RESEARCH ARTICLE



Speech Treatment in Parkinson's Disease: Randomized Controlled Trial (RCT)

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ABSTRACT: Background: As many as 89% of people with Parkinson's disease (PD) develop speech disorders. **Objectives:** This randomized controlled trial evaluated two speech treatments for PD matched in intensive dosage and high-effort mode of delivery, differing in subsystem target: voice (respiratory-laryngeal) versus articulation (orofacial-articulatory).

Methods: PD participants were randomized to 1-month LSVT LOUD (voice), LSVT ARTIC (articulation), or UNTXPD (untreated) groups. Speech clinicians specializing in PD delivered treatment. Primary outcome was sound pressure level (SPL) in reading and spontaneous speech, and secondary outcome was participant-reported Modified Communication Effectiveness Index (CETI-M), evaluated at baseline, 1, and 7 months. Healthy controls were matched by age and sex.

Results: At baseline, the combined PD group (n = 64) was significantly worse than healthy controls (n = 20) for SPL (P < 0.05) and CETI-M (P = 0.0001). At 1 and 7 months, SPL between-group comparisons showed greater improvements for LSVT LOUD (n = 22) than LSVT

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ARTIC (n = 20; P < 0.05) and UNTXPD (n = 22; P < 0.05). Sound pressure level differences between LSVT ARTIC and UNTXPD at 1 and 7 months were not significant (P >0.05). For CETI-M, between-group comparisons showed greater improvements for LSVT LOUD and LSVT ARTIC than UNTXPD at 1 month (P = 0.02; P = 0.02). At 7 months, CETI-M between-group differences were not significant (P = 0.08). Within-group CETI-M improvements for LSVT LOUD were maintained through 7 months (P =0.0011).

Conclusions: LSVT LOUD showed greater improvements than both LSVT ARTIC and UNTXPD for SPL at 1 and 7 months. For CETI-M, both LSVT LOUD and LSVT ARTIC improved at 1 month relative to UNTXPD. Only LSVT LOUD maintained CETI-M improvements at 7 months. © 2018 The Authors. *Movement Disorders* published by Wiley Periodicals, Inc. on behalf of International Parkinson and Movement Disorder Society

Key Words: speech treatment; RCT; Parkinson's disease; voice; articulation

Research indicates that as many as 89% of patients living with Parkinson's disease (PD) develop speech signs,^{1–5} termed *hypokinetic dysarthria*,^{6,7} including disorders of *voice* (e.g., reduced loudness, monotone, and hoarse, breathy quality),^{8–14} *articulation* (e.g., imprecise consonants, vowel centralization),^{15–25} and *rate* (increased, decreased, or variable).^{26–28} In contrast to previous reports suggesting long latencies from PD diagnosis to onset of identifiable speech signs (median 84 months),²⁹ more recent data from prospective studies using objective, reliable measures sensitive to speech changes suggest that speech signs may appear early^{22,30–33} and progress in severity,^{25,33–38} leading to significant declines in functional communication and quality of life.^{4,31,39} Reductions in vocal loudness are among the first and most pervasive changes in speech,^{1,6,7,14,40} having negative effects on speech intelligibility when patients are not sufficiently audible to be heard by listeners.^{8,41–44}

The neural bases of speech disorders in PD are complex. Reductions in vocal loudness are attributed partly to hypokinesia (reduced amplitude of movement) and rigidity caused by underlying dopaminergic deficiency.^{42,45–49} However, abnormalities in central sensory processing (reduced awareness of soft voice), internal cueing (difficulty self-generating increased loudness), and selfmonitoring of speech output are now reported to contribute.^{50–60} These central sensory and cueing deficits may explain why speech disorders in PD are generally unresponsive to pharmacological or neurosurgical interventions alone^{40,61–65} given that such treatments primarily address motor deficits,^{12,61,66–73} and why traditional speech therapy effects often are not sustained because sensory processing disorders typically are not addressed in these approaches.^{74–78}

Since the 1990s, development and evaluation of the Lee Silverman Voice Treatment (LSVT LOUD®) has advanced speech treatment efficacy for patients with PD by addressing the complex etiology of the speech disorder.41,52,79 LSVT LOUD differs from traditional PD speech treatment in key ways: (1) the singular target of treatment is *voice* (respiratory-laryngeal subsystem), specifically increasing amplitude of vocal motor output to override hypokinesia throughout the speech mechanism^{48,80}; (2) treatment is intensive (16 individual 1-hour sessions in 1 month, with a high-effort mode of delivery), consistent with principles promoting activitydependent neuroplasticity⁸¹⁻⁸⁶; and (3) the sensory component of the speech disorder is addressed by retraining sensory perception of normal loudness (self-monitoring) and internal cueing (self-generating normal loudness).^{42,50,52} In contrast, traditional speech treatment for PD focused on multiple targets (loudness, respiration, articulation, and rate), was delivered at low dosage (once/twice a week) without high-effort training, and did not directly address sensory and cueing deficits.⁷

