioural intervention	Set realistic treatment goals, optimise treatment adherence

PVFM: paradoxical vocal fold movement.

pathology treatment for chronic cough: education, cough control strategies reducing laryngeal irritation, and psychoeducational counselling (Table 1). The education component emphasises the rationale for a behavioural approach to treatment and the capacity for voluntary control of cough. This concept is supported by functional magnetic resonance imaging studies that demonstrate cortical activation with an urge to cough, and activation of the dorsomedial prefrontal and anterior mid-cingulate cortices when inhibiting a cough[17]. Education is also needed to reassure patients that although the urge to cough is real and distressing, there is no physiological need to cough. The cough is occurring due to irritation of the larynx and airways, and can be safely suppressed even when a direct cause for the cough cannot be identified.

The second component of speech pathology treatment involves active cough suppression techniques. Here patients are encouraged to develop awareness of an impending cough or urge to cough, no matter how slight, and to implement a competing response to the cough behaviour. These competing responses range from simple distraction techniques to more sophisticated laryngeal deconstriction and breathing techniques. These techniques focus on abducting the vocal folds preventing them forcing shut in a cough, relieving cough with gentle vocal fold adduction that is less likely to cause vocal fold trauma, and increasing the speed of airflow through the larynx without associated hard glottal attacks. For patients with coexisting VCD/ILO, responding to an urge to cough with techniques designed to address the laryngeal spasms occurring as a result of VCD/ILO, can relieve the urge to cough and reduce cough frequency. The aim of these suppression techniques is to teach patients to respond to an urge to cough in a way that does not promote phonotrauma or perpetuate the cycle of hypersensitivity.

Reducing laryngeal irritation is the third component of speech pathology treatment. The aim of this component is to reduce exposures or behaviours that increase laryngeal irritation and the urge to cough. Strategies include reducing exposure to irritating substances, such as alcohol and excessive caffeine, improving hydration, and reducing phonotraumatic vocal behaviours such as hard glottal attacks or excessive laryngeal constriction when speaking. In some cases systematic desensitisation might be used particularly if patients sense an urge to cough following exposure to a particular non-tussive stimuli.

The final component of speech pathology treatment for chronic cough is psychoeducational counselling, which facilitates the individual's motivation to undergo behavioural therapy. Many patients want a quick fix for their cough, whereas behavioural intervention takes time and effort. The success of the intervention depends upon adherence to the treatment program. Patients who are unable to complete the intervention due to time, cognitive ability, or beliefs may not be candidates for therapy. Speech pathologists support patients to set realistic treatment goals. For example, it is unlikely that patients will be able to stop coughing immediately and progress is more likely to be slow and steady. Patients are advised that while speech pathology treatment will reduce the severity of their symptoms, symptoms might not fully resolve.

2. Effectiveness of speech pathology treatment for chronic cough

The outcome of speech pathology treatment has been assessed in two randomised controlled trials involving 162 adult participants[18-20]. Both studies employed four therapy sessions, using treatment similar to that described above, compared with placebo involving healthy lifestyle education. Therapy resulted in decreased objective cough counts, improvements in symptom scores and cough quality of life. A systematic review by Ilicic et al.[21] reported that in comparison with control interventions, nonpharmacological therapy improves cough specific health related quality of life, as measured by the Leicester Cough Questionnaire (LCQ), by 1.53 points. This improvement is more than the minimally clinically important difference of 1.3[22]. Nonpharmacological treatment also reduces cough frequency, and urge to cough[19,23], as well as noncough symptoms such as breathing difficulty, upper airway sensitivity, and dysphonia[24]. Speech pathology treatment for cough is cost-effective, noninvasive and safe and no adverse events have been reported[25].

A recent pilot study analysed the effectiveness of speech pathology for treating cough and laryngeal sensation in patients with chronic refractory cough[26]. Eleven patients were randomised to receive a traditional therapy program for chronic cough as described above, or a vocal rehabilitation program. The vocal rehabilitation program involved education, orientation to voice, and vocal exercises targeting the subsystems of voice. Outcomes included the Brazilian Portuguese version of the Laryngeal Hypersensitivity Questionnaire (BP-LHQ)[27] and the cough severity index[28]. There was a large effect for time with a significant change in pre- and post-treatment scores, but no significant difference between treatment groups. There was an interaction effect between group and time for the BP-LHQ. Although this study had a small sample size, it provides

some preliminary data to suggest that laryngeal retraining in chronic cough can take a number of forms, and may be successful in treating cough and laryngeal symptoms. Laryngeal dysfunction is common in chronic cough[29] and perhaps targeting the larynx directly in treatment can reduce cough symptoms.

3. Mechanisms of speech pathology treatment for chronic cough

The mechanisms for improvement following speech pathology treatment for chronic cough are not fully understood but are likely to be multifactorial, targeting sensory, motor, and cognitive systems[25]. In chronic cough, there is an increase in sensory afferent input into the brainstem due to peripheral sensitisation[30]. Increased sensory input can intrinsic, for example upper respiratory tract infection, or reflux episodes, or extrinsic such as environmental exposure. Descending inhibitory control of cough is also decreased in patients with chronic cough with reduced activity in the dorsomedial prefrontal and anterior mid-cingulate cortices[17]. The combination of reduced inhibitory control and increased sensory input leads to increased efferent output in the form of cough. This process can continue even when the sensory input is removed or reduced. In some cases the sensory afferent input to the brain stem may reduce but the plastic changes in the central nervous system are sustained leading to central sensitisation.

