PHYSIOTHERAPY, SPEECH AND LANGUAGE THERAPY INTERVENTION FOR PATIENTS WITH REFRACTORY CHRONIC COUGH: A MULTI-CENTRE RANDOMISED CONTROL TRIAL.

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What is the key question?

Is Physiotherapy, speech and language therapy intervention (PSALTI) effective for patients with refractory chronic cough?

What is the bottom line?

PSALTI significantly reduced objective cough frequency and significantly improved quality of life when compared to control intervention.

Why read on?

This study is the first multi-centred randomised controlled trial that demonstrates improvements with Physiotherapy and Speech and Language Therapy Intervention (PSALTI) compared to control intervention using objective outcome measures.

Twitter Feed (140 characters including spaces): Physiotherapy, speech and language therapy (PSALTI) reduces cough and improves quality of life in refractory chronic cough patients

AUTHORS' CONTRIBUTIONS

Conception/design of work: RG, SSB, KL, HB; Study Recruitment: SCM, SSB, SP, SF, JH, KC; Assessments/Treatment delivering in the trial: SCM, LC, JE, SL; Data analysis: SCM, AD, AP, SSB; Drafting manuscript: SCM, RG, SSB; Revised manuscript: All.

ABSTRACT

Background Physiotherapy and Speech and Language Therapy are emerging non-pharmacological treatments for refractory chronic cough. We aimed to investigate the efficacy of a Physiotherapy, Speech and Language Therapy Intervention (PSALTI) to improve health related quality of life (HRQoL) and to reduce cough frequency in patients with refractory chronic cough.

Methods In this multi-centre randomised controlled trial, patients with refractory chronic cough were randomised to four weekly 1:1 sessions of either: PSALTI consisting of education, laryngeal hygiene and hydration, cough suppression techniques, breathing exercises and psycho-educational counselling or control intervention consisting of healthy lifestyle advice. We assessed the change in health related quality of life at week 4 with the Leicester Cough Questionnaire (LCQ). Secondary efficacy outcomes included 24-hour objective cough frequency (Leicester Cough Monitor) and cough reflex sensitivity. The primary analysis used an analysis of covariance adjusted for baseline measurements with the intention-to-treat population. This study was registered at UK Clinical Research Network (UKCRN ID 10678)

Findings Between December 2011, and April 2014, we randomly assigned 75 patients who underwent baseline assessment (34 PSALTI and 41 control). In the observed case analysis, HRQoL (LCQ) improved on average by 1·5 (95%CI: 0·21 to 2·85) points more in PSALTI group than with control (p=0·024). Cough frequency improved by 41% (95%CI: 36% to 95%) in PSALTI group relative to control (p=0·030). The improvements within the PSALTI group were sustained up to three months. There was no significant difference between groups in the concentration of capsaicin causing 5 or more coughs.

Interpretation Greater improvements in HRQoL and cough frequency were observed with PSALTI intervention. Our findings support the use of PSALTI for patients with refractory chronic cough.

INTRODUCTION

Chronic cough, defined as a cough lasting more than eight weeks, [1] is a prevalent disorder in both the community, [2] and secondary care sectors, accounting for up to 20% of respiratory out-patient clinic referrals. [1, 3] The most common causes of cough in a non-smoking patient with a normal chest radiograph and spirometry are asthma, gastro-oesophageal reflux disease, and rhinitis (upper airway cough syndrome). [1, 4, 5] For a significant number of patients, the cough may remain unexplained or refractory to treatment despite extensive investigation and therapeutic trials. [6] Cough is associated with significant physical and psychological morbidity as well as impaired quality of life. [7-9] There are few effective antitussive therapies for refractory chronic cough. [10, 11] Recent studies suggest a potential role for gabapentin, pregabalin, amitriptyline, morphine and P2X3 receptor inhibitors but they are all associated with significant side effects. [12-16]

Non-pharmacological therapies for refractory chronic cough have shown promising results in a few studies and no significant adverse effects. [17] Non-pharmacological therapies are generally delivered by physiotherapists or speech and language therapists and key components include: education, cough suppression techniques including breathing exercises, vocal hygiene and hydration and psycho-educational counselling. [15, 17-23] Vertigan et al, [19] conducted the only randomised controlled trial of a non-pharmacological intervention for refractory chronic cough and found significantly greater improvements in symptoms of cough for speech pathology management compared to control (general healthy lifestyle advice). The benefits of speech pathology management on objectively measured cough frequency, cough reflex sensitivity and health related quality of life (HRQoL) have not been assessed in a controlled clinical trial, limiting the generalisability of the findings. The minimal clinically important difference of the cough symptom score used in this study has not

been defined. Furthermore, the longer term effect of therapy is not known. [17] A recent study by Patel et al [20] investigated cough-suppression physiotherapy for refractory chronic cough in 23 participants and found a significant improvement in cough related quality of life but this study also did not include a control intervention.

