

Rehabilitating Cough Dysfunction in Parkinson's Disease: A Randomized Controlled Trial

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Background: Disorders of airway protection (cough and swallowing) are pervasive in Parkinson's disease (PD) resulting in a high incidence of aspiration pneumonia and death. However, there are no randomized controlled trials comparing strength and skill-based approaches to improve airway protection in PD.

Objectives: The goal of this study was to compare Expiratory Muscle Strength Training (EMST) and sensorimotor training for airway protection (smTAP) to improve cough-related outcomes in people with PD.

Method: Participants with PD and dysphagia were recruited for this prospective phase II randomized-blinded controlled clinical trial. Participants completed baseline assessment, five weeks of EMST or smTAP, and a post-training assessment. Primary outcome measures included maximum expiratory pressure (MEP) and voluntary cough peak expiratory flow rate (PEFR). Mixed effects models were used to assess effects of EMST and smTAP on outcomes.

Results: 65 participants received either EMST ($n = 34$) or smTAP ($n = 31$). MEP improved from pre- to post-treatment for smTAP ($p < .001$, $d = 0.19$) and EMST ($p < .001$, $d = 0.53$). Voluntary PEFR increased from pre- to post-treatment for smTAP ($p < .001$, $d = 0.19$) and EMST ($p < .001$, $d = 0.06$). Moreover, reflex cough PEFR ($p < .001$, $d = 0.64$), reflex cough expired volume ($p < .001$, $d = 0.74$), and urge-to-cough ($p = .018$, OR = 2.70) improved for the smTAP group, but not for the EMST group.

Conclusions: This clinical trial confirmed the efficacy of smTAP to improve reflex and voluntary cough function, above and beyond EMST, the current gold standard.

By the year 2030 Parkinson's disease (PD) is projected to affect nine million people globally¹. Airway protective disorders, including swallowing (dysphagia) and cough (dystussia) disorders, are a pervasive consequence of PD and result in severe health consequences including malnutrition, dehydration, and aspiration pneumonia²⁻⁵, negatively impacting quality of life^{2,3} and increasing caregiver burden⁶⁻⁸. In fact, aspiration pneumonia is the leading cause of death in individuals with PD^{4,5,9-11}, and this cannot be explained by disordered swallowing alone¹²⁻¹⁴. People with PD have multi-factorial deficits of airway protection, including the need for more intense

cough stimuli to trigger a cough^{14,15}, reductions in the perception of cough stimuli (i.e., urge-to-cough)^{15,16}, disordered voluntary control of cough¹⁷⁻¹⁹, and peripheral respiratory muscle weakness²⁰⁻²². Furthermore, these cough impairments are often worse when patients have dysphagia^{14,16-18,23}. Therefore, reducing adverse health effects and improving quality of life in PD should involve a comprehensive approach to rehabilitating airway protection which includes targeting sensorimotor cough dysfunction.

Only expiratory muscle strength training (EMST) has been found to improve airway protection via RCTs in individuals with PD^{24,25}. EMST is an exercise-based, treatment approach which uses a calibrated device with a one-way, spring-loaded valve to primarily overload the expiratory muscles. In PD, studies have shown that EMST improves maximum expiratory pressure, voluntary cough effectiveness²⁶, swallowing safety and efficiency^{24,25}, and swallowing-related quality of life²⁴. Although PD can result in reductions to muscle

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The data that support the findings of this study are available from the corresponding author upon reasonable request.

strength, the primary deficits are often in the motor organization for airway protection and a blunted perception of cough-inducing stimuli²⁷, leading to reduced cough effectiveness to clear aspirated material^{14,28}. Despite these deficits, people with PD can volitionally up-regulate both reflex and voluntary cough function^{29,30}. These data led to the development of a cough training approach, namely sensorimotor training for airway protection (smTAP), that targets three key components to improve cough coordination for improved airway protection: 1) a cue for immediate enhancement of peak expiratory flow rate (PEFR) and 2) visual biofeedback, in the presence of 3) a sub-threshold level of a cough-inducing stimulus (i.e., capsaicin). Several studies have begun to define the feasibility and effect of cough skill training approaches in PD and related disorders^{26,31,32}.

