Study Title: Internet-Behavioral Cough Suppression Therapy

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Study Protocol

Background

Refractory chronic cough (RCC), defined as a chronic cough that has not responded to medical guideline-based treatment for the most common causes of cough, affects millions of people annually (Chung & Pavord, 2008; Song et al., 2015). Behavioral cough suppression therapy (BCST) provided by voice and upper-airway specialized speech-language pathologists is a highly efficacious treatment for RCC (Yi et al., 2024) but is underutilized (Chamberlain et al., 2015; Slovarp et al., 2021). For patients with RCC living in rural areas, the lack of BCST providers combined with accessibility barriers compound this issue (Towey, 2012, Meit et al., 2014). Innovations in treatment modality are needed to increase the availability and accessibility of BCST. Internet-based interventions offer an avenue to connect more patients with specialized healthcare services.

Objective

The primary aim of this study was to investigate the efficacy of internet-based behavioral cough suppression therapy (IBCST) compared to a healthy-lifestyle education control in patients with RCC.

Design

This was a prospective, single-blind, randomized, controlled trial.

Method

This study was conducted with approval and oversight from the University of Montana Institutional Review Board (protocol #163-22). Individuals with refractory chronic cough (RCC) in the United States were recruited for the study via social media campaigns, newspaper advertisements, flyers sent to voice and upper airway clinics, word-of-mouth, and Facebook

support groups. Participants provided informed consent online via the study website (hosted by the iTerapi ePlatform). Prior to study recruitment, participant identification numbers were sorted by a random number generator to determine grouping and then were assigned to participants based on chronological study enrollment. Participants were blinded to their group assignment. They were contacted by a member of the study team and participated in a short training phone call or HIPAA-compliant audio/video call instructing them on how to navigate the study website and access the study materials.

Intervention

The IBCST and control treatments included five weeks of content presented in weekly modules consisting of video explanations and demonstrations, supplemental text explanations, and a downloadable handout. Participants were prompted to answer a treatment adherence question at the beginning of each week to indicate whether they consistently followed the recommendations for the previous week. The participants received automated reminders via their preferred mode of communication (email or text) to complete the study questionnaires and alert them when new content was available.

The IBCST intervention included education on cough hypersensitivity syndrome and the rationale for BCST, vocal hygiene education, instruction in cough suppression strategies, functional practice of cough suppression in daily life, and implications for long-term management. The healthy lifestyle education control treatment was informed by the control treatments described in prior BCST randomized controlled trials (Chamberlain Mitchell et al., 2016; Vertigan et al., 2006) and was based on publicly available information from the Centers for Disease Control and Prevention. Topics included general education, physical activity, healthy

eating, stress management, and relaxation techniques. Control participants were provided with the opportunity to participate in the IBCST intervention after their study participation ended.

Assessments/Outcome Measures

Changes in cough-related quality of life and perception of cough severity were used to assess the efficacy of IBCST compared to the control treatment. The LCQ is a 19-item, validated, reliable, and repeatable self-report questionnaire about cough-related quality-of-life (Birring et al., 2003) and was the primary outcome measure. A higher score indicates better cough-related quality-of-life. The secondary outcome measure was the Cough Severity Visual Analog Scale (VAS) which is a 100-millimeter line with anchors of 0 “no problem” and 100 “worst possible problem” where participants place a mark to represent the severity of their current cough problem. These assessments were administered online using the iTerapi ePlatform at baseline (T0), one-week post-treatment (T1), and one-month post-treatment (T2). A change of 1.3 is considered the minimally important clinical difference on the LCQ (Raj et al., 2009) and a reduction of at least 30-millimeters is considered clinically meaningful for the Cough Severity VAS (Martin Nguyen et al., 2021).