This study therefore aimed to assess the effect of an intervention utilising both physiotherapy and speech and language therapy techniques (Physiotherapy, Speech and Language Therapy Intervention, PSALTI) on HRQoL, objective cough frequency, cough reflex sensitivity and cough severity using a randomised controlled design.

METHODS

A multi-centre, single blinded randomised controlled trial was conducted across three hospitals in the UK (King's College Hospital NHS Foundation Trust, Lancashire Teaching Hospitals NHS Foundation Trust and Northumbria Healthcare NHS Foundation Trust). Two further sites, Royal Brompton & Harefield NHS Foundation Trust and Guy's and St Thomas' NHS Foundation Trust) were recruitment only sites and patients were referred to King's College Hospital to receive the intervention. The study was undertaken between December 2011 and April 2014.

Participants and randomisation

Eligible patients were identified as adults with chronic cough (defined as duration greater than 2 months), with normal chest x-ray, minimal sputum production (less than 10ml sputum a day) and who had negative investigations and/or failed treatment trials for asthma, gastroesophageal reflux and, rhinitis as per British Thoracic Society guidelines. [1] Patients were excluded if they: had an upper respiratory tract infection in past four weeks, were taking

angiotensin converting inhibitor (ACE-I) medication, were current smokers, or had a known respiratory disease (such as lung cancer, pneumonia, pulmonary fibrosis, sarcoidosis, pleural effusion, bronchiectasis). Patients were also excluded if they had vocal cord nodules, malignancy, or evidence of active aspiration.

Once participants had given written consent and completed baseline assessments, they were registered into the randomisation service provided by the King's Clinical Trials Unit, King's College London. This prevented foreknowledge of treatment assignment for the study researchers. Group allocation was concealed from participants until they had completed the study and all post-intervention assessments. Patients were block randomised, stratified by age (above and below 50 years old) and gender.

Control intervention

Participants attended weekly sessions and received one to one standardised healthy lifestyle advice from a health care professional (nurse, physiotherapist or speech and language therapist) over four weeks. The control intervention was based on that used in the trial reported by Vertigan et al. [19] The initial session covered general advice on exercise and physical activity, second session dietary and nutritional advice, third session stress management and fourth session relaxation. The material covered in each session was based on healthy lifestyle advised by the United Kingdom Department of Health and National Health Service. [24-26] The sessions were standardised for all sites by using the same written prompts for therapists and educational information. Face to face training was provided for all site therapists who delivered the healthy lifestyle intervention. The duration of all trial sessions was 45 minutes except the initial session which was one hour.

PSALTI intervention

Participants attended weekly sessions, and received one to one treatment from a health care professional (physiotherapist or speech and language therapist) over four weeks. Session durations were the same as for the control group. The intervention was based on previous speech pathology management and cough-suppression physiotherapy studies for refractory chronic cough reported by Vertigan et al and Patel et al respectively (Table 1). [19, 20] The first session focused on educating participants about chronic cough, introduction to laryngeal hygiene and hydration techniques and cough suppression/distraction. The second and third sessions covered cough suppression techniques in more detail including breathing exercises (table 1). Nasal douching or steam inhalations were recommended to patients with nasal congestion. In the third session psycho-educational counselling techniques were covered with the aid of an information booklet developed jointly by the lead researcher and clinical psychologist at the primary research site. The fourth session consisted of reinforcing all aspects of PSALTI. All components of PSALTI were delivered, however the focus and emphasis on individual techniques varied for each participant, determined by the treating therapist. Airway clearance techniques were included in the PSALTI treatment if the participant's sputum production was close to the upper limit of sputum exclusion criteria. The standardisation of treatment between different hospitals was increased by the use of written treatment plans and educational material. All therapists delivering the treatment were trained in PSALTI prior to commencing the study by the main study researcher.