There are no randomized controlled trials comparing the efficacy of strength and skill-based approaches for improving airway protection in PD. Therefore, the objective of this study was to compare the efficacy of EMST and smTAP for improved airway protection in individuals with PD and dysphagia. We hypothesized that both treatments would result in improvements to cough, with more robust improvements following smTAP.

Methods

Participants

Procedures were performed in accordance with ethical standards approved by the institutional review boards of the two study sites: Teachers College, Columbia University (#16-098) and the University of Florida (# IRB201601082) and the trial was registered with Clinicaltrials.gov (NCT02927691). Informed consent was obtained from all participants prior to enrollment in this study. Participants were recruited from Teachers College and the Columbia University Movement Disorders Division and the University of Florida Norman Fixel Institute for Neurological Diseases between November 2016 and March 2020. Participants were diagnosed with PD by a Movement Disorders Fellowship-trained Neurologist using strict UK Brain Bank criteria³³. Participants also met the following criteria: 1) Dysphagia – defined as a Penetration-Aspiration Scale score >2 on at least one bolus trial seen during endoscopic and/or fluoroscopic swallowing assessments³⁴; 2) Dystussia – defined as a maximal voluntary cough PEFR <5 L/s; and 3) Not actively receiving swallowing therapy. Exclusion criteria included: 1) Other neurological disorders; 2) Head and neck cancer;

3) Breathing disorders or diseases; 4) Smoking in the last five years; 5) Uncontrolled hypertension; and 6) Difficulty complying due to neuropsychological dysfunction (i.e., severe depression, dementia with score of less than 23 on the Montreal Cognitive Assessment³⁵). The target sample size of 60 participants (30 in each group) was determined based on a power analysis guided by data from an RCT investigating the effects of EMST to improve airway invasion in PD²⁴. Specific to cough outcomes, assuming between- (SD = 0.59) and within-subject (SD = 0.38) variability, based on pilot data in 16 individuals with PD³⁶, a simulation-based power analysis showed that a sample size of 65 would provide 80% power to detect a post-treatment difference of 0.22 L/s between EMST and smTAP groups.

Study Design

Participants in this prospective phase II RCT were randomly assigned with allocation concealment to either the EMST or smTAP groups. Simple computer-generated random allocation sequence was completed prior to study initiation and allocation sequence was concealed from the investigators enrolling and assessing eligibility. Randomization was revealed sequentially after enrollment. No comment was made to participants about whether better outcomes were expected with either treatment. Participants were further randomized to receive immediate or delayed training, where there was a five-week wait-to-start followed by a second baseline. The delayed training group served to identify whether there were any potential improvements in primary outcomes with repeated assessment, which would confound treatment effects. Once treatment commenced, all participants received five weeks of intensive training including weekly meetings with a trained study clinician and four days of home practice each week. Following the treatment, participants were seen for a post-training assessment.

Assessment Visits

The same assessment protocol was completed at pre- and post-treatment visits. Participants were tested one-hour following the intake of their dopaminergic medications to ensure they were in a practically defined “on” state. The first assessment visit was also used to screen for inclusion criteria. Assessment visits were completed by trained research speech-language pathologists (SLPs) who were blinded to participant treatment group assignment and did not participate in treatment visits.

In order to assess voluntary and reflex cough function, participants were outfitted with a facemask covering the nose and mouth. The facemask was coupled to a pneumotachograph, differential pressure transducer, and a side port with a one-way inspiratory valve for nebulizer connection. The nebulizer was a DeVilbiss T-piece connected to a dosimeter that delivered aerosolized solution during inspiration with a delivery duration of 2 seconds. The cough airflow signal was digitized (Power Lab Data Acquisition System) and recorded (LabChart 8; ADInstruments, Inc) to a computer.