Speech pathology treatment might reduce sensory afferent input by reducing laryngeal irritation and stimulation of the cough reflex, thus reducing peripheral and central sensitisation. The education, and cough suppression components of the treatment target the descending inhibitory control of cough. Simultaneously targeting sensory input and descending inhibitory control is hypothesised to lead to decreased efferent output (cough). Treatment outcomes can be sensory (e.g., reduced urge to cough, reduced laryngeal hypersensitivity and reduced cough reflex sensitivity[23]), motor (e.g., reduced laryngeal constriction, improved phonation times and decreased cough frequency[18,19]), or cognitive. Cognitive changes can include improved patient understanding of their cough and the role of behavioural intervention, increased coping skills and decreased anxiety and depression.

Emerging Concepts in Nonpharmacological treatment for Chronic Cough

Emerging concepts in nonpharmacological treatment for chronic cough are summarised in Table 2.

1. Somatic cough points

Somatic cough points are an emerging concept in chronic cough and may assist in our understanding of chronic mechanisms. Mannini et al.[31] examined the response to stimulation of somatic cough points in patients with chronic cough. Participants included 58 who had cough for more than 4 weeks and aged matched controls. The mean age was 60 years and the majority were female. Somatic cough points included the sternocledomastoid, jugular notch, lower cervical vertebrae, sternum, head extension, and head flexion. Outcome measures included the urge to cough, cough frequency and the minimum pressure required to evoke a cough. Stimulation of somatic cough points triggered cough in 52% of the patients compared with none of the controls. Neck flexion, neck extension, and jugular notch pressure were the most frequently identi-

Table 2. Summary of emerging concepts in nonpharmacological treatment for chronic cough

Treatment	Participants	Study design	Outcome
Stimulation of somatic cough points	Patients with cough >4 weeks Aged matched controls	Cross sectional study	Cough stimulated in a subset of patients with chronic cough
Transcranial direct current stimulation	Healthy young adults	Single arm intervention	Increased cough reflex threshold
Expiratory muscle strength training	Patients with chronic cough	Single arm intervention	Improved mid-inspiratory pressure, mid-expiratory pressure, laryngeal airway resistance and maximum phonation time
Nebulised capsaicin	Patients with chronic cough	Randomised control trial	Improvement in cough quality of life, urge to cough and cough frequency

fied somatic points for cough. The mean force required to evoke response was 2.6±0.6 kg. Cooling with dry ice abolished all responses. The impact of somatic cough points on treatment for chronic cough is unknown. Is cough triggered by somatic cough point stimulation a phenotype of clinical significance, and could it be used as part of a systematic desensitisation program? Further research is needed to answer this question.

2. Transcranial direct current stimulation

Another emerging concept is transcranial direct current stimulation (tDCS). Gui et al.[32] investigated the effects of tDCS on the cough reflex and urge to cough in 23 healthy young adults. Participants randomly received tDCS anodal stimulation, cathodal stimulation and sham stimulation with at least 1 week between stimulation sessions. The tDCS involved a constant current of 2 mA, applied for 30 minutes, and which stimulated the right dorsolateral prefrontal cortex region. The cough reflex threshold and urge to cough were evaluated immediately after stimulation by inhalation of citric acid-saline solution. Compared with sham stimulation, the cough reflex thresholds of logC2 and logC5 (the log transformation of the lowest concentration of citric acid that elicited two and five coughs respectively), increased under tDCS anodal stimulation ($p=0.023$ and $p<0.001$, respectively). In contrast, there was no significant change in urge to cough sensitivity. The mechanism for change is unknown, but is hypothesised to target central sensitisation. This preliminary study suggests that tDCS could be investigated further either as a standalone treatment for chronic cough, or as an adjunct to other established nonpharmacological therapies.

3. Expiratory muscle strength retraining

Expiratory muscle strength training (EMST) is a component of speech pathology treatment for a number of disorders including dysphagia, dysphonia, and VCD/ILO. EMST involves breathing through a resistive breath training device to improve control of the respiratory system and increase expiratory muscle strength[33]. Quibin et al.[33] investigated the use of EMST for 19 female patients with refractory cough. Each patient had a pre-assessment and training for the EMST device at their first visit. They then had EMST consisting of five sets of five repetitions per session, five sessions a week for 4 weeks. The resistance of the EMST device was increased by one quarter clockwise turn of the resistance valve every week. There was a significant pre-post-treatment improvement in mid-inspiratory pressure (62 vs. 78, $p<0.001$), mid-expiratory pressure (90 vs. 112, $p<0.001$), laryngeal airway resistance (73.3 vs. 60.7, $p=0.05$), and maximum phonation time (14.9 vs. 16.2, $p=0.01$). Importantly, the patient reported outcome measures showed an improvement in cough severity index scores (19.4 vs. 15.0) and Voice Handicap Index scores following treatment. The authors hypothesised that improvement in cough may be associated with a reduction in subglottic pressure, and increased airflow resulting in lower laryngeal airway resistance. Although this was a single arm study, it provides some useful preliminary data that could be used to plan future randomised trials, either as a standalone treatment or in combination with the traditional speech pathology treatment.

