Non-pharmacological interventions for chronic cough: the past, present and future

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Abstract

Non-pharmacological interventions have been explored in people with refractory chronic cough. Normally delivered by Physiotherapists and or Speech and Language Therapists, these interventions aim to educate patients about their cough, provide them with cough suppression techniques and breathing exercises, improve vocal/laryngeal hydration and psychoeducational counselling to help them gain greater control of their cough. Six key studies have been completed over the past 12 years that have consistently found non-pharmacological interventions help to improve quality of life and reduce cough frequency. Some studies also found improvements in cough reflex sensitivity and severity. Despite promising results there now needs to be further work to optimise these interventions. There is a need to standardise terminology used such as relabelling the intervention as cough control therapy and move away from uni-disciplinary terms. Standardised patient selection, including screening protocols, optimal timing and delivery of the interventions as well as the outcome measures used to evaluate interventions need further exploration.

Keywords: Refractory chronic cough, speech pathology, Physiotherapy, Non-pharmacological interventions

Abbreviations:

ACE-I – Angiotensin converting enzyme inhibitors

C2 – Concentration of capsaicin at which a participant cough 2 or more times

C5 - Concentration of capsaicin at which a participant cough 5 or more times

ENT – Ear, Nose and Throat

GERD – Gastroesophageal reflux disease

ILO – Inducible Laryngeal Obstruction

LCQ – Leicester cough questionnaire

PSALTI – Physiotherapy, Speech and Language Therapy Intervention (PSALTI)

PVFM – Paradoxical vocal fold movement

RCT – Randomised control trial

SPEICH-C – Speech pathology evaluation and intervention for chronic cough

VAS – Visual Analogue Scale

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Introduction

Chronic cough, defined as a cough lasting >8weeks in duration, has an estimated prevalence of 12% in the general population (Morice et al 2006, Ford et al 2006). Studies have shown repeatedly the impact of chronic cough on individuals that include physical, psychological and social symptoms (Brignall et al 2008, Birring et al 2003). In patients with chronic cough with a normal chest x-ray the common causes of cough are asthma, gastroesophageal reflux disease (GERD) and rhinitis (Morice et al 2004, Morice et al 2006). However despite extensive assessments and medical management in up to 40% of chronic cough cases the cough persists (Haque et al 2005). A variety of terms have been used in the literature for this patient group including: idiopathic chronic cough, refractory chronic cough and cough hypersensitivity syndrome (Patel et al 2011, Morice et al 2006, Morice et al 2014); for this paper we will use the term refractory chronic cough. Treatments for refractory chronic cough have historically largely been pharmacological interventions, some of which have shown promising results however many have side-effects (Chung, 2014). However over the past 12 years there has been a series of progressive studies that have investigated the role of non-pharmacological inventions for refractory chronic cough which have found promising results. This review will explore the components of non-pharmacological interventions for refractory chronic cough, the eligibility of refractory chronic cough patients for non-pharmacological interventions, the treatment effects of these interventions, as well as the proposed mechanisms of action and the future direction for non-pharmacological interventions for people with refractory chronic cough.

1. Non-pharmacological interventions: components

Non-pharmacological interventions for refractory chronic cough in the literature have largely been delivered by either speech and language therapists or physiotherapists (Chamberlain et al 2014). The variation in therapist delivering these interventions in the literature appears to be country-dependant and may reflect the differing roles of these professions in these countries. However within the UK it is known clinically there is also variation in different NHS trusts as to whether Speech and Language Therapists or Physiotherapists deliver these interventions, the reasons for variations are unknown but could be related to service provision differences within trusts.

The first non-pharmacological studies that were conducted were small case studies (all n≤5). Blager et al (1988) explored the effect of speech pathology; consisting of diaphragmatic breathing exercises, cough suppression and identification of cough trigger and additional psychotherapy on patients with psychogenic habit cough (n=4) and found subjectively reported improvements in cough. Riegel et al (1995) was a single case study that explored the use of biofeedback therapy; consisting of EMG-assisted muscle relaxation, relaxed diaphragmatic breathing, ice massage for muscle spasm, postural advice and exercises and additional psychotherapy which resulted in the patient's self-reported reduction in cough frequency and severity. Murry et al (2004) explored the effect of two to six sessions of respiratory retraining to improve breathing pattern technique over two to six months which resulted in a mean reduction of cough severity of 7.9points (range 7 to 8.5 points) on cough severity VAS pre and post treatment.

Since these initial case studies there have been at least six non-pharmacological studies have been completed over the past 12 years, lead predominantly by two research groups. The first in Newcastle, Australia whose non-pharmacological interventions have been delivered by Speech and Language Therapists. The second in London, England whose service is Physiotherapy led and have investigated non-pharmacological interventions for refractory chronic cough delivered by Physiotherapists solely and by Physiotherapists and Speech and Language therapists in a multi-centre trial within England.

Due to the different professions providing non-pharmacological interventions for refractory chronic cough, a variety of terms have been used to name and describe these non-pharmacological interventions (Table 1). Chamberlain Mitchell et al (2017) is the only study that investigated the effects of non-pharmacological interventions for refractory chronic cough which was provided by Physiotherapists and Speech and Language Therapists. The profession delivering the intervention depended on the site the participants were treated at, and therefore a joint professional name was used to name the intervention used in this study.

Table 1. Different names for non-pharmacological intervention for chronic cough in the literature.