Participants were seated for an initial 45 seconds of quiet breathing. Participants then completed a capsaicin challenge with three randomized blocks of 0, 50, 100, and 200 μM dissolved in a vehicle solution (80% physiological saline, 20% ethanol). Participants were instructed to “cough if you need to” prior to capsaicin or placebo (0 μM) delivery. The solution was administered upon detection of an inspired breath with at least one-minute rest between each trial. Following each trial, participants rated their urge-to-cough (UTC) on a modified Borg rating scale, where 0 was no UTC and 10 was maximal UTC and provided information regarding participants’ perceived magnitude of the cough-inducing stimuli. Participants were provided water to drink between trials. To assess voluntary cough function, participants were asked to ‘cough as if something went down the wrong pipe’ without the presentation of any stimulus.

Maximum expiratory pressures (MEP) were obtained using a pressure manometer coupled to a mouthpiece. Nose clips were used to prevent nasal air escape. The participants were then instructed to inhale as deeply as possible, seal their lips and teeth around the mouthpiece, and blow into the manometer with maximal effort. Verbal encouragement was provided to the participants.

Treatments (Video 1; Figure 2)

All treatment visits were completed by trained research SLPs who were not involved in the assessment visits.

EMST: Participants in the EMST group used a calibrated EMST150 device (Figure 2) with a one-way, spring-loaded pressure relief valve. The adjustable spring allowed for discrete changes to the valve blocking the flow of air until sufficient expiratory pressure was produced, thus modifying the physiologic load placed on the muscles. Once opened, air flowed through the device. Training targets were set at 75% of

the participant’s MEP. The device’s pressure range was from 30-150 cm H₂O. Participants were instructed to: (a) occlude their nose with the nose clips, (b) take a big breath in, and (c) blow as forcefully as possible into the device to open the valve. Participants completed 25 repetitions (5 sets of 5 repetitions) with the clinician.

smTAP: Participants in the smTAP group were seated at a computer with the same spirometry setup used for reflex cough testing. Given that the ultimate goal of treatment was to improve cough effectiveness during airway invasion, participants were presented with a background dose of sub-threshold capsaicin, defined as a concentration that was half that of their baseline reflex cough threshold, to allow for training in the context of a sensation similar to airway invasion. Following presentation of the sub-threshold sensory stimulus, participants were instructed to direct their attention to their UTC and “cough hard” in order to elicit a cough with sufficient intensity to hit a target line provided via real-time cough airflow visual biofeedback. The target line was set 25% above maximum PEFR based on baseline reflex cough testing. Participants completed 25 repetitions (5 sets of 5 repetitions) of sequential volitional coughs with the clinician.

Home practice (Video 2): In addition to one therapy session per week with a research clinician, all participants completed four days of home practice, totaling 5 days of training per week. The home practice protocol was identical to the protocol described above for EMST (at 75% MEP). For smTAP, participants completed 25 repetitions (5 sets of 5 repetitions) of single volitional coughs using an analog peak flow meter and a target set 25% above baseline PEFR (Figure 2). No capsaicin and no visual cough airflow biofeedback was used for the smTAP home practice. However, participants were able to visualize their PEFR at the conclusion of each cough using the analog peak flow meter in order to assess whether they had met their target PEFR. Participants were provided with written home practice instructions and a practice log to track adherence.

Data Analyses and Outcome Measures

All data analyses were completed by trained raters with experience in cough analysis who were blinded to participant identity, time point, and training group. Inter and intra-rater reliability was completed on 20% of the data. Voluntary cough PEFR and MEP were selected as the primary treatment outcomes given that each was the central target of treatment for smTAP and EMST, respectively. Additionally, voluntary cough

PEFR served as the primary treatment outcome measure of cough effectiveness given that it has been found to be related to the ability to clear aspirate material from the airway³⁷. PEFr was derived from cough waveforms obtained via voluntary cough spirometry and was measured from the first cough in each cough epoch. MEP served as the primary treatment outcome measure of respiratory strength^{24,26,38}. Three values within 10 percent of each other were targeted to achieve a representative sample of MEP scores.

