Prospective study of efficacy of sham CPAP vs. straight CPAP on cough intensity in patients with chronic cough.

NCT03172130

Document Date: 4/1/2019

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Protocol Summary

IRB Approval Date of Current Version:	4/1/2019
University of Utah IRB #:	IRB_00062049
Sponsor:	PULMONARY
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Internal Staff and Sub-Investigators:	**Site Name** / **Staff Names** University of Utah: Krishna Sundar, Robert Paine, Cheryl Pirozzi, Heather Howe, Sanjeev Raman

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Background and Introduction

Chronic cough patients are treated for the etiologies of gastroesophageal reflux disease (GERD), cough variant asthma (CVA), upper airway cough syndrome (UACS) formerly called postnasal drip syndrome with varying benefit (4). Despite prolonged therapies with agents directed at GERD, UACS and CVA, these patients continue to experince persisting cough that is termed as idiopathic cough or unexplained cough. Studies have shown that cough can be unexplained or idiopathic in upto 42% of patients (5).

Obstructive sleep apnea (OSA) is a highly prevalent condition in the general population (6). A large retrospective study performed at Utah Valley Pulmonary Clinic identified a 44% prevalence of OSA in chronic cough population. 93% of patients treated with CPAP showed improvement in cough (2). Besides this study, a number of case reports have identified OSA as a perpetuating cause for chronic cough (7-8). Based on this, a number of mechanistic pathways by which OSA can lead to or perpetuate chronic cough have been identified (3).

Despite above reports, no study has conclusively shown that CPAP therapy alone provides improvement in cough relief as patients with treated for chronic cough are often rendered multiple different therapies for GERD, CVA and UACS. Additionally no study till date has used a placebo arm to demonstrate improvement in cough intensity measurements with CPAP therapy.

The current study purports aims to establish a definitive relationship using a CPAP vs. sham CPAP arm to assess changes in subjective and objective cough measures in chronic cough patients with comorbid OSA. Sham CPAP therapy is a well-established modality to demonstrate efficacy of OSA therapy on a multitude of disease states, ranging from metabolic syndrome to reflux disease (9).

Purpose and Objectives

AIM: To demonstrate that therapy of conomitant OSA in patients with chronic cough improves or resolves chronic cough.

Chronic cough is an important clinical problem in primary care and subspecialty practice (1). Besides the distress experienced by patients with chronic cough, signficant healthcare resources are expended to understand the role of gastroesophageal reflux, asthma and post-nasal drip in understanding their contribution to cough.

Recently obstructive sleep apnea (OSA) has found to be common in patients with chronic cough (2). More importantly, treatment of OSA with continuous positive airway pressure (CPAP) led to improvement in cough in chronic cough patients (2). Mechanisms by which

OSA therapy with CPAP can improve cough includes beneficial effects on reflux and airway inflammation (3).

Our study purports to definitively establish that CPAP therapy for treatment of OSA in chronic cough patients improves cough. While these patients with chronic cough are not routinely screened and treated for OSA, our study aims to evaluate these chronic cough patients with screening questionnaires for OSA and if necessary with polysomnography and randomize them to either CPAP or sham CPAP for 6 weeks. During this 6 weeks patients will undergo assessments for cough using the following

- Validated cough questionnaires

- Objective cough monitoring using cough monitors provided by Dr Birring in UK

- Measures of airway inflammation using exhaled breath condensate.

Study Population

Age of Participants: 18-70

Sample Size:
At Utah: 58 subjects
All Centers:

Inclusion Criteria:
Patients will be recruited from outpatient pulmonary clinics that meet the following criteria:

1. Cough of more than 2 month duration
2. Age more than 18 years
3. Smoking < 5pk-years with history of tobacco use more than 10 years prior.
4. Evaluation and treatment by other providers for suspected GERD, UACS or CVA for at least 1 month
5. Normal chest radiography or CT scans (patients with upto 2 lung nodules less than 3 mm to be allowed if there is no history of malignancy elsewhere).
6. Normal spirometry with predicted DLCO more than 50% predicted. PFT criteria: No evidence of airflow limitation (FEV1/FVC >0.7) or significant chest restriction (FVC>70% predicted) with predicted DLCO more than 50% predicted.
7. STOP-BANG score of 3 or more requiring OSA evaluation