Speech and Language Led non-pharmacological studies		**Physiotherapy led non-pharmacological studies**
Speech pathology management/ treatment		Cough-suppression physiotherapy
Speech pathology evaluation and intervention for chronic cough (SPEICH-C)		
Physiotherapy and Speech and Language Therapy Intervention (PSALTI)		

However despite the varying terms used to name these interventions the key treatment components of these interventions have been very similar, as seen in Table 2.

Table 2: Key components of treatment in non-pharmacological intervention studies. Adapted from Chamberlain et al, 2014.

Components	Vertigan et al 2006	Ryan et al 2009	Ryan et al 2010	Patel et al 2011	Vertigan et al 2016	Chamberlain Mitchell et al 2017
Education on chronic cough and identifying cough triggers	√	√	√	√	√	√
Cough suppression techniques	√	√	√	√	√	√
Breathing exercises	√	√	√	√	√	√
Vocal/Laryngeal hygiene and hydration strategies	√	√	√	√	√	√
Counselling	√	√	√	√	√	√
Throat massage				√		

All of the six key studies that have explored non-pharmacological interventions for refractory chronic cough have included: education, cough control/suppression techniques, breathing exercises, vocal hygiene and hydration strategies and counselling (Chamberlain et al 2014, Chamberlain Mitchell et al 2017). In the literature these components have been summarised as four key components of non-pharmacological interventions as the breathing exercises are included within the cough suppression component. Table 3 explains these four key components in more detail.

Table 3. Non-pharmacological interventions' treatment components

Non-pharmacological component	Technique
Education	Educate patients on cough: the anatomy of the reflex, that the cough reflex is both an involuntary and voluntary reflex, what chronic cough is and current understanding of how it can develop including the role of repeated irritation of vocal folds through repeated coughing as well as cough reflex hypersensitivity. Explain the negative effects of repeated coughing and throat clearing. Explain the aims and benefits of non-pharmacological interventions.
Vocal/Laryngeal hygiene and hydration	Increase frequency and volume of water and non-caffeinated drinks (at least 2 litres a day) Reduce caffeine and alcohol intake Promote nasal breathing – nasal douching may be recommended to help nasal breathing if patient is congested. Nasal steam inhalation may be recommended to help humidification of the vocal tract.
Cough control/suppression techniques	Teach patients to identify their cough triggers so they are able to use cough suppression or distraction techniques at the first sign or sensation of the need or urge to cough. Cough suppression/distraction techniques include: forced/dry swallow, sipping water, chewing gum or sucking non-medicated sweets or lollies over a short period of time. Breathing pattern re-education promoting a relaxed abdominal breathing pattern technique whilst inhaling through the nose. May include PVFM release breathing, Cough Control Breathing and purse lip breathing

Psycho-educational counselling	Behaviour modification: to try to reduce over-awareness of the need to cough and facilitate individuals' internalisation of control over their cough. Motivate patients, reiterate the techniques and the aims of therapy Stress and anxiety management

Modified from Chamberlain Mitchell et al 2017

Education is a very important component of non-pharmacological interventions. Patients need to understand what the cough reflex is, how chronic cough can develop and the negative effects of repeated coughing, as well as that the cough reflex is both an involuntary and voluntary reflex. Emphasising these aspects will help patients understand the aims of non-pharmacological interventions. Non-pharmacological interventions aim to increase patients' control of their cough, giving them techniques to help them suppress their cough, which over time is hoped will help to reduce their cough reflex sensitivity as well as reduce localised irritation that initiates the cough (Chamberlain Mitchell et al 2017, Vertigan et al 2006, Vertigan and Gibson 2016).

The vocal/laryngeal hygiene and hydration techniques aim to improve vocal tract hydration as dryness of the vocal tract is a prevalent throat symptom in refractory chronic cough, which can increase laryngeal irritation and initiate cough. All of the six key studies for non-pharmacological interventions have included advice on increasing hydration and promoting nasal breathing. However, only Chamberlain Mitchell et al (2017) included the option of recommending nasal douching for patients who struggle to breathe nasally. The cough control/suppression techniques aim to equip the patients with strategies to use when they first feel an urge to cough

to try to suppress their cough early. Although all the studies have included cough control/suppression techniques whether they advised chewing gum or sucking medicated lollies or sweets has varied between the studies (Chamberlain Mitchell et al 2017, Vertigan et al 2006, Vertigan and Gibson 2016).

All the studies in Table 2 have included breathing exercises, however the exercises included as well as the terminology for the exercises varies between the studies. Limited detail is provided in Vertigan et al (2006), Ryan et al (2009) and Ryan et al (2010) studies regarding the breathing exercises apart from that relaxed throat breathing was used for patients with inspiratory dyspnoea. Vertigan and Gibson (2016) provided more detail on the breathing exercises included and describes the techniques as PVFM release breathing and Cough Control Breathing. PVFM release breathing is a technique that encourages patients to practice a relaxed abdominal breathing pattern technique, working to reduce upper body, shoulder and neck tension, inhaling through pursed lips, via their nose or via a sniff and exhaling through pursed lips with their mouth relaxed (Vertigan and Gibson 2016). Cough Control Breathing is a technique taught to patients to be used to interrupt/prevent their cough when they feel an urge to cough, they are required to breathe in through their nose and blow out quickly through pursed lips, the technique can be altered so participants can also sniff prior to breathing out through tight lips (Vertigan and Gibson 2016). Patel et al (2011) and Chamberlain Mitchell et al (2017) included similar breathing exercises but with some variation and different terminology for the exercises. The breathing exercises were labelled as breathing pattern re-education during which patients were encouraged to breathe through their nose and out through their mouth focusing on a relaxed abdominal breathing pattern technique, however they were not required to breath out through pursed lips or inhale via a sniff

(Patel et al 2011; Chamberlain Mitchell et al 2017). In addition both studies included a technique called pursed lip breathing for which participants were instructed to inhale via their nose and exhale gently through pursed lips, so the technique was less forceful than cough control breathing described above (Patel et al 2011; Chamberlain Mitchell et al 2017). Again these variations in techniques used highlight the differences used by Speech and Language Therapists and Physiotherapists.