Secondary outcomes included other measures of voluntary and reflex cough function and effectiveness. All cough airflow measures were derived from cough waveforms obtained via voluntary or reflex cough spirometry. The total number of coughs were counted for each cough epoch (CrTot) for both reflex and voluntary cough and was used as a covariate and outcome measure. Reflex cough PEFr and voluntary and reflex cough expired volume (CEV) was measured from the first cough in each cough epoch. Reflex cough airflow measures were made from each trial of 200 μ M capsaicin. The concentration of capsaicin that elicited the reliable two-cough response (Cr2) was recorded as the reflex cough threshold^{14,16}. A reliable Cr2 was defined as at least two coughs produced within 30 seconds following presentation of the stimulus in two of three trials of that concentration. UTC ratings were collected for each trial of capsaicin across concentrations.

Statistical Analyses

Multilevel models with main effects of treatment, time, and their two-way interaction were used. A random effect of participant was used in order to include multiple trials (e.g., three trials of MEP at each time point). In the presence of an interaction, differences in the magnitude of change between groups, as well as changes within each group, were examined. For primary outcomes, separate models were performed for delayed to pre-training and pre-training to post-training cohorts. More specifically, for participants randomized to the delayed treatment group, MEP and voluntary cough PEFr were tested between delayed (first baseline) and pre-training (second baseline). For the active treatment phase, all outcomes were tested between pre-training (which was the second baseline for those in the delayed treatment group) and post-training. Alpha was set at .05 and multiple pairwise comparisons were adjusted via Holm-Bonferroni corrections. Unadjusted p-values are presented in text. Standardized effect sizes were computed by dividing mean difference by the er-

ror and random effect variance³⁹. Single measure, absolute agreement intraclass correlation coefficients (ICC) and weighted Cohen's kappa were used for cough airflow and number of coughs, respectively, for reliability⁴⁰. Analyses were performed in R⁴¹.

Results

Participants

Seventy-five participants were recruited and screened (Figure 1). Ten participants declined to participate in the study; therefore, sixty-five participants were randomized to either the EMST ($n = 34$) or smTAP ($n = 31$) group. Fifteen and 13 participants were randomly allocated to the delayed baseline in EMST and smTAP groups, respectively. A total of 30 participants completed the study in the EMST group and 28 in the smTAP group. Recruitment occurred between January 2017 and February 2020, the last participant completed the study March 2020. Dropout rate was calculated at 11% including participants who were discontinued due to COVID-19 laboratory closure (Figure 1). A decision was made to close the study several months into the COVID-19 pandemic given the proximity to the target sample and to avoid confounding factors introduced through recruitment of participants after the pandemic. Following closure of participant enrollment and blind rating of airway invasion utilizing strict criteria to maximize reliability of visuo-perceptual measures (i.e, VASES⁴²), three participants were found to have maximum Penetration-Aspiration scores of 1 or 2 (Table 1). A review of additional measures (Swallowing-related quality of life⁴³ (SWAL-QOL), FOIS⁴⁴, residue⁴², and cough outcomes) was completed to confirm the participants had dysphagia. All three participants had PEFr values well below inclusion cut-off (range: 3.06 - 3.44) and SWAL-QOL scores indicating complaints of dysphagia and significant impact of swallowing symptoms on their quality of life. One of the participants was on a modified diet. Therefore, the determination was made to include them in this analysis which focuses on cough outcomes. Return rates for home training logs were similar between the two training groups and treatment adherence rates were high (Table 1). No adverse events, including laryngeal pathology, were reported or endoscopically observed during the study. Both groups demonstrated similar demographic characteristics, including age, duration from symptom onset, and disease severity (Table

1). All sixty-five participants were analyzed with intent-to-treat statistical analyses.