Table 1: PSALTI components

PSALTI component	Technique
Education	Educate patients on the cough reflex, chronic cough and cough reflex hypersensitivity. Explain the negative effects of repeated coughing Educate patients on voluntary control of cough
Laryngeal hygiene and hydration	Increase frequency and volume of water and non-caffeinated drinks Reduce caffeine and alcohol intake Promote nasal breathing
Cough control	Teach patients to identify their cough triggers Teach patients to use cough suppression or distraction techniques at the first sign or sensation of the need or urge to cough. These cough suppression/distraction techniques include: forced swallow, sipping water and sucking sweets. Teach patients breathing exercises: breathing pattern re-education promoting relaxed abdominal breathing pattern technique; pursed lip breathing to use to control cough.
Psycho-educational counselling	Motivate patients, reiterate the techniques and the aims of therapy Behaviour modification: to try to reduce over-awareness of the need to cough Stress and anxiety management

Modified from Chamberlain et al [18]

Primary Efficacy Endpoint

HRQoL was assessed with the Leicester Cough Questionnaire (LCQ) at week four, the primary endpoint. [8] The LCQ is a validated 19-item cough-specific health-related quality of life questionnaire. Overall scores range from three to twenty-one with a higher score indicating a better HRQoL. The minimal important difference for this outcome is 1·3. [27] Participants independently completed questionnaires at baseline, at four weeks (after 4th

213 treatment session) and at three month follow up. Questionnaires were then placed in sealed
214 envelopes to avoid influencing the treating therapist.
215
216 **Secondary Efficacy Endpoints**
217 Secondary endpoints were assessed at baseline, 4 weeks and 3 months. Objective cough
218 frequency was assessed with the Leicester Cough Monitor (LCM) a validated, objective,
219 automated and ambulatory cough monitoring device. [28] The LCM consists of a MP3
220 recording device (Phillips 662 MP3 recorder, UK), external microphone and automated cough
221 detection software. The LCM has been used in previous clinical trials of gabapentin and
222 erythromycin. [12, 29] Participants wore the device for 24 hours at baseline, at four weeks
223 (after fourth treatment session) and three month follow up and were instructed to resume their
224 normal daily activities during this time period. The number of coughs per hour ($CF_{perhour}$)
225 were recorded.
226
227 Capsaicin cough challenge was assessed in a subset of the participants (Kings College
228 Hospital Foundation Trust and Northumbria Healthcare NHS Foundation Trust) to measure
229 participants' cough reflex sensitivity at baseline and at four weeks (after fourth treatment
230 session). Doubling concentrations of capsaicin solution ranging from 0 (saline), 0·49µm to
231 1000 µm were administered as per European Respiratory Society guidelines. [30] A dose-
232 response capsaicin cough testing method was used. [30] The nebuliser output was set to
233 0·01mL·breath-^{1}. The test was discontinued when five or more coughs were induced (C5). In
234 addition, the dose that induced two or more coughs (C2) was recorded.
235
236 Cough severity in the past 2 weeks was assessed by a visual analogue scale (0-100mm) as per
237 American College of Chest Physicians guidelines. [31] The vocal performance questionnaire

(VPQ), [32] a 12 item tool was used to assess patients' perceived impact on their voice, since a high prevalence of voice disorders in patients with chronic cough has been reported [33]. A score >12 indicates dysphonia. [32] General health and mood was assessed by Short-Form 36 (SF36) and Hospital Anxiety and Depression scale (HADs). [34, 35] HADs is 14-item questionnaire, a score for either subscale ≥eight indicates mild symptoms, ≥11 moderate and ≥15 severe. SF-36 generates two summary scores, physical component summary score (PCS) and mental component summary score (MCS); both range from zero to hundred and a higher score indicates better self-reported health. [36]

Ethics and trial registration

All protocols were approved by the London-Chelsea National Research Ethics Service (NRES) Committee (11-LO-0504). All participants provided written informed consent, and the study was registered with the UK Clinical Research Network (UKCRN ID 10678) and ISRCTN (ISRCTN 73039760).

Role of funding source

The funding bodies had no role in study design, collection, analysis and interpretation of data, in the writing of the report or in the decision to submit for publication.