The psychoeducational counselling component of the treatment aims to motivate patients to continue to engage in the treatment and techniques taught, reinforcing to patients that techniques take time to master for them to notice a difference (Chamberlain Mitchell et al 2017, Vertigan and Gibson 2016).

For our PSALTI study we also included stress and anxiety management within this component which explains to patients the effect of over awareness of sensations and the need to try and change their thoughts about managing their cough to help facilitate individuals' internalisation of control over their cough and reinforce to patients that their cough isn't a phenomenon outside of their control (Chamberlain Mitchell et al 2017).

Patel et al (2011) is the only study that has included throat massage as an additional treatment for patients with muscle tension from excessive coughing.

Eligibility of patients for non-pharmacological interventions for refractory cough

Within the six key non-pharmacological interventional studies these treatments have only been studied in patients with refractory chronic cough, who have undergone

extensive medical assessment and treatment for the main causes of cough, as seen in Figure 1.

		Vertigan et al 2006	Ryan et al 2009	Ryan et al 2010	Patel et al 2011	Vertigan et al 2016	Chamberlain Mitchell et al 2017
Inclusion criteria	Age>18 years old	√	√	√	√	√	√
	Age <80 years old		√	√		√	
	Treatment and assessment for asthma, postnasal drip syndrome, gastro-oesophageal reflux and withdrawal of ACE-I	√	√	√	√	√	√
	Hypertonic saline challenge	√	√				
	Induced sputum analysis	√	√				
	Non-smokers		√	√	√	√	√
	Ex-smokers< 10 pack year		√	√			
	Normal chest X-ray	√	√	√	√		√
	No respiratory disease	√	√	√		√	√
	No cardiac disease		√	√			
	Minimal sputum production (<10ml per day)						√
	PVFM confirmed by laryngoscopy		√				
Exclusion Criteria	Upper respiratory tract infection	√			√	√	√
	Untreated allergy	√					
	Eosinophilic bronchitis	√					
	Neurological voice disorder	√					
	Significant change in cough severity in past 4 weeks				√		
	Abnormal lung function tests				√		
	Vocal cord nodules or malignancy						√
	Active aspiration						√
	Cough productive of mucopurulent sputum					√	
	Pregnancy/ breastfeeding					√	
	Significant psychiatric or neurologic disorder					√	
	Previous Speech pathology treatment for cough in past 12 months					√	

ACE-I angiotensin converting enzyme inhibitors, PVFM paradoxical vocal fold movement

Figure 1 Inclusion and Exclusion criteria for non-pharmacological interventions

Despite the participants groups within non-pharmacological interventions initially appearing similar as all have described the populations included as refractory chronic cough patients. Figure 1 highlights the variation in the population groups. A standardised inclusion/exclusion criteria for these interventions has yet to be developed.

2. Treatment effects of non-pharmacological interventions

Non-pharmacological interventions have consistently been found to improve cough related quality of life (Table 4). The PSALTI study has been the only study to explore cough related quality of life in a Randomised Control Trial (RCT) comparing a non-pharmacological intervention with a control intervention of healthy lifestyle advice and education and found the improvement in quality of life to be significantly greater in the intervention group. The mean improvement in cough related quality of life was also greater than the minimally clinically important difference for Leicester Cough Questionnaire (LCQ).

In the studies that have investigated the effects of non-pharmacological interventions on cough frequency, all have found the interventions to significantly reduce cough frequency. Chamberlain Mitchell et al (2017) study was the only study to investigate cough frequency in a RCT compared to a control intervention and found a significant reduction in the intervention group compared to the control.

Less conclusive and consistent results have been found for cough severity (measured with symptom scales) and cough reflex sensitivity. Vertigan et al (2006) found a significantly greater improvement in patient rated cough severity score in the intervention group than the control group. Vertigan et al (2016) also found a significant reduction in cough severity for both the speech pathology and placebo

medication group and the speech pathology and Pregablin group but there was no control group (received no non-pharmacological intervention) for comparison. In Chamberlain Mitchell et al's (2017) study a significant within group reduction in cough severity VAS was only found in the PSALTI group but there was no significant between group difference. This may be due to an insufficient sample size for the VAS outcome measure in the Chamberlain Mitchell et al (2017) study.

Ryan et al (2009), Ryan et al (2010) and Vertigan et al (2016) all found significant improvements in cough reflex sensitivity for their non-pharmacological interventions however again these were not replicated in Chamberlain Mitchell et al (2017) which was the only study that included a control group (received no non-pharmacological intervention) for comparison. The reasons for these different results found between studies is not clear. It may be due to the Ryan and Vertigan studies being conducted over a longer time period however Ryan et al (2010) found significant improvements in capsaicin cough challenge even after 1 session of therapy. A potential problem with C2 and C5 capsaicin cough reflex sensitivity testing in patients, who have received non-pharmacological interventions for their cough, is that during their treatment they have been taught cough suppression techniques and repeatedly encouraged by their therapist to actively suppress their cough. This may then affect the results of C2, C5 capsaicin cough testing as although instructed to ''allow yourself to cough if you need to, and as much as you need to', some participants may not and there may be variation in how strictly individual patients follow this instruction especially having received cough suppression techniques. Instead previously used measures of cough suppression may be more appropriate such as Hutchings et al (1993) and Cho et al (2017) whereby the participants received increasing dosages of capsaicin and were instructed to try to not cough. This would

give an idea of the patients' ability to suppress their cough which may be a more appropriate outcome measure as it would give greater insight into the effectiveness of their cough suppression ability post intervention.