Reliability

For inter-rater reliability, estimates were 0.90 for voluntary cough PEFR (95% CI: 0.85 – 0.93), 0.82 for reflex cough PEFR (95% CI: 0.77 – 0.86), 0.93 for voluntary cough CEV (95% CI: 0.90 – 0.95), 0.81 reflex cough CEV (95% CI: 0.975 – 0.85), 0.99 for voluntary CrTot (95% CI: 0.99 – 0.99), and 0.93 for reflex CrTot (95% CI: 0.93 – 0.93).

For intra-rater reliability, estimates were 0.99 for voluntary cough PEFR (95% CI: 0.99 – 1.00), 0.98 for reflex cough PEFR (95% CI: 0.97 – 0.98), 0.85 for voluntary cough CEV (95% CI: 0.76 – 0.91), 0.87 reflex cough CEV (95% CI: 0.82 – 0.90), 0.82 for voluntary CrTot (95% CI: 0.82 – 0.82), and 0.77 for reflex CrTot (95% CI: 0.77 – 0.77).

Primary Outcomes

Delayed (No-Treatment) Effects - Primary Outcomes (MEP & Voluntary PEFR)

Voluntary cough peak flow decreased by 0.30 L/s after 5 weeks of no treatment ($p < .001$, $d = 0.34$), whereas there was no change in MEP ($p = .79$, $d = -0.01$).

Treatment Effects - Primary Outcomes (MEP & Voluntary PEFR – Table 2)

MEP increased from pre- to post-treatment for smTAP by 8 cmH₂O ($p < .001$, $d = 0.19$) and for EMST by 22 cmH₂O ($p < .001$, $d = 0.53$). EMST showed greater improvements in MEP compared to smTAP ($p < .001$, $d = -0.34$).

Voluntary PEFR increased from pre- to post-treatment for smTAP by 0.51 L/s ($p < .001$, $d = 0.19$) and for EMST by 0.17 L/s ($p < .001$, $d = 0.06$). smTAP showed greater improvements in PEFR compared to EMST ($p < .001$, $d = 0.12$).

Secondary Outcomes

Voluntary Cough (CEV, CrTot – Table 2)

Voluntary CEV increased from pre- to post-treatment for smTAP by 0.18 L ($p < .001$, $d = 0.16$) and by 0.07 L for EMST ($p = .001$, $d = 0.06$). smTAP showed greater improvements in CEV compared to EMST ($p < .001$, $d = 0.10$).

The number of voluntary coughs (CrTot) decreased from pre- to post-treatment for smTAP ($p < .001$, OR =

0.68) and EMST ($p < .001$, OR = 0.69). There were no between-group differences in the magnitude of change ($p = .846$).

Reflex Cough (PEFR, CEV, CrTot, Reflex cough threshold, UTC- Table 2)

Reflex cough PEFR at 200 μ M increased for smTAP from pre- to post-treatment by 0.53 L/s ($p < .001$, $d = 0.64$), whereas EMST decreased by 0.23 L/s ($p < .001$, $d = -0.28$). smTAP showed greater improvements in PEFR compared to EMST ($p = .022$, $d = 0.93$).

Reflex CEV improved for smTAP from pre- to post-treatment by 0.22 L ($p < .001$, $d = 0.74$) but was unchanged for EMST ($p = .48$, $d = -0.10$). smTAP showed greater improvements in CEV compared to EMST ($p < .001$, $d = 0.84$).

There were no significant differences in the total number of reflex coughs (CrTot) at 200 μ M ($p = .20$) or in the reflex cough thresholds ($p = .147$).

