STUDY TITLE: Cough Desensitization Therapy for Cough Hypersensitivity Syndrome

Clinicaltrials.gov identifier: NCT04256733

Document Date: 2/22/22

STUDY TITLE: Cough Desensitization Therapy for Cough Hypersensitivity Syndrome

Clinicaltrials.gov identifier: NCT04256733

Protocol:

Purpose: The purpose of this study is to investigate a modified behavioral treatment for chronic cough due to cough hypersensitivity syndrome (CHS). This type of CC is a non-productive cough that is due, in part, to over-expression of transient receptor potential vanilliod (TRPV) receptors in the airway epithelium[5-9], which contributes to a dry cough elicited by typically non-tussive stimuli (e.g., cold air, smells) or by low doses of tussive stimuli (e.g., smoke). Currently available treatment options are limited to neuromodulator medications (e.g., gabapentin, amytriptiline)[10-12] and behavioral cough suppression therapy (BCST)[13-16], neither of which is 100% effective. The primary component of BCST is teaching patients to suppress their cough in the presence of an urge-to-cough. Studies have confirmed a reduction in cough sensitivity (as tested with inhaled capsaicin) following 1-4 weeks of successful cough suppression[13,17,18]. However, patients with severe CHS are not able to suppress their cough in the presence of uncontrollable environmental stimuli and, hence, do not respond well to the therapy. **The purpose of this study is to determine the potential of treating CHS by implementing BCST while stimulating cough with progressive concentrations of inhaled diluted aerosolized capsaicin. The therapy is called cough desensitization therapy (CDT).** The advantage of using capsaicin as a cough stimulant in the therapy is that it can be diluted to any concentration, which allows us to control the strength of the cough stimulant. Current research suggests BCST works by reducing cough sensitivity via neuroplasticity, as a result of suppressing cough when an urge-to-cough exists. The theoretical basis for CDT is exactly the same except that aerosolized capsaicin affords control over the cough stimulant, so that an urge-to-cough, that is strong enough to be felt but weak enough to suppress, can easily be produced. We hypothesize this treatment will result in a reduction in cough-reflex sensitivity, improvement in cough-related quality of life, and reduction in cough frequency.

Study design: Single-blind, sham-controlled randomized control trial
Study population: Non-smoking males or females at least 18 years of age currently suffering from a non-productive cough that started at least 8 weeks ago, who meet the following inclusion/exclusion criteria:

1. have seen at least one physician for the cough;
2. have received medical treatment without success (i.e., refractory chronic cough);
3. have normal chest x-ray, pulmonary function testing, and laryngoscopy;
4. not diagnosed with a respiratory or pulmonary condition (e.g., asthma, COPD, emphysema, lung cancer, bronchitis);
5. not currently a smoker;
6. not taking any of the following medications within one month of enrollment: lisinopril/Prinivil/Zestril, captopril/Capoten, enalapril/Epaned/Asotec, ramipril/Altace, benazepril/Lotensin, fosinopril/Monopril, moexipril/Univasc, perindopril/Aceon, quinapril/Accupril, trandolapril/Mavik; and
7. willing to sign an informed consent form;

8. not pregnant and willing to take a pregnancy test before enrollment (if applicable).
9. Women who are of childbearing age, and have any potential of becoming pregnant, must agree to use contraception during the study.

Study duration: Six weeks per participant. 18 months to complete data collection.
Number participants planned: 20 (10 per group)
Study procedures: three phases

Phase I: Baseline Outcome Testing

Pulmonary function testing: Pulmonary function testing (PFT) will be completed using standard procedures. A minimum of two trials will be given to ensure reliability. Cough sensory testing will only proceed if PFT is normal.