Vertigan et al (2016) is an interesting study as it is the only study that has explored speech pathology treatment in combination with antitussive medication. In this trial both groups received speech pathology treatment, but one group received Pregablin in addition. It was hoped that combining speech pathology with Pregablin would result in better cough outcome improvements as well sustained improvement after the discontinuation of Pregablin. For cough related quality of life and cough severity a greater improvement was found for speech pathology and Pregablin then speech pathology and placebo medication.

Table 4. Treatment effects of non-pharmacological interventions

	Study Design and participant numbers	Frequency and length of treatment sessions	Outcome measures*	Results	Limitations
Vertigan et al 2006	RCT n=87 participants(43 in treatment group and 44 in placebo group)	4 x 30minute sessions over a 2 month period with a Speech and Language Therapist. SPEICH-C received intervention as described earlier. Placebo group received healthy lifestyle advice.	Patient rated subjective symptom severity scores on a 5 point Likert scale covering cough, respiratory, voice and upper airway symptoms Limitations of symptoms on everyday activity were also rated on a 5 point Likert scale Treating speech pathologist rated post participant's outcome as successful, partially successful or unsuccessful.	Significant improvement in cough scores for Rx group (95% CI 3 to 4.9; p<0.001) and placebo groups (95% CI 0.3 to2.2; p<0.001). However improvement was significantly greater in Rx group (95% CI 1.3 to 4.0; p<0.001) Significant improvements in total symptom score (95% CI 9.0 to 16.1; p<0.001) and limitation to daily activities (95% CI 0.4 to 1.0; p<0.001) in treatment group only. 88% reported as having a successful outcome in the treatment group compared to only 14% in the control treatment.	No Objective outcome measures used
Ryan et al 2009	Uncontrolled trial n=14 received speech pathology treatment	4 weekly sessions with a Speech and Language Therapist	Cough-related quality of life: LCQ at baseline and at follow up. Generic Quality of life measure: SF-36 at baseline and at follow up. Cough reflex sensitivity: Capsaicin cough challenge performed at baseline.	Cough related quality of life significantly improved (LCQ P=0.001) post treatment. Cough reflex sensitivity significantly improvement (C5 p=0.008) post treatment. No information given in article regarding sf-36 scores or changes.	Uncontrolled trial Small sample size

Ryan et al 2010	Uncontrolled trial n=17	Up to 4 treatment sessions with a Speech and Language Therapist (baseline visit, 4 treatment visits and post treatment visit were over 14 to 18 week period)	Cough Frequency: ~1 hour Leicester Cough monitor performed at each session and at follow up Cough reflex sensitivity: Capsaicin cough challenge performed at each session and follow up. Cough-related quality of life: LCQ at baseline and follow up.	Significant decrease in cough frequency post treatment (p=0.009). Significance of difference was only reached after treatment 3 and continued to decrease at treatment session 4 and post treatment session. Cough reflex sensitivity significantly decreased post treatment (mean ± SD log C5, 1.65 ± 0.88, p<0.0001). Cough threshold and urge to cough also significantly improved post treatment (p=0.001; p=0.01 respectively). Cough reflex sensitivity significantly reduced after each session. Significant improvement in cough-related quality of life (p=0.002) post treatment.	Uncontrolled trial Small sample size Cough monitor only used for 1 hour which is less than the validated time for Leicester cough monitor (Lee et al, 2012)
Patel et al 2011	Uncontrolled trial n=23	Up to 3 weekly treatment sessions with a Physiotherapist. Post treatment assessment completed 2 months after treatment	Cough-related quality of life: LCQ measured at baseline and 2 month follow up. Cough frequency was measured with a 7 point Likert scale.	Cough related quality of life significantly improved (mean difference 2.7, 95% confidence interval of difference -4.1, -1.3; p<0.001). In all the three domains of the LCQ, physical (p=0.001), psychological (p<0.001) and social (p<0.04) Significant reduction in reported cough frequency (Mean difference 1.1; 95% confidence interval of difference 0.5-1.8; p=0.002).	Uncontrolled trial Small sample size No objective outcome measures
Vertigan et al 2016	RCT n= 40 (20 participants received	All participants received 5 speech pathology treatment sessions over a 14	Cough-related quality of life as measured by Leicester cough questionnaire Cough severity measured by	Cough related quality of life improved significantly in both groups (geometric mean difference (SD) SP+Preg 6.6 (4.5) vs SP+Plac 3.3 (2.3). Significantly greater improvement in SP+Preg (	Lack of long term follow up.