UTC at 50 μ M capsaicin increased for smTAP ($p = .018$, OR = 2.70), but not EMST ($p = .102$, OR = 0.58). smTAP showed greater improvements in UTC compared to EMST ($p = .018$, OR = 4.70). At 100 and 200 μ M capsaicin, there were no significant differences in UTC ($p > .05$; Figure 3; supplemental materials)

Discussion

The results of this first RCT comparing a strength and skill-based approach to rehabilitation for airway protection demonstrated that five weeks of EMST and smTAP are safe and efficacious for the rehabilitation of critical aspects of airway protection, specifically cough effectiveness, in PD. More specifically, both EMST and smTAP resulted in significant improvements to MEP and voluntary cough PEFR. However, only smTAP improved reflex cough effectiveness. These findings are particularly impactful given that the delayed-treatment group demonstrated a significant worsening of voluntary cough effectiveness with no treatment over five weeks.

Voluntary cough PEFR improved in both the EMST and smTAP groups, though the smTAP group demonstrated a significantly larger improvement. On average, the EMST group improved PEFR from 2.98 L/s to 3.15 L/s (6% improvement) and the smTAP group improved PEFR from 3.05 L/s to 3.60 L/s (18% improvement). These values remain below those seen in healthy older adults where voluntary cough PEFR is estimated at 4.16 L/s²⁹. However, these improvements are of particular clinical importance given recent findings indicating that voluntary cough PEFR values of

3.41 L/s differentiate between “effective” and “ineffective” airway clearance for $\geq 80\%$ of subglottic residue (aspirate material)³⁷. Therefore, smTAP improved PEFR to levels that are associated with 80% of aspirate material expelled after a voluntary cough. Cough expired volume, another measure of cough effectiveness, also increased significantly in both groups, though significantly more for the smTAP group. On average, voluntary cough CEV increased from 0.53 L to 0.60 L (13% increase) for the EMST group and increased from 0.54 L to 0.72 L (33% increase) for the smTAP group. This is the first RCT demonstrating the efficacy of a sensorimotor skill-based approach (i.e., smTAP) to improve voluntary cough effectiveness (i.e., PEFR and CEV) in PD, having led to greater improvements to voluntary cough outcomes than those observed in the EMST group.

EMST has as its primary treatment target an increase in MEP to improve expiratory force generation. In PD specifically, the average increase in MEP has been around 24%^{24,45}. The findings of this study are consistent with prior EMST studies. Participants in the EMST group increased MEP from 97 cmH₂O to 118 cmH₂O (22% improvement) on average. Interestingly, the smTAP group also had an improvement in MEP with an increase from 112 cmH₂O to 120 cmH₂O (7% improvement) on average; however, the EMST group had a larger magnitude of change in MEP. Though an increase in MEP is favorable, the translation of these improvements to airway protective function is more critical.

Another key contribution of this work was to test the efficacy of these treatments for improving reflex cough function given the need for patients with dysphagia to detect aspirate material and cough effectively enough to clear aspirate from the airway. The EMST group did not show any changes in reflex cough outcomes. In contrast, the smTAP group showed a significant improvement in both reflex cough PEFR and CEV. On average, reflex cough PEFR increased from 2.48 L/s to 3.01 L/s (21%) and CEV increased from 0.57 L to 0.79 L (39%). Of note, following training, the smTAP group demonstrated higher reflex cough PEFR and CEV than what has been found in healthy older adults, 2.85 L/s and 0.19 L, respectively²⁹. We also sought to understand whether EMST or smTAP would improve the perception of cough stimuli in PD. We found that UTC significantly increased at 50 μ M capsaicin for the smTAP group, but not the EMST group, post-training. These data support the notion that the blunted perception of sub-threshold cough stimuli in PD can be up-regulated with rehabilitation. This is the

first RCT to identify an improvement in reflex cough function and detection of cough stimuli in PD following a behavioral therapeutic approach.