Exclusion Criteria:
Exclusion criteria

1. Pregnancy
2. Positive methacholine challenge test (if it is performed).

3. Prior history of asthma for which inhaled or systemic corticosteroids have been used. Patients with wheezing on auscultation will also be excluded.
4. Recent pneumonia (less than 6 months)
5. Congestive heart failure, acute or chronic renal disease, jaundice or decompensated chronic liver disease, pulmonary embolism, stroke or neurodegenerative disease, malignancy
6. Age more than 70 years

8. Use of supplemental oxygen or PAP therapy (if patients have been diagnosed with OSA in past but were non-compliant with PAP therapy, they will not be excluded)

7. Use of opiates, benzodiazepines (cough suppressant solutions containing codeine derivatives not excluded)
8. Alcoholism, drug dependence (including chewing tobacco) or illicit drug use
9. Prior Nissen fundoplication, esophageal or laryngeal surgery.
10. Craniofacial abnormalities that preclude CPAP placement.

Design

Prospective Clinical Research
Double Blind
Randomized

Use of a Sham CPAP machine

Study Procedures

Recruitment/Participant Identification Process:

Participants will be recruited from pulmonary clinics, ENT clinics, primary care clinics, sleep clinics within the University of Utah healthcare system. Patients will be consented at either Clinic 3, pulmonary clinic or at the University of Utah Sleep Center.

Posters with information about the study will be hung in the clinic workrooms where they can be seen by clinic personnel but not by patients.

Informed Consent:

Description of location(s) where consent will be obtained:

Clinic 3 (Pulmonary) at University of Utah Hospital Sleep-Wake Center, University of Utah

Description of the consent process(es), including the timing of consent:

Once patients meet study criteria based on results of STOP-BANG questionnaire and polysomnography, they will be eligible to be consented by the investigators.

Procedures:

Patients with chronic cough that meet criteria for study inclusion will undergo screening and evaluation for OSA. This will be part of routine care. OSA is an important clinical problem that needs to be treated for impact on cardiovascular, metabolic and behavioral outcomes. It is anticipated that patients will undergo the following procedures as a part of their initial evaluation for chronic cough and OSA that will be done as part of their standard care.

CLINICAL PROCEDURES:

We anticipate these will already be performed as part of **clinical evaluation prior to enrollment in the study (this is done as part of routine evaluation for chronic cough**).

- Chest radiography
- Pulmonary function testing (spirometry, single breath diffusion capacity measurement)
- Exhaled nitric oxide testing if available
- STOP-BANG screening questionnaire
- Full-night attended or unattended polysomnography if STOP-BANG questionnaire abnormal with clinical suspicion for sleep-disodered breathing.

STUDY PROCEDURES

- Consent Form
- Study Questionnaires:
- Leicester-cough questionnaire (LCQ) at baseline, 6 weeks, 12 weeks and at 24 weeks
- GERD-QoL questionnaire (GERD-QoL) at baseline and 6 weeks
- Sino-nasal outcome test (SNOT-20) at baseline and 6 weeks
- Asthma Life questionnaire (ALQ) at baseline and 6 weeks
- Laryngeal dysfunction scores (LDQ) at baseline and 6weeks
- Leicester cough monitoring for 24 hours at baseline , at 6 weeks and 12 weeks.
- Exhaled breath condensate at baseline, 6 weeks and 12 weeks.
- CPAP data download at 6 weeks, 12 week

Procedures performed for research purposes only:

Once individuals with chronic cough that meet inclusion criteria are found to have OSA o polysomnography, they will be given an option to enroll in the current study. These procedures will be done as part of the research study.

STUDY PROCEDURES

1. CONSENT FORM
2. STUDY QUESTIONNAIRES

- Leicester-cough questionnaire (LCQ) at baseline, 6 weeks, 12 weeks
- Cough VAS scale at baseline, 6 weeks and at 12 weeks
- GERD-QoL questionnaire (GERD-QoL) at baseline and at 6 weeks
- Sino-nasal outcome test (SNOT-20) at baseline and at 6 weeks
- Asthma life questionnaire at baseline and at 6 weeks

- Laryngeal dysfunction scores (LDQ) at baseline and at 6 weeks

3. Cough monitoring for 24 hours, at baseline and at 6 weeks and 12 weeks.
4. CPAP data download at 6 weeks, 12 weeks
5. Exhaled breath condensate at baseline, 6 weeks and 12 weeks.