STATISTICAL ANALYSIS AND SAMPLE SIZE

Power calculations for the primary outcome (LCQ score) were performed based on estimates from a previous study, [37] reporting a mean LCQ score in patients with chronic cough of 14·03 (SD: 3·87). [37] Group sample sizes of 33 in each group achieve 80% power with a significance level of 5% to detect a LCQ change of 2·7 (seen in our pilot study). Allowing for a 25% drop out we aimed to recruit 88 patients in total.

For each of the variables analysed, univariate descriptive statistics were summarised by randomised group to provide an overview of the data. Summary measures for the baseline characteristics of each group were presented as mean and standard deviation for continuous 'approximate' normally distributed variables, medians and interquartile ranges for non-normally distributed variables, and frequencies and percentages for categorical variables. Univariate analyses were performed to compare study group using appropriate statistical tests according to the type and the distribution of the data: independent t-test or Mann-Whitney for continuous variable. Cough frequency and capsaicin data were log transformed prior to analysis.

Primary efficacy analysis, change in LCQ at week 4, was based on analysis of covariance (ANCOVA) adjusted for the baseline LCQ measurements. The ANCOVA analysis was repeated to adjust for centre and speciality of treating therapist. The analysis used data from the intention-to-treat basis (ITT) population, which included all randomised participants who had received at least one treatment session. In this analysis only observed data were included and no imputation was used for missing data. We also performed an analysis on a per-protocol population (PP) which included patients who completed end of treatment (week 4) cough assessments and who did not deviate from the protocol (established before unmasking). Sensitivity analyses were performed for missing data according to different predefined populations using ANCOVA, with multiple imputations (Online appendix - Table 1). [38] Similar sensitivity analyses were also performed for objective log-transformed cough frequency endpoints (Online appendix - Table 2).

The secondary efficacy analysis used data from the intention-to-treat population. In these analyses ANCOVA was used adjusting for baseline variables and only observed data were included without imputation for missing data. A p-value of less than 0·05 was considered statistically significant. All analyses were made using STATA version 12 software (StataCorp LP, College Station, TX).

RESULTS

Participants

Seventy-five participants were randomised and had baseline assessments. One additional patient was randomised to the PSALTI group but did not attend baseline assessments. Four participants did not receive any treatment (PSALTI group (n=3): myocardial infarction prior to treatment, unable to travel to hospital and insufficient time for the study; control group (n=1): undisclosed illness prior to start of treatment). The intention to treat population for LCQ primary analysis consisted of 71 participants (Figure 1 and Online Appendix - Table 1). A total of four participants in the control group and eight participants in the PSALTI group did not receive or complete all treatments for reasons stated in Figure 1. Forty-nine participants completed three month follow up. The consort study flow is described in Figure 1. The baseline characteristics of the randomised participants are described in Table 2. The groups were well-matched with the exception of SF36 Physical Component Summary Scores (higher in the control group).

Table 2. Baseline demographic and clinical characteristics of randomised study participants.

Characteristic	Control (n=41)	PSALTI (n=34)	p value
Age (years)	56 (48 to 67)	61 (53 to 67)	0.239
Female, n (%)	26 (63)	25 (71)	0.459
Cough duration (months)	48 (24 to 126)	60 (30 to 126)	0.279
FEV1 (L, observed), mean(SD)	2.7 (0.9)	2.6 (0.7)	0.517
FEV1/FVC (%), mean(SD)	76 (8.2)	76 (5.0)	0.686
LCQ, mean(SD)	11.9 (3.5)	10.4 (3.6)	0.073
Cough Severity VAS	65 (40 to 83)	63 (49 to 75)	0.652
SF-36 PCS,	47.1 (41.7 to 53.6)	41.1 (35.6 to 49.1)	0.033*
SF-36 MCS	47.7 (38.3 to 54.9)	49.9 (40.5 to 57.0)	0.763
HADs –Anxiety	7 (3 to 10)	7 (4 to 10)	0.785
HADs – Depression	4 (1 to 8)	5 (2 to 6)	0.620
VPQ	17 (11 to 22)	21 (13 to 27)	0.158
$CF_{perhour}$ #	17.0 (0.4)	17.0 (0.4)	0.983
C2 (µm) #	4.01(0.69)	4.74 0.62)	0.677
C5 (µm) #	9.33 (0.56)	8.25 (0.51)	0.708

Data presented as median (IQR) unless otherwise stated.