A previous randomized controlled trial (RCT) in PD compared LSVT LOUD voice treatment (respiratorylaryngeal target) to an alternative respiratory treatment (respiratory target only), both designed to increase vocal loudness and retrain sensory perception and internal cueing of normal loudness. Outcomes demonstrated that LSVT LOUD produced significant immediate and long-term improvements (through 24 months) in a key acoustic measure—sound pressure level (SPL), the objective correlate of loudness—supporting treatment efficacy. Furthermore, the magnitude of these changes exceeded those following treatment matched in dosage and mode of delivery, but focusing only on the respiratory system.^{87–89} A second RCT⁹⁰ compared LSVT LOUD to untreated control groups (untreated PD [UNTXPD] and healthy controls [HCs]) and demonstrated that changes in SPL following LSVT LOUD exceeded those for UNTXPD and were maintained for 6 months post-treatment.⁹⁰ Effect sizes (ESs) for SPL in these RCTs ranged from 0.65 to 2.03.^{51,87–90} We concluded from the comparison of two treatment targets, both focused on improving vocal loudness, that the target of *voice* was critical for improvements whereas the *respiratory* target alone was insufficient.^{87–89}

Following LSVT LOUD, improvements were also documented in objective measures of articulation,^{19,20,91} rate,⁸⁷ intonation,⁸⁹ aerodynamics,⁹² and perceptual measures of speech intelligibility^{41,87} and voice quality,⁹ as well as measures of swallowing⁹³ and facial expression.⁹⁴ These findings suggest that driving amplitude through a single treatment target of *voice* may optimize treatment efficiency through engagement of biomechanical and neurophysiologic linkages between the vocal and articulatory subsystems.^{95,96}. Given that articulatory movements have been shown to influence a range of laryngeal behaviors, with some correlating strongly with vocal loudness,^{95,97–100} it could be speculated that directly targeting the articulatory subsystem in a similarly intensive manner would have an equal or greater potential for generating speech mechanism-wide improvements.

To address this, treatment for disordered *articulation* (orofacial-articulatory subsystem) was chosen as the *treatment target comparator* for the current study. Although articulation disorders are commonly observed in PD,^{20,21,25} and have been treated with modest success,^{101–103} they have not been treated intensively,^{104,105} with the goal to increase amplitude of articulatory motor output to override speech mechanism hypokinesia while retraining sensory perception and internal cueing of articulatory effort.

To dissociate the specific contributions of treatment intensity and target, the current RCT compared a treatment protocol targeting *voice* (LSVT LOUD), with a treatment protocol targeting articulation (LSVT ARTICTM), equally matched for intensive dosage and mode of delivery and contrasted with no treatment (UNTXPD). We chose not to use a sham treatment to adhere to the ethical principle of equipoise¹⁰⁶ and to avoid placing undue time and effort burden on the UNTXPD participants without the potential of therapeutic effect benefit.¹⁰⁷ Rather, the UNTXPD group represents natural progression of speech disorders in PD within the framework of scheduled trial visits and medical treatment. This study responds to the need to establish relative efficacy of speech treatments for PD^{108,109} and follows CONSORT reporting guidelines for behavioral RCTs.^{110,111}

Outcomes were measured at 1 and 7 months. The primary outcome reflects amplitude change measured using SPL. The secondary outcome reflects functional change measured by the participant-reported Modified Communication Effectiveness Index (CETI-M).

The following are bidirectional hypotheses, a conservative approach which allows for the possibility of differences in either direction:

Hypothesis 1: There is a significant difference at baseline between the combined group of all PD participants and HC participants regarding SPL and CETI-M.

Hypothesis 2: There are significant differences among LSVT LOUD, LSVT ARTIC, and UNTXPD regarding changes in SPL over 7 months.

Hypothesis 3: There are significant differences among LSVT LOUD, LSVT ARTIC, and UNTXPD regarding changes in CETI-M over 7 months.

Materials and Methods

Trial Design

The design was an unblinded RCT in PD participants using two behavioral speech treatments relative to untreated PD controls. Clinicians administering treatment could not be blinded; participants were aware that they were receiving one of two possible treatments, but specific treatment names (LSVT LOUD, LSVT ARTIC) were never disclosed. UNTXPD were offered complementary treatment poststudy.

Speech data were collected at the National Center for Voice and Speech-Denver, an affiliate of the University of Colorado-Boulder (UCB). Additional screening/inclusion and demographic data were collected from neurology and otolaryngology offices in Denver, and the radiology department of the University of Colorado Health Sciences Center-Denver (UCHSC).