4. Cough desensitisation with nebulised capsaicin

A treatment targeting peripheral responses investigated nebulised capsaicin as a treatment for cough desensitisation. This feasibility study investigated 19 females with chronic cough using a sham controlled parallel randomised control design[34]. Participants were randomly assigned to one of two treatments. Both treatments included behavioural cough suppression with a speech pathologist. In addition, the first treatment included six treatment sessions involving exposure to nebulised capsaicin in progressively larger concentrations. The second received six sessions of exposure to a single subthreshold dose of capsaicin—referred to as the sham treatment. Outcome measures included the LCQ, urge to cough rating (from 0 to 10), and cough frequency during a challenge test. The mean change in LCQ score at 3-week post-treatment was 2.95 and 1.75 in the treatment and sham groups, respectively. Although the response in both groups was more than the minimally clinically important difference for the LCQ, there was no significant difference between groups ($p=0.23$). Cough frequency during urge to cough testing reduced by 97% and 56% in treatment and sham groups respectively ($p<0.0001$), at 3 weeks post. This trial had small participant numbers, but had a robust study design, and provides useful data for further investigations of desensitisation treatment.

5. Cough suppression during awake craniotomy

A novel implementation of speech pathology treatment for chronic cough was reported in a case study of cough suppression therapy during awake craniotomy, involving tumor resection with intraoperative language mapping[35]. The patient was a 46-year-old man with a 10-year history of chronic cough and recurrent anaplastic ependymoma. He had undergone two previous partial resections and adjuvant radiotherapy. Brain

imaging, after developing seizures, revealed a lesion within the left frontal, anterior, and superior insula extending into the anterior temporal lobe. The patient required tumor resection with intraoperative language mapping which was undertaken to delineate cortical and subcortical sites of functional significance, to preserve motor and language skills, and identify functional resection boundaries. The patient was accompanied by a speech pathologist intraoperatively to assist with cough suppression during the mapping studies. The patient displayed successful control of his cough using suppression techniques during surgery, which enabled 90% of the recurrent tumor to be resected.

Future Directions

There are a number of additional issues need to be investigated in nonpharmacological treatment of chronic cough. Many of the studies outlined above have small participant numbers or use single arm designs. Randomised control trials of behavioural intervention for chronic cough are difficult due to the challenges designing the control intervention. Despite these difficulties, it is important that new studies of nonpharmacological treatments employ appropriate study designs, adequate sample sizes, robust outcome measures, and provide detailed treatment descriptions including processes to optimise treatment fidelity. Studies to date have largely focused on adults, with no randomised controlled trials of behavioural intervention for children. Suggestion therapy for cough in children has been described[36]; however, there is little data from randomised trials. Therefore, the efficacy of behavioural interventions in children must be extrapolated from adult data.

Most studies of speech pathology treatment for chronic cough have used face to face intervention. There is limited data on the efficacy of providing therapy via telehealth. Conceptually the education and counselling components can be provided virtually. However some therapy techniques, targeting changes in breathing and voice behaviour, may require a tactile approach and therefore be less feasible to provide via telehealth.

Further research is also needed into the combination of speech pathology treatment with newly developed pharmaceutical treatments. A randomised trial compared combined speech pathology and pregabalin to combined speech pathology and placebo[14]. While both groups improved following treatment, there was greater improvement in cough quality of life and cough severity for patients receiving combined speech pathology and pregabalin. Whether speech pathology would enhance the outcome of other pharmaceutical treatments for cough, such as the new P2X3 inhibitors, requires further research.

Training of speech pathologists to deliver nonpharmacological treatment for chronic cough is critical. Internationally, there is variability in the training of undergraduate speech pathologists to treat patients with laryngeal disorders. Post-graduate education is conducted opportunistically. Although there is a growing network of speech pathologists offering intervention for chronic cough, there remain gaps in services. Further, while treatment adherence is essential for successful patient outcomes, there are limited guidelines to measure adherence in nonpharmaceutical treatments for chronic cough. There are several possible targets for addressing adherence including frequency and quantity of home practice, accuracy of home practice, and actively employing the cough suppression strategies when an urge to cough is experienced. Further research is needed to identify, measure and address the important components of treatment adherence.

Conclusion

Nonpharmaceutical management of chronic cough is a useful adjunct to medical management. It is not a replacement for appropriate medical management and requires coordination with other medical treatments. The advantages of speech pathology treatment for chronic cough include safety, effectiveness, and few side effects. A further benefit is that speech pathology treatment addresses associated symptoms including dysphonia and laryngeal discomfort. One main disadvantage of speech pathology treatment is that the treatment requires dedicated intervention from a therapist and patient adherence is required for successful outcome.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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