*p<0.05, # Geometric mean (log SD)

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; LCQ, Leicester cough questionnaire; VAS, visual analogue scale; SF-36, short-form 36 questionnaire; PCS, Physical component score; MCS, Mental component score; HADs, hospital anxiety and depression scale; VPQ, vocal performance questionnaire; $CF_{perhour,}$ cough frequency per hour over a 24 hour period; C2, capsaicin cough challenge – concentration that resulted in two or more coughs; C5, capsaicin cough challenge – concentration that resulted in five or more coughs.

HRQoL - Primary Efficacy Endpoint

There was an improvement in the mean total LCQ score at four weeks with PSALTI; baseline 10.4 vs. four-weeks 14.4, mean difference 3.4, p<0.001. This improvement was larger than that in the control group; baseline mean 11.9 vs. 13.4 at four-weeks, mean difference 1.66, p<0.001 (Online Appendix – Table 3). Total LCQ score at four weeks improved by a mean 1·53 (95% CI 0·21 to 2·85) units more in the PSALTI group than in control (p=0·024), table 3. When adjusted for centre and speciality of therapist, the LCQ score at four weeks improved

by a mean of 1.53 (95% CI 0.20 to 2.86), p=0.024. The improvement in LCQ with PSALTI was consistent in the per-protocol and sensitivity analyses (Online Appendix - Table 1). The LCQ improvement was sustained from week 4 to 3 months for both groups but there was no significant difference between groups at 3 months (table 3). The LCQ scores and within group differences are presented in online supplement Table 3 and Table 4 respectively. Primary outcome LCQ data (baseline or week 4) was missing in 6.7% of participants. There were no adverse or serious adverse events reported for both interventions.

Table 3. Primary and Secondary efficacy endpoint analysis: Change between PSALTI and control groups at baseline to four weeks and four weeks to three month follow up

	Between group difference Baseline to four weeks		Between group difference Four weeks to three month follow up	
	Mean Difference (95% CI)	**p value**	**Mean Difference (95% CI)**	**p value**
LCQ Total	1.53 (0.21 to 2.85)	0.024	0.01 (-1.62 to 1.64)	0.994
$CF_{perhour}$ (fold change)	0.59 (0.36 to 0.94)	0.030	1.01 (0.55 to 1.86)	0.966
VAS severity	-9.72 (-20.80 to 1.36)	0.084	1.6 (-15.48 to 18.74)	0.848
SF36 PCS	0.56 (-2.52 to 3.64)	0.717	0.48 (-3.27 to 3.37)	0.977
SF36 MCS	0.81 (-3.10 to 4.72)	0.680	0.72 (-3.06 to 4.51)	0.703
VPQ	3.90 (-0.33 to 8.12)	0.070	-0.20 (-3.43 to 3.03)	0.901
HADS – Anxiety	-0.42 (-1.96 to 1.13)	0.590	0.88 (-0.57 to 2.34)	0.225
HADS – Depression	-0.44 (-1.69 to 0.81)	0.486	-0.18 (-1.36 to 0.99)	0.753
C2 (fold change)	1.11 (0.76 to 1.61)	0.575	NA	NA
C5 (fold change)	1.11 (0.80 to 1.54)	0.512	NA	NA

Between group differences were calculated using ANCOVA adjusted for baseline values.
Positive change in LCQ, SF36 PCS, SF36 MCS, and C5 indicates improvement in symptoms. Negative change in VAS, VPQ, HADS indicates improvement in symptom.
LCQ, Leicester cough questionnaire; $CF_{perhour}$, cough frequency per hour over a 24 hour period; VAS, visual analogue scale; SF-36, short-form 36 questionnaire; PCS, Physical component score; MCS, Mental component score; VPQ, vocal performance questionnaire HADS, hospital anxiety and depression scale; C2, concentration of capsaicin that caused ≥2 coughs, C5,concentration of capsaicin that caused ≥5 coughs, NA – not assessed at this time point.
*$p<0.05$

Objective Cough Frequency

There was a greater reduction in cough frequency after four weeks of treatment in the PSALTI group; geometric mean (SD) 17·0 (2·4) to 9·0 (3·3) coughs per hour (p=0·002) versus 17·0 (2·3) to 16·0 (2·2) coughs per hour after control (p=0·205), table 4. The control-adjusted improvement in cough frequency per hour in PSALTI was 41% (95% CI [36-95%], p=0·030, ANCOVA) at 4 weeks in the primary ITT analysis, (table 3). This improvement was also sustained at three months (Figure 2). The reduction in cough frequency with PSALTI was consistent in per-protocol and sensitivity analyses (Online Appendix - Table 2).