Once patients are enrolled, they will be randomized to either straight CPAP or sham CPAP. Randomization will be done by study coordinator, Thi-Ly Downing and treating physicians (and investigators) will be blinded to whether the patient received straight CPAP or sham CPAP. Patients will be evaluated at 6 and 12 weeks after randomization as part of study. At 6 weeks, patients will be unblinded and placed back on straight CPAP. The pressure on straight CPAP will be determined according to the results of the polysomnography or they will be kept on 10cm of CPAP (adjustments to this may be made by the study coordinator, Thi-Ly Downing who is the CPAP coordinator for the Sleep Center). For sham CPAP, patients will be kept at 1-2cm of pressure as per sham CPAP recommendations and no adjustments to this will be made although there may be adjustments made in mask or interface used for the CPAP.

Statistical Methods, Data Analysis and Interpretation

PRIMARY END-POINT

1. Change in LCQ score in CPAP-treated patients vs. sham CPAP-treated patients. This will be compared between baseline LCQ score prior to initiation of CPAP or sham CPAP and compared to the LCQ score at 6 weeks.
2. Change in Leicester cough monitoring measured at baseline and at 6 weeks after CPAP or sham-CPAP therapy.
3. Change in measurements of exhaled breath condensate 8 isoprostane, IL-6, nitrite/nitrate, H2O2 and LTB4 at baseline and at 6 weeks.

SECONDARY END-POINTS

- Change in GERD-QoL scores, change in LDQ scores at 6 weeks
- Change in LCM at 12 weeks compared to 6 weeks in sham CPAP patients
- CPAP compliance at 6 weeks and 12 weeks.

STUDY PROTOCOL

Subjects with randomized to straight CPAP (either at 10cm or at a pressure determined during PSG) OR sham CPAP (1-2cm) following mask-fitting session during PSG or prior to that. After 6 weeks of therapy, patients will evaluated for above-mentioned end-points and study analyses will be done. Patients will be then placed on CPAP (as prescribed by PSG) and followed at 12 weeks again.

VISIT 1 SCREENING AND ADMINISTRATION OF QUESTIONNAIRES (LCQ, GERD-QoL, SNOT-20, LDQ, ALQ; MEASUREMENT OF EBC AND COUGH MONITORING FOR 24 HOURS)

PATIENTS WILL BE ON STRAIGHT CPAP FOR 6 WEEKS OR ON SHAM CPAP FOR 6 WEEKS.

VISIT 2 (+6wk) ADMINISTRATION OF LCQ, GERD-QoL, LDQ, SNOT-20, ALQ, SMART-CARD DATA DOWNLOAD, EBC, COUGH MONITORING FOR 24 HOURS

PATIENTS ON STRAIGHT CPAP FOR 6 WEEKS

VISIT 3 (+12 wk) ADMINISTRATION OF LCQ, SMART-CARD DATA DOWNLOAD, EBC

STATISTICAL ANALYSES

Each patient will serve as his or her control in terms of 6 weeks assessment of LCQ change following sham CPAP or straight CPAP therapy. Similar analyses are expected for GERD-QoL scores, Cough moniroting and EBC assessments.

NUMBER OF SUBJECTS TO BE ENROLLED

Based on the results of a recently concluded CPAP intervention study for chronic cough, mean change in LCQ with CPAP was + 4.1 (with 4.14 SD in baseline and followup LCQ scores)

Mean change in LCQ with placebo was 1.1 (Lancet 2012)

Expected difference between mean LCQs of two groups 3.0

- To achieve 80% difference to detect a significant difference of 0.05 level for a difference means of 2.58, 19 subjects per group needed assuming no attrition using a mixed models analysis of repeated measures data.

- Assuming 33% attrition rate due to CPAP noncompliance, 29 subjects per group needed.