	speech pathology and placebo, 20 participants received speech pathology and Pregablin)	week period The speech pathology and Pregablin group in addition received Pregablin (max dose 300mg/day) for 14 weeks The speech pathology and placebo group received placebo tablet for 14 weeks Follow up outcome measures completed 4 weeks post treatment	cough visual analogue scale (VAS) 24 hour cough frequency measured by Leicester cough Monitor Cough reflex sensitivity measured by Capsaicin cough challenge (c5 end point) Urge to cough measured by urge to cough scale at end of cough reflex sensitivity testing (c5)	mean difference (SD) 3.5 (1.2), p=0.024) Cough severity decreased in both groups (geometric mean difference (SD) SP+Preg 38.8 (23.4) vs SP+Plac 14.5 (20.1). Significantly greater improvement in SP+Preg (mean difference (SD) 25.1 (7.1), p=0.02). Cough frequency significantly decreased in both groups (geometric mean difference (SD) SP+Preg 11.2 (18.3) vs SP+Plac 8.9 (18.1). No significant difference between the groups (p=0.671). Cough reflex sensitivity significantly decreased in both groups (mean difference (SD) SP+Preg 136.3 (230.6) vs SP+Plac 89.3 (176.8). No significant difference between the groups (p=0.362). Urge to cough at C5 significantly decreased in both groups (mean difference (SD) SP+Preg 2.0 (2.8) vs SP+Plac 3.1 (3.0). No significant difference between the groups (p=0.949).	
Chamberlain Mitchell et al 2017	Multi-centred RCT n=66 completed treatment at 4 weeks (26 completed PSALTI treatment, 37	4 weekly treatment sessions with either a Physiotherapist or with a Speech and Language Therapist PSALTI group received intervention as described earlier	Primary outcome: Cough-related quality of life as measured by Leicester cough questionnaire Cough severity in past two weeks measured by cough visual analogue scale (VAS) Objective 24 hour cough frequency measured by	Cough related quality of life improved mean 1.53 (95% CI 0.21 to 2.85) units more in PSALTI group then control, p=0.024. However both groups did improve significantly (mean difference (95%CI) PSALTI 3.40 (2.26 to 4.55) p<0.001, control 1.66 (0.78 to 2.54) p<0.001). No between group difference was observed between centres/profession delivering the intervention. LCQ improvements were sustained at 3 month follow up. Cough severity decreased significantly in both groups (mean difference (95%CI) PSALTI -21.18 (-	Attrition rate however intention to treat analysis was performed in mitigation.

	completed control intervention.	Control group include healthy lifestyle and education	Leicester cough Monitor Cough reflex sensitivity measured by Capsaicin cough challenge (C2 and C5 end point) Urge to cough measured by urge to cough scale at end of cough reflex sensitivity testing (c5) Generic Quality of life measure: SF-36 at baseline and at follow up.	29.83 to -12.53) p<0.001, control -11.84 (-20.11 to -3.57) p=0.007) However there was no significant between group difference (p=0.084). Cough frequency improved by a mean 41% (95%CI 36% to 95%) more in the PSALTI group compared to the control group, p=0.030. Within group cough frequency only significantly improved in the PSALTI group (fold change (95%CI) 0.55 (0.33 to 0.75), p=0.002. Cough frequency improvements were sustained at 3 month follow up. Cough reflex sensitivity only significantly decreased for C5 in the PSALTI group (fold change (95%CI) 1.24 (1.02 to 1.50), p=0.035. However there were no significant difference between the groups for C2 or C5 (p=0.575 and p=0.512 respectively). No significant between or within group changes were found for SF-36.	

RCT randomised control trial, NCS non-comparative study, C2 concentration of capsaicin at which the participant coughs 2 or more times, C5 concentration of capsaicin at which the participant coughs 5 or more times, PSALTI – Physiotherapy, Speech and Language Therapy Intervention, SPEICH-C – Speech Pathology evaluation and intervention for chronic cough.

*Only cough related outcome measures have been included. Modified from Chamberlain et al (2014)

3. Mechanisms of action of non-pharmacological interventions

There is still quite a debate as to the potential mechanisms of action of non-pharmacological interventions for refractory chronic cough. Patients with refractory chronic cough have been shown to have increased peripheral and central sensitisation of the cough reflex as well as decreased descending inhibitory control of their cough (Ando et al 2016, McGovern et al 2017, Mazzone and Undem 2016). As a result of the increased peripheral and central sensitisation of the cough reflex refractory chronic cough patients suffer with hypertussia; increased sensitivity to tussive triggers, such as chilli and smoke; as well as allotussia, an increased sensitivity to non-tussive triggers, such as talking, laughing and changes in air temperature (Vertigan and Gibson., 2011). Studies have shown that patients with refractory chronic cough have lower thresholds before both a sensory response, "the urge to cough" is reported, and motor response in the form of a cough is triggered (Mazzone et al 2011).

Ryan et al (2009) and Ryan et al (2010) found non-pharmacological interventions increase the concentration of capsaicin people with refractory chronic cough are able to tolerate before reporting an urge to cough. Chamberlain Mitchell et al (2015) found similar findings in a subset of our study population for whom urge to cough was explored. Therefore non-pharmacological interventions may help to re-adjust/normalise the hypersensitive cough reflex observed in refractory chronic cough to at least effect the sensory response to the reflex. Whether non-pharmacological interventions affect the cough reflex motor response is less conclusive at present as this has not be replicated in all studies that have investigated this and needs to be explored further, potentially including a change in the current outcomes we use to measure this as previously discussed.

The higher brain centers are involved in the cough reflex as well and is where the airway sensory nerve inputs are processed and either a cough is generated or suppressed (Mazzone and Undem, 2016). Non-pharmacological interventions for refractory chronic cough may improve patients' cough by improving descending inhibitory control, affecting cognitive behavior and therefore stimulating higher brain center's processing of the sensory nerve inputs from the cough reflex. During the education and psycho-educational counselling components of non-pharmacological interventions it is hoped patients' understanding of their condition improves, as well as their understanding of the aims of the interventions, the harmful effects of repeated coughing and the need for them to actively and repeatedly work to suppress their cough. Chamberlain Mitchell et al (2017) also included anxiety management and discussion of over awareness of sensations which may have also helped with this.