Other questionnaire data

There were no significant between group differences for change (week four minus baseline) in VPQ, depression, anxiety or SF36 (Table 3). There was a greater reduction in VAS cough severity in the PSALTI group compared to control (p=0·084, Table 3). There was a reduction in cough severity VAS within groups between week 4 to baseline; control p=0·007, PSALTI p<0·001 (Table 4).

Table 4: Primary and Second Efficacy Endpoints : within group change

	Change from baseline to four weeks				Change from four weeks to three month follow up			
	PSALTI	**P**	**Control**	**P**	**PSALTI**	**P**	**Control**	**P**
	Mean Difference (95% CI)		**Mean Difference (95% CI)**		**Mean Difference (95% CI)**		**Mean Difference (95% CI)**	
LCQ Total mean	3.40 (2.26 to 4.55)	0.001*	1.66 (0.78 to 2.54)	<0.001*	-0.17 (-1.49 to 1.15)	0.794	0.27 (-0.82 to 1.35)	0.616
$CF_{perhour}$ (fold change)	0.55 (0.33 to 0.75)	0.002	0.82 (0.60 to 1.22)	0.2053	1.26 (0.84 to 1.90)	0.236	0.91 (0.59 to 1.39)	0.655
VAS severity	-21.18 (-29.83 to -12.53)	< 0.001*	-11.84 (-20.11 to -3.57)	0.007*	9.74 (-3.60 to 23.08)	0.143	0.79 (-10.73 to 12.31)	0.888
C2 (fold change)	1.28 (0.96 to 1.71)	0.089	1.06 (0.81 to 1.36)	0.666	NA	NA	NA	NA
C5 (fold change)	1.24 (1.02 to 1.50)	0.035*	1.08 (0.87 to 1.36)	0.469	NA	NA	NA	NA
SF36 PCS	1.62 (-0.96 to 4.21)	0.208	0.50 (-1.30 to 2.31)	0.574	0.54 (-1.82 to 2.89)	0.639	0.76 (-1.66 to 3.18)	0.522
SF36 MCS	0.53 (-2.69 to 3.75)	0.736	-0.26 (-2.92 to 2.40)	0.843	1.09 (-1.91 to 4.09)	0.456	0.49 (-2.35 to 3.32)	0.727
VPQ	4.04 (0.12 to 7.97)	0.044*	0.73 (-1.94 to 3.39)	0.582	-1.63 (-4.17 to 0.91)	0.193	-0.57 (-3.29 to 2.15)	0.666
HADS – Anxiety	-1.27 (-2.51 to -0.032)	0.045*	-0.90 (-1.96 to 0.17)	0.095	-0.11 (-1.16 to 0.94)	0.826	0.95 (-0.22 to 2.11)	0.104
HADS – Depression	-0.68 (-1.57 to 0.21)	0.126	-0.21 (-1.11 to 0.69)	0.641	0.06 (-1.42 to 1.53)	0.937	0.05 (-0.66 to 0.76)	0.878

Positive change in LCQ, SF36 PCS, SF36 MCS indicates improvement in symptoms. Negative change in VAS, VPQ and HADS indicates improvement in symptoms. LCQ, Leicester cough questionnaire; $CF_{perhour}$, cough frequency per hour over a 24 hour period; C2, capsaicin cough challenge concentration that resulted in two or more coughs - C5, capsaicin cough challenge – concentration that resulted in five or more coughs; VAS, visual analogue scale; SF-36, short-form 36 questionnaire; PCS, Physical component score; SF-36 MCS, Mental component score; VPQ, vocal performance questionnaire HADS, hospital anxiety and depression scale. NA – not assesses at this timepoint

Cough reflex sensitivity

Sixty participants (80% of ITT group) underwent capsaicin challenge. No significant differences between groups were observed for C2 (p=0·575) or C5 (p=0·512) (Table 3). There was a within group reduction in C5 with PSALTI (p=0.035) but not with control (p=0.469), table 4.