Cough sensory testing: Standardized procedures that have been established and previously approved by the FDA (IND #69642 and #076866) will be used to determine participants' cough sensory threshold. All participants will complete spirometry testing before and after cough sensory testing. The following diluted capsaicin concentrations: .49, .98, 1.95, 3.9, 7.8, 15.6, 31.2, 62.5, 125, 250, 500, and 1000 μM will be made prior to testing under the direct supervision of Dr. Sarjubhai Patel. Participants will inhale single breaths of capsaicin aerosol through the DeVilbiss 646 nebulizer that is connected to a dosimeter (KoKo Digidoser). The single-dose method will be used during inhalation trials, with a delivery time of .6 second, which yields .002mL/inhalation. Table 1 shows the amounts of capsaicin per concentration that will be given per inhalation.. The initial concentration will be .49 μM followed by subsequent doubling doses. We will determine the capsaicin concentration that causes two coughs (C2) and five coughs (C5) within 15 seconds of capsaicin inhalation. Capsaicin trials will be discontinued once the C5 level is determined, or the 1000 μM dose is given, whichever comes first. We will also measure perceived urge-to-cough (UTC) following each inhalation of capsaicin on a scale from 0 (no UTC) to 10 (maximum UTC). This testing session will take approximately 30 minutes.

Table 1: Amount of capsaicin ingested per inhalation at each concentration.

Capsaicin [19]		**g Capsaicin Nebulized per inhalation**
0.49		2.980e-10 (.000298 μg)
0.98		5.970e-10
1.95		1.193e-9
3.9		2.386e-9
7.8		4.772e-9
15.6		9.544e-9
31.2		1.908e-8
62.5		3.817e-8
125		7.635e-8
250		1.527e-7
500		3.054e-7
625		3.817e-7

750		4.581e-7
1000		6.108e-7

Cough frequency testing: Participants will be asked to wear a small digital mp3 audio recording device for 24 consecutive hours[20]. The participant will simply clip the audio recorder to his/her belt or place the recorder in a pocket or fanny pack. A small microphone will be attached to the participant's shirt. The recordings will be analyzed by a software program to determine the exact frequency of coughs during the 24-hour period. The audio recordings will be deleted after they have been analyzed. The analysis is fully confidential and the recordings are deleted following analysis. Dr. Surrinder Birring, who conceptualized the assessment and created the computer program to analyze the recordings, named this method the Leicester Cough Monitor. The exact mp3 recorder (Sony ICD PX333 digital recorder) and microphone recommended by Dr. Surrinder Birring have been purchased for this use.

Cough-related quality of life (QOL) testing: The Leicester Cough Questionnaire (LCQ)[21] will be used to measure cough-related QOL.

Phase II: Treatment phase

Participants will attend treatment sessions 2 times per week for up to three weeks, with at least 3 days between each session. Each session will begin with PFT. Treatment will only proceed if PFT is normal. During treatment sessions participants will be exposed to aerosolized capsaicin in progressive doses while implementing cough suppression strategies. The first capsaicin dose will be one dose below each participant's C2 cough threshold dose. At least one minute will lapse between each capsaicin exposure and a sip of water will be allowed between each trial. The capsaicin concentration will increase when the participant is able to receive two exposures of the same dose without coughing. Each increase of capsaicin will be a doubling dose up to 500 μM. Two concentrations between 500 and 1000 μM (i.e., 625 and 750 μM) will be used to minimize the large increase between 500 and 1000 μM. No more than 6 inhalations of capsaicin will be given in any single session and no more than 3 inhalations above 500 μM will be given in a single session. Each session will last 35-45 minutes (depending on scheduling constraints). We will measure the participant's number of coughs, urge-to-cough, and discomfort level (0-10) following each capsaicin inhalation.

Phase III: Post-Treatment Outcome Testing

Cough-sensory, cough-frequency, and cough-related QOL testing, as outlined in Phase I, will be completed at one week and three-weeks following the final treatment session. During cough-sensory and cough-frequency testing, participants will be instructed to NOT attempt to suppress their cough.

Statistical Analysis Plan:

The data will be analyzed with linear or generalized linear mixed models with a random subject effect to account for three repeated measurements (baseline, PT1, and PT2) on each participant, with fixed effects for the three time points and group (treatment, placebo) and their interaction, incorporated.