Statistical Analyses

The original sample size goal was calculated with a power analysis (G*Power 3.1, Faul et al., 2009) and determined to be 48 participants based on a one-tailed independent samples (pre-post) *t*-test with an effect size of 0.80, alpha level of .05, and power set at .85. The power level of .85 was deemed sufficient based on the only prior randomized control trial examining the efficacy of BCST that used the LCQ as a primary outcome measure (Chamberlain Mitchell et al., 2016). A large effect size of .80 was chosen as a conservative value which would be advantageous as we planned to run an analysis of covariance (ANCOVA) and not a *t*-test to

analyze LCQ score change. To account for the possible attrition rate of 16.5% reported in a previous study (Chamberlain Mitchell et al., 2016), we had a goal to recruit 56 participants. This sample target size number was modified as the study progressed due to multiple factors, including a shorter than anticipated recruitment timeline related to a funding delay, and interim analyses that showed a large difference in the primary outcome measure between groups.

Analyses were conducted using R-4.4.2 (R Core Team, 2021). Group differences in mean total LCQ and VAS scores from T0-to-T1 and T0-to-T2 were examined, accounting for T0 assessment scores using an ANCOVA. The variance in responses for both LCQ and VAS scores was very high, making it difficult to determine linearity between T0 and T1 and T2 scores. Therefore, an interaction term between the treatment group and T0 score was considered to account for the potential different treatment effects at different T0 scores. All interaction terms were not statistically significant ($p = .26$, $p = .46$, $p = .95$, $p = .36$) for LCQ at T1, LCQ at T2, VAS at T1, or VAS at T2, respectively, suggesting homogeneity of the regression slopes. Shapiro-Wilk tests suggested insufficient evidence of non-normality of residuals ($p = .89$, $p = .09$, $p = .29$, $p = .38$). Lastly, Levene's test found no evidence of error variance heterogeneity ($p = .30$, $p = .74$, $p = .58$, and $p = .47$). Thus, the basic assumptions necessary for the ANCOVA were met.

Results

Thirty-nine individuals with RCC enrolled in the study between July 2023 and June 2024. Twelve participants completed the control treatment (11 women; mean age, 60 years) and 18 completed the IBCST treatment (16 women; mean age, 62 years). One IBCST participant was lost to follow up at T2 and so was not included in T2 analyses.

Leicester Cough Questionnaire

At T1, 72% of IBCST participants achieved a meaningful improvement in LCQ total score and this increased to 76% at T2. Mean domain and total LCQ scores for both groups during each assessment period are shown in Table 1. Change in mean total LCQ scores from T0-T1 was 3.74 and 0.58, and from T0-T2 was 4.10 and 0.83, for the IBCST and control groups, respectively. ANCOVA analysis revealed mean total LCQ score changes were significantly greater in the IBCST group than in the control group from T0-to-T1 (mean difference between groups = 3.24, 95% CI = 0.72-5.76, standard error = 1.227, p = .014, ηp^2 = 0.205), and T0-to-T2 (mean difference between groups = 3.30, 95% CI = 0.286-6.32, standard error = 1.467, p=0.033, ηp^2 = 0.163).

Cough Severity Visual Analog Scale (VAS)

Mean VAS scores for both groups at each assessment period are shown in Table 1. Change in mean total VAS scores from T0-T1 was -15 and 1, and from T0-T2 was -7 and 7, for the IBCST and control groups, respectively. ANCOVA analysis revealed there was mild evidence of a larger decrease from T0-to-T1 for the IBCST group compared to the control group (mean difference between groups = -16.1, 95% CI= -32.7-0.46, Std error = 8.804, p = .056, ηp^2 = 0.128), with no evidence of a difference in the mean score change from T0-to-T2 (mean difference between groups = -11.73, 95% CI = -28.53-5.06, Std. error = 8.170, p = .338, ηp^2 = 0.073).

Table 1

Mean LCQ and VAS Scores

		LCQ				VAS
		Physical	Social	Psych	Total (SD)	Total (SD)
IBCST	**T0**	3.58	2.82	2.64	9.04 (2.76)	49 (15.97)
	T1	4.62	4.03	4.13	12.78 (3.69)	33.94 (21.32)
	T2	4.71	4.22	3.88	13.03 (4.3)	44.18 (22.85)
Control	**T0**	3.67	2.75	2.45	8.87 (2.76)	49.08 (22.39)
	T1	3.74	3.04	2.67	9.45 (3.50)	50.08 (22.39)
	T2	3.75	3.17	2.79	9.70 (4.29)	56.42 (23.74)

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