Beyond the positive treatment effects identified in both groups, both treatments also appear to be safe and feasible for participants. This study included a wide range of patients with mild to severe PD, all of which had dysphagia. In this study there were no adverse events, supporting the safety of these treatment approaches in PD. Though both treatments were intensive, requiring one weekly visit to the laboratory and four days of home practice, there was low drop-out related to issues other than COVID-19 lab closure. Additionally, most participants returned their home treatment logs and most participants reported completion of all of their home practice. Therefore, these findings indicate that this type of treatment approach is well tolerated and accepted by patients with dysphagia and various severity levels of PD.

This RCT is not without limitation. Treatment adherence to the home program was measured via patient logs, which have potential to be unreliable. Another limitation is that capsaicin is not immediately available to clinicians, which can limit translation of our findings to clinical settings. Capsaicin, a cough-inducing stimulus derived from hot peppers, was selected for this study and treatment approach because of its superior reliability versus acid-based cough-inducing agents on multiple cough tests and because the affective sensations associated with capsaicin as compared to acid-based agents have been reported to be more pleasant⁴⁶. However, other tussive agents which are more readily available can be considered^{47,48}. Additionally, studies have identified that cough skill training without capsaicin still translate to improvements in reflex cough function and that this can be completed via telehealth, further supporting the clinical translation³¹. Lastly, though this study included patients with mild to severe PD and dysphagia, it will be necessary to study whether these findings are replicated in a larger cohort of patients with severe PD and dysphagia.

Overall, this clinical trial has confirmed the safety and efficacy of a novel sensorimotor approach to cough skill training (smTAP) for the improvement of both motor and sensory aspects of voluntary and reflex cough function, above and beyond the changes seen with EMST, the current gold standard for treatment of airway protection in PD. These differences in airway protective treatment outcomes between the EMST and smTAP group point to differences in the mechanistic targets of treatment (i.e., strength vs skill-based training), with EMST leading to greater improvements in

MEP, but smTAP resulting in greater improvements to voluntary and reflex cough function. The value of skill-based training for individuals with PD is further supported by studies demonstrating improvement to speech and gait^{49,50}. For the smTAP group, the improvements to voluntary and reflex cough function to levels indicative of improved airway clearance are of

clear health impact, especially given that these individuals have dysphagia. This study supports the consideration of skill-based training approaches for cough rehabilitation in individuals with PD and dysphagia. Future studies should test combined strength and skill-based approaches for the rehabilitation of airway protective disorders in PD and should assess the long-term health outcomes associated with these approaches.