DISCUSSION

This study evaluated the efficacy of a physiotherapy and speech and language therapy intervention for patients with refractory chronic cough in a randomised controlled trial. There was a clinically and statistically significant improvement in health-related quality of life with PSALTI compared to control intervention. This was supported by a significant reduction in cough frequency measured objectively. The improvement in health-related quality of life was sustained at a three-month follow-up visit. There was no significant change in cough reflex sensitivity between groups.

Our findings represent an advance from those reported in an earlier study by Vertigan et al. [19] Our study is the first multi-centre trial reported in chronic cough and has the potential to provide the evidence base for access to therapy. Vertigan et al reported a statistically significant reduction in cough symptoms scores but did not include HRQoL or objective assessment with cough frequency monitors. [19] In contrast we assessed HRQoL, objective cough frequency, cough severity VAS and cough reflex sensitivity. We were also able to demonstrate both a clinically and statistically significant improvement in our primary endpoint because the minimally important difference (MID) of the LCQ has been defined.

[27] We have shown that the benefits of PSALTI are sustained after discontinuation of therapy, in contrast to Vertigan et al who did not report follow up data for their participants. [19] One of the strengths of our study was the involvement of multiple centres, the use of standardised treatment protocols and the inclusion of both physiotherapists and speech and language therapists delivering the treatment.

HRQoL, as assessed with the Leicester Cough Questionnaire (LCQ) was selected as the primary outcome measure because it is perhaps the most important outcome measure from the patient's perspective. [7, 8, 39] The HRQoL of our patients was severely impaired, affecting physical, psychological and social domains, comparable to that reported in previous studies of refractory chronic cough. [29, 40] The improvement of HRQoL with PSALTI was large, LCQ 3·4 units. This improvement was greater than the MID of the LCQ, 1·3 units, [27] and that reported for Gabapentin therapy in patients with refractory chronic cough (LCQ improvement 2·5 units). [12] The improvement with PSALTI was smaller when adjusted for the change in the control group (LCQ score control group 1.66 units). HRQoL also improved with control intervention, but to a lesser extent than PSALTI. The aim of the control intervention was to provide patients with an equivalent quantity of clinical attention to the PSALTI intervention. This is additional to what most patients with refractory chronic cough would receive as usual care since physiotherapy and speech and language therapy services are not widely available for refractory chronic cough. It is possible that the control intervention had an anti-tussive effect and that the difference between PSALTI and control group may have been larger if compared to usual care (no active treatment). The control intervention was intended to be non-specific but it is possible that some of its components such as stress/anxiety and lifestyle management may have had a positive benefit, particularly on the central sensitisation pathways that regulate cough.

The improvement in cough frequency assessed objectively with 24-hour cough monitoring supports the improvement in HRQoL with PSALTI occurred because of an actual reduction in coughing. Cough frequency outcome measures are increasingly being used as end-points in clinical trials to validate the efficacy of anti-tussive therapy. [41, 42] The Leicester Cough Monitor (LCM) has been reported to be a valid method of counting coughs objectively. [28, 43] An advantage of cough monitors over subjective measures is that they are not susceptible to the patient's or clinician's perception of cough severity. PSALTI intervention was associated with an additional 41% reduction in cough frequency, which can be considered a large change and is comparable to that observed with pharmacotherapy such as the P2X3 inhibitor AF-219. [13] The minimal clinically important difference for cough monitor frequency in chronic cough has not been studied. The reduction of cough frequency was comparable to the minimal important difference reported for acute cough. [42] We also assessed cough severity subjectively with VAS. There was a reduction in cough severity with PSALTI compared to control intervention, and the difference approached statistical significance. The reason for the discrepancy in effect size between HRQoL and VAS findings is not clear. A larger study would be needed to confirm whether PSALTI impacts cough assessed with VAS. Despite their widespread use, VAS have been poorly validated in comparison to HRQoL questionnaires and cough monitoring tools, as acknowledged by the American College of Chest Physicians' Cough Guidelines. [31] There were no between group differences in reported voice related problems. We chose the VPQ, a patient reported questionnaire, to assess voice since it has been reported to have excellent internal consistency, repeatability and responsiveness. [44] There are alternative questionnaires available to assess voice such as the voice handicap index and voice symptom scale [45, 46]. A comparison of

these scales by Webb et al concluded all were valid and reliable questionnaires for assessing patient's perceived voice dysfunction [44].