Another potential mechanism of action for these non-pharmacological interventions is treating conditions associated with refractory chronic cough. Up to 40% of refractory chronic cough patients have been found to have PVFM now termed Inducible Laryngeal Obstruction (ILO), (Vertigan et al 2007, Vertigan and Gibson 2011). Some of the techniques used within the non-pharmacological interventions are also used to treat ILO. In addition Chamberlain Mitchell et al (2017) found that 51% of our refractory chronic cough patients have dysfunctional breathing which again is treated using the breathing exercises included as part of PSALTI study (Chamberlain Mitchell et al 2016a). Interestingly when Chamberlain Mitchell et al (2016a) explored whether there was a difference in the response to PSALTI treatment for those who had breathing dysfunction or not, significant improvements in cough related quality of life, cough frequency and cough severity were only

observed in those who had breathing dysfunction prior to treatment which was corrected post treatment compared to those who had no change in their breathing pattern. However this was observed in a small subset of patients so needs further exploration. Figure 2 shows a schematic of the above.

Figure 2a. Normal Cough reflex

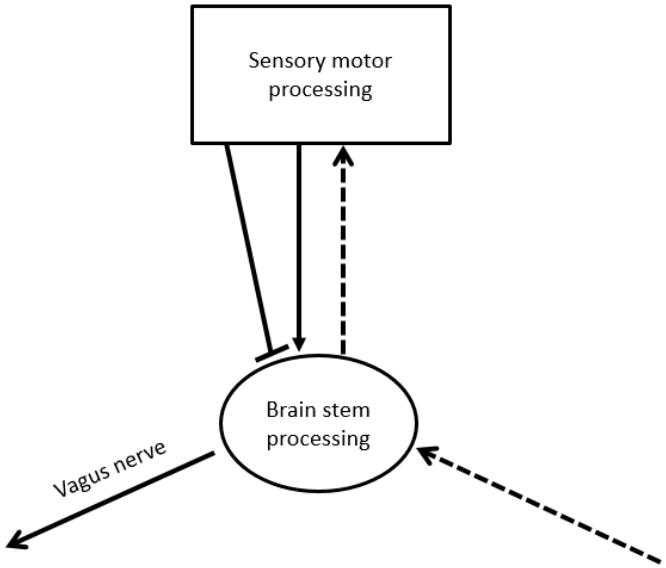

Figure 2b. Refractory chronic Cough reflex

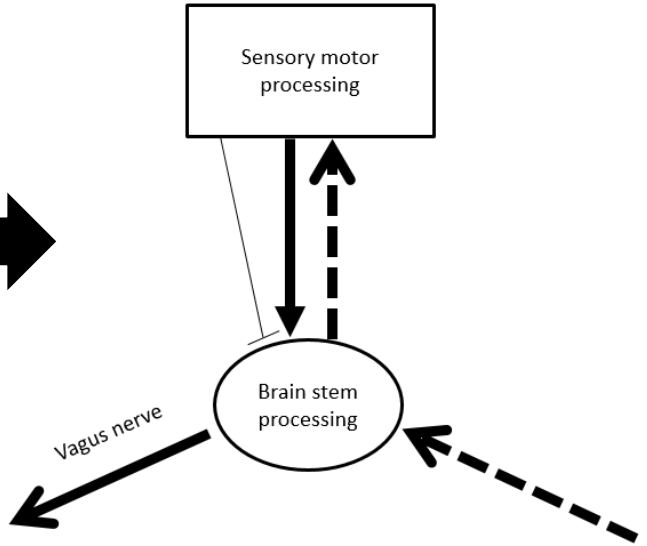

Figure 2c. Non-pharmacological intervention mechanisms

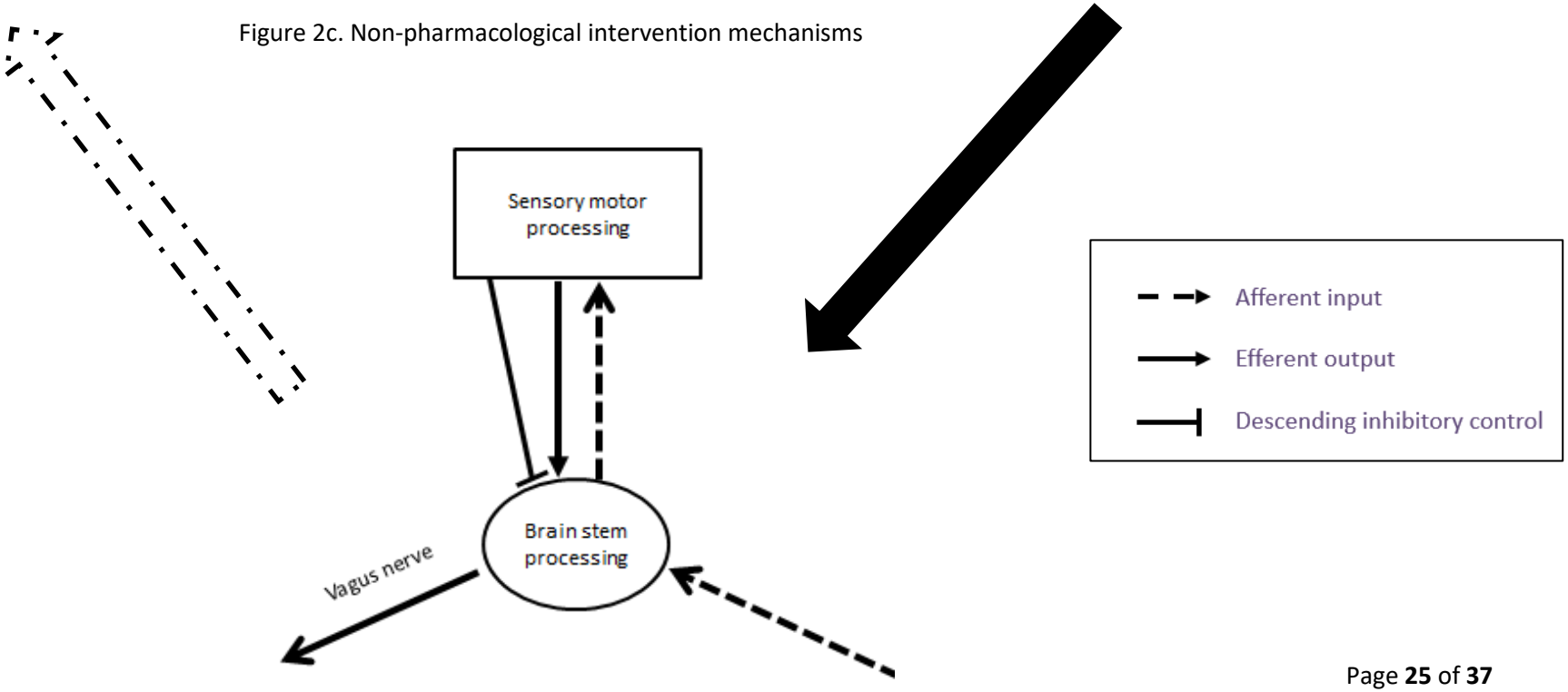

Figure 2a shows a schematic of a normal cough reflex network. Figure 2b shows the changes that occur in the normal cough reflex network in refractory chronic cough. In refractory chronic cough there is an increase in sensory afferent input due to peripheral sensitisation, which leads to increased central sensitisation which in combination with a decreased descending inhibitory control causes an increase in efferent output (cough). It is possible that in certain cases of refractory chronic cough the sensory afferent input to the brain stem may reduce but the plastic changes (increased central sensitisation) in the central nervous system are sustained. Figure 2c shows the changes that are hypothesised to occur to the refractory chronic cough reflex as a result of nonpharmacological interventions. It is hypothesised that elements of the nonpharmacological interventions such as avoiding cough triggers initially and vocal hygiene and hydration as well as breathing techniques which may help to treat underlying conditions (such as breathing pattern disorder or inducible laryngeal obstruction) may reduce the sensory afferent input due to a reduction in irritation and stimulation of the cough reflex; helping to reduce the peripheral and central sensitisation. The education, psychoeducational counselling and cough suppression technique components of the non-pharmacological interventions are hypothesised to help increase the descending inhibitory control. Thus resulting in a decrease in efferent output (cough). Overtime it is hoped and in an ideal world the cough reflex may return to normal.