Figure 1

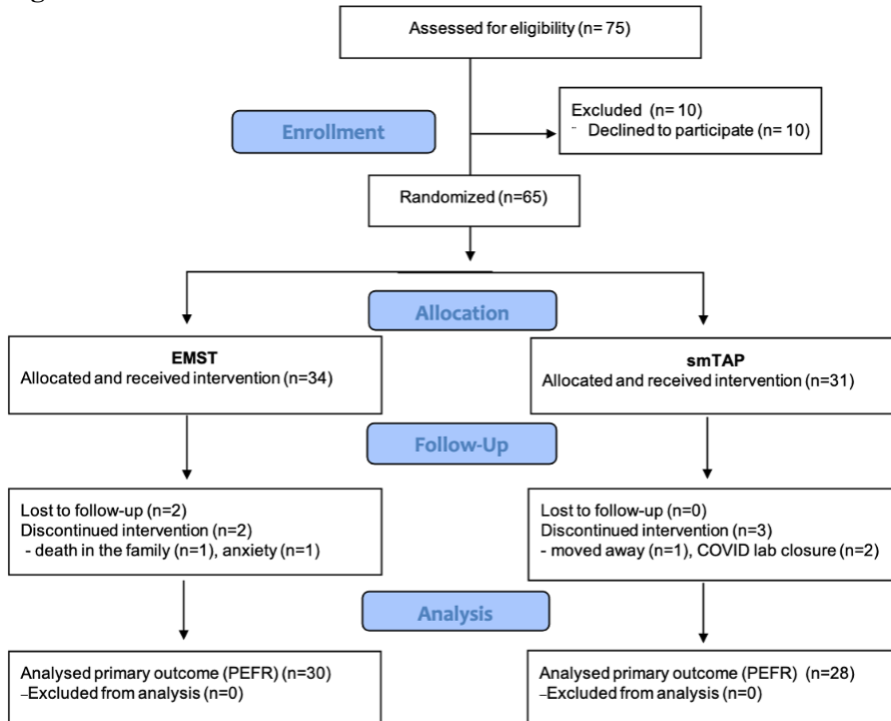


Figure 2:

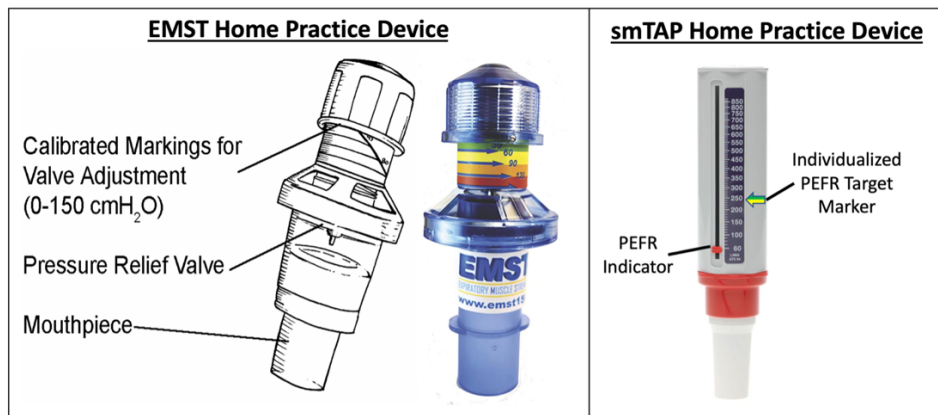
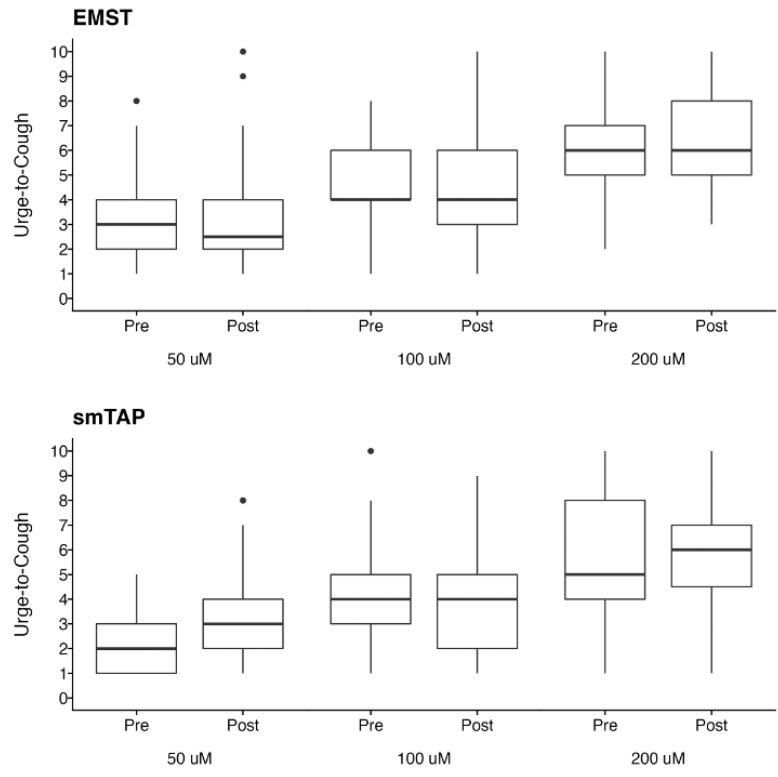


Figure 3:



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