There were no adverse events associated with PSALTI, specifically no episodes of pulmonary infections. Patients with significant sputum production were excluded because of the potential risk of pulmonary infections associated with cough suppression. Longer-term data with PSALTI is required to fully assess its safety. The mechanism by which PSALTI reduces cough is not clear, nor which component of PSALTI is most effective. PSALTI was not associated with a reduction in cough reflex sensitivity assessed with capsaicin when compared to the change in control group. There was however a significant within group reduction in C5 in the PSALTI group which is consistent with studies by Ryan et al and Vertigan et al, who reported a reduction in cough reflex sensitivity with speech pathology management. [15, 21] The Ryan et al and Vertigan et al studies however did not have a control group (no speech pathology management) for comparison. It is possible that we did not find a between group difference in cough reflex sensivity due to the small sample size of participants that underwent capsaicin cough challenge testing; further studies are needed to investigate this. [15, 21]

We investigated PSALTI in patients with refractory chronic cough. Our patients had a troublesome chronic cough despite numerous investigations and trials of therapy. A refractory chronic cough may also be referred to as idiopathic, difficult to treat, unexplained, sensory neuropathic and vagal neuropathy cough although some differences exist between groups. [47] PSALTI type treatments have only been studied in patients with refractory chronic cough once they have undergone extensive investigations and/or trials of therapy. The role of PSALTI type treatments earlier in the management of such patients has not been explored and

needs to be studied. The efficacy of PSALTI is also unknown in other difficult to treat coughs, such as that associated with lung cancer, idiopathic pulmonary fibrosis and sarcoidosis and this should be investigated. Further studies are needed to explore the optimum frequency and duration of PSALTI and other non-pharmacological treatments.

There were some limitations to our study. The study was single-blinded. It was not possible to blind the treating therapist to the intervention the patient received. The possibility that unconscious bias could have been conveyed to participants during the course of intervention cannot therefore be discounted. Double blinding is not possible in studies of behavioural intervention. The potential bias was minimised by asking patients to complete their primary outcome measures independently from the treating therapist and participants remained blinded until after completion of the final post-intervention outcome measures. Capsaicin cough reflex tests in some patients were performed by the treating therapist but it is unlikely this influenced the outcome since our findings suggest no change with intervention when adjusted for control. Some components of PSALTI were tailored to the individual, according to clinical need. This may be considered both a limitation and a strength since it reduces the uniformity of intervention delivered but reflects real life clinical practice addressing the needs of an individual. Our study did not meet the intended sample size. This may have affected the power of our analyses and undermined the robustness of the results. Despite this, there was a clinically and statistically significant improvement in the primary outcome measure with PSALTI. Thirty-six (22%) of subjects screened were uncontactable or declined to participate. The clinical characteristics of participants recruited were however consistent with previously reported studies of refractory chronic cough [29]. A significant number of patients were lost to follow up for the 3 month visit where secondary endpoints were assessed. This was largely from the control group. There was no significant difference in LCQ between groups at 3

months; this could be a consequence of a smaller sample size or a reduction in the long term benefit of PSALTI following cessation of therapy. The long term benefits of PSALTI needs to be confirmed in larger studies. It is possible that some of the benefit of PSALTI may have been a consequence of intense supervision. The control intervention was however identical in frequency and duration of visits.

In conclusion, PSALTI is an effective therapy for patients with refractory chronic cough. It is associated with a significant improvement in health-related quality of life, and cough frequency compared to control. The optimal components of PSALTI and number of sessions of therapy need to be determined in future studies. The effectiveness of PSALTI used earlier in the treatment of chronic cough and other patient groups with difficult-to-treat cough, should be evaluated. There is also a need for improved access to physiotherapy and speech and language therapy services for patients with refractory chronic cough.

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FIGURE LEGENDS

Figure 1. Trial CONSORT flow diagram

Figure 2. Change in objective cough frequency in PSALTI and control groups

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