4. The future of non-pharmacological interventions

This review has highlighted that non-pharmacological interventions for patients with refractory chronic cough have shown promising results, however it has also highlighted a number of areas within the research of these interventions that need to be improved and further developed in the future.

Patient selection

This review has highlighted that in the six key studies of non-pharmacological interventions, there is large variation in the inclusion/exclusion criteria of these studies. This then makes it difficult when translating these research findings into clinical practice and trying to develop a clinical care pathway for refractory chronic cough patients. In addition it reinforces the heterogeneity of refractory chronic cough. Future research studies need to explore within the patient group of refractory chronic cough who is most appropriate for non-pharmacological interventions. Does there need to be an upper age limit of participants as seen in some studies. Age is unlikely to have an effect on treatment but other factors such as ability to follow instructions are more relevant and has not been studied. Does smoking history affect the outcome of treatment, is there a reason to exclude ex-smoker. As well as establishing what investigations and screening processes need to be completed prior to referring patients to non-pharmacological treatment for their cough, there is variation in screening tests in the literature and clinically. Laryngoscopy has not always been performed prior to non-pharmacological interventions for refractory chronic cough in the research or clinical setting and there is ongoing debate about this. Laryngoscopy/ Ear Nose and Throat (ENT) review may be important to rule out other medical reasons for the refractory chronic cough e.g. GERD, nasal disease or

voice disorder. Laryngoscopy with provocation challenge is also required to diagnose ILO and some clinicians argue by giving visual feedback after laryngoscopy to patients it helps to educate patients about their ILO and/ or cough hypersensitivity diagnosis. Some clinicians argue that the diagnosis of ILO is needed so that additional specific breathing techniques can be given alongside treatment for the chronic cough. However having said this ILO was not screened for and diagnosed in all the six key studies included in this review and in those that did include screening for ILO the non-pharmacological interventions delivered were the same as in studies that did not screen for ILO and beneficial results were still found. ~~More research is therefore needed to resolve these complex issues of the benefits of ILO diagnosis in chronic cough patients and whether there is a need for differences in the management of these patients or not.~~

None of the key studies included in this review screened for evidence of breathing dysfunction. However Chamberlain Mitchell et al (2017) found that there may be differences in responses to non-pharmacological interventions in those with refractory chronic cough and breathing dysfunction than in those without breathing dysfunction however this needs further exploration. In the future if these additional screens are felt to be required refractory chronic cough treatment delivery may become more multidisciplinary and similar to breathlessness management clinics where patients are initially assessed by a multi-disciplinary team. The difficulty with assessing breathing pattern technique is that there currently is no gold standard measure (Boulding et al, 2016). Clinically respiratory Physiotherapists assess breathing pattern based on observation as part of their assessment. In the research literature there have been studies exploring different devices to measure breathing

pattern which are either remote from the patient or attached to the patient such as structured light pleythsmography, respiratory inductance pleythsmography and respiratory movement measurement instrument (RRIM) (Niérat et al, 2017; Tehrany et al, 2018; Olsén et al 2010). Others have also explored easier to use, less costly and technologically dependent measures of breathing pattern such as the Brompton breathing pattern assessment tool (BPAT) which provides an interval scale and structured format to the traditional respiratory Physiotherapy assessment (Todd et al 2018); or Manual assessment respiratory motion (MARM) which requires the therapist to judge the thoracic and abdominal movement occurring through palpation (Courtney et al 2008). Therefore more research is needed to explore these techniques of measuring breathing pattern to establish a gold standard that can be used in future studies.

As this review highlights these non-pharmacological interventions have only been investigated in people with refractory chronic cough, however are there other patient groups who share similar cough presentations that these interventions could be effective for, such as idiopathic pulmonary fibrosis and sarcoidosis. There is now some emerging preliminary evidence that this may be the case (Mohammed et al, 2018).

Standardisation of terminology

Table 1 highlighted the variation in terminology used to label these non-pharmacological interventions. Currently this is a hindrance to the promotion of these interventions as at first they may appear more heterogenous in the components of treatment then they are. In the future it would be an improvement if a standardised

non-disciplinary term was used to label these non-pharmacological interventions such as cough control therapy. This would enable future research and clinical studies to be labelled using the same term, it is also an easy to understand name for patients and explains exactly what the treatment aims to achieve. In addition a non-disciplinary label helps both physiotherapists and speech and language therapists evidence their involvement with these patients as we know there is variation as to the profession delivering these interventions between different trusts in the UK and between different countries.

Standardisation of treatments

Despite the similarity of treatment components across the six key studies included in this review. There is variation in some of the techniques used in the studies such as throat massage, breathing exercises and which cough suppression techniques are included. The effects of these differences have not been explored. The greatest variation between the treatments in the six key studies is the frequency and duration. This again makes it hard for translation of these treatments in clinical practice. Variation in the studies included in this review in number of treatments has been between 3 to 4 sessions, received from weekly to over a 14 to 18 week period. There is also variation in delivery of non-pharmacological interventions in clinical practice.

Timing of non-pharmacological interventions

Currently clinically and in the literature non-pharmacological interventions are used as a last resort or when all other pharmacological interventions have been exhausted. Not only does this review highlight the beneficial effects of non-

pharmacological interventions for chronic cough but these interventions have been found to be cheaper than some antitussive medication. The cost of PSALTI was £323.17 per patient compared to £471.42 for gabapentin (1800 mg dose per day and 3 out-patient clinic visits for initiation and supervision), an antitussive used for PSALTI (4 outpatient sessions), (Birring et al 2017). In addition none of the studies included in this review have reported any adverse events from treatment. Therefore the delivery of non-pharmacological intervention earlier in the patients' treatments needs to be explored. This may provide even better outcomes for the treatments as it would reduce the cough duration prior to treatment.

Future research also needs to explore the effects of combining cough control therapies with pharmacological interventions as Vertigan et al (2016) did with Pregablin. There are a number of emerging pharmacological treatments for cough such as inhibitors of the P2X3 sensory nerve ion channel which be interesting to explore whether non-pharmacological interventions enhanced their effectiveness.

Outcome measures used

Table 4 highlights the variation that has been used in the cough outcome measures used in non-pharmacological studies for refractory chronic cough. However in the more recent studies there has been an increase in the objective cough outcome measures used and this needs to continue. As well as continuing to use validated objective cough outcome measures in these studies, the outcome measures used may need to be reviewed. As previously discussed capsaicin cough challenge with C2 and C5 may not be the most appropriate measure to use to measure change in cough reflex sensitivity in this patient group having received cough control therapy. Instead previously used measures of cough suppression may be more appropriate

such as Hutchings et al (1993) and Cho et al (2017) whereby the participant receives increasing dosages of capsaicin and are instructed to try to not cough.

Treatment delivery

In other respiratory conditions such as asthma there has been research into the delivery of face to face treatments such as breathing retraining and comparing it to the intervention being delivered in a DVD with a printed booklet and similar improvements have been found in both groups compared to standard care (Bruton et al 2018). This as yet has not been replicated for non-pharmacological interventions for people with refractory chronic cough however interestingly Kapela et al (2019)) compared the use of pre-recorded supplemental videos of non-pharmacological techniques with face to face treatment to face to face treatment alone and found no additional significant improvement in either group.

Others have started to explore the use of group classes instead of individual classes and found group classes to be beneficial however as yet these have only been presented as abstracts at conferences and there have been no comparative studies of classes versus individual treatment (Selby et al, 2017; Selby et al 2018). Interestingly Chamberlain Mitchell et al (2016b) found that when they asked their participants who had completed the PSALTI intervention at 3 month follow up which was 1 to 1 sessions in their trial whether they would have preferred group sessions rather than 1 to 1 79% of those asked reported no.

Further studies are needed to explore treatment delivery of non-pharmacological interventions.

5. Conclusion

Non-pharmacological interventions for refractory chronic cough have consistently been shown to improve quality of life and reduce cough frequency. There is a need for standardisation of these therapies and a change in terminology to cough control therapy may also help and to encourage a multi-disciplinary approach to therapy. Future studies need to explore patient selection for these treatments, standardisation of treatments included, timings of these interventions as well as outcome measures used.

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