Participants

PD patients were recruited from outpatient clinics, support groups, and physicians. HCs were recruited through senior centers and service organizations. All participants (aged 45-85 years) were eligible if they had normal hearing for age and had not smoked within the preceding 4 years.¹¹² PD patients were required to be diagnosed by a neurologist, clinically stable on their antiparkinsonian medication, and within Stages I to IV on the Hoehn and Yahr scale.¹¹³ Patients were included if they had no more than mild dementia (Mini-Mental State Examination [MMSE] ≥ 25),¹¹⁴ no greater than moderate depression (Beck Depression Inventory-II [BDI-II] ≤ 24), ¹¹⁵ and any severity of speech and voice disorder (see Supporting Information). Primary exclusion criteria for patients included diagnosis of atypical PD or other neurological condition at time of screening, speech or voice disorder unrelated to PD, neurosurgical treatment, laryngeal surgery or pathology, intensive speech treatment within 2 years, LSVT LOUD at any time, or swallowing problem requiring immediate attention (see Supporting Information).

The study was approved by institutional review boards (IRBs) at UCB and the UCHSC, with written informed consent obtained from all participants; all procedures for de-identifying shared data were followed. ClinicalTrials.gov Identifier: NCT00123084.

Screening and Randomization

Initial eligibility screening occurred by telephone. Those who satisfied the phone screening (N = 106; 81 PD and 25 HC) participated in face-to-face screenings of speech, voice, hearing, depression (BDI-II), and cognition (MMSE). If this screening was successful, participants underwent videolaryngostroboscopy (Ear Nose Throat [ENT] examination) and modified barium swallow examinations for further screening^{116–118} (see Supporting Information).

Sixty-four PD participants met inclusion criteria and were randomized to LSVT LOUD, LSVT ARTIC, and UNTXPD using a ratio of 1:1:1. Twenty HC participants met inclusion criteria. Randomization used a minimization program that incorporated inclusion/exclusion criteria for each participant. A statistician generated a written allocation from the program, which was forwarded to the treating clinician (assigned according to availability) to enroll the participant (Fig. 1). All participants were compensated for their time.

Treating Speech Clinicians

Speech treatments were administered by three speech clinicians specializing in treating PD and certified in LSVT LOUD treatment delivery. The principal investigators and these clinicians developed and extensively piloted LSVT ARTIC.^{119–121} Clinicians followed established protocols for both treatments, provided the same encouragement and positive reinforcement during treatment, and conferred frequently to ensure treatment fidelity. All clinicians were compliant with IRB requirements and trained according to the University's required standards of clinical research.^{122,123}

Treatments

LSVT LOUD and LSVT ARTIC are PD-specific, neuroplasticity-principled, standardized protocols, matched on all key variables (intensive dosage, high-effort exercises, amplitude rescaling, and sensory retraining) and differing only in treatment target (Table 1).

Control of Bias

Clinicians were made aware that they could impart bias in this unblinded trial and focused their effort to deliver treatments with equipoise¹²⁴ and reported they were equally invested in both treatments. In posttreatment interviews, participants were asked their perception of whether their treatment was effective.¹²⁵

One and 7-month data collection followed scripted protocols, and interview and experimental data were collected



FIG. 1. CONSORT diagram outlining the flow of participants through the trial. PD-Parkinson's disease; HC-Healthy Control; BDI-II Beck Depression Inventory-II; MMSE-Mini Mental Status Exam; ENT-Ear Nose Throat examination.

by trained research staff or clinicians. No clinician collected post-treatment data from a participant he or she treated.

Outcomes

The primary outcome of SPL in reading and spontaneous speech is an objective, acoustic measure with established reliability in studies of PD.⁸ SPL would be expected to change as a result of driving increased amplitude of motor output across the speech mechanism through vocal or articulatory effort. The secondary outcome was a participant-reported measure of communicative effectiveness (CETI-M), which has demonstrated significant correlation with intelligibility¹²⁶ and voice handicap,¹²⁷ with established reliability for PD^{127,128} (see Supporting Information). For both measures, the unit of analysis was change from baseline.

Data Collection and Analysis

SPL

Data were collected by research staff on 2 separate days (days 1 and 2) within 1 week to allow assessment

| | LSVT LOUD | LSVT ARTIC |
|---|--|---|
| Focus of treatment | Loudness | Enunciation |
| Dosage | Increased movement amplitude directed predominately to respiratory-laryngeal systems Individual treatment session of 1 hour, 4 consecutive days per week over a 4-week period | Increased movement amplitude directed predominately to orofacial-articulatory system Individual treatment session of 1 hour, 4 consecutive days per week over a 4-week period |
| Effort Daily Exercises | Push for maximum participant perceived effort | Push for maximum participant perceived effort |
| minutes 1 to 30 Maximum sustained movements completing multiple repetitions of tasks, minutes 1 to 12 | Sustain the vowel "ah" in a good-quality, loud voice, for as long as possible | Sustain articulatory placement for "p" (lips closed) and "t" (tongue tip behind upper teeth) with Iowa Oral Pressure Instrument (IOPI); hold for 4 second for each trial Repeat as many as possible in 5-second trials, each of the following single consonants with precise articulation (voiceless productions): /p/ /t/ /k/ |
| Directional movements completing multiple repetitions of tasks, minutes 13 to 23 | Say the vowel "ah" in a good-quality, loud voice gliding high in pitch; hold for 5 seconds Say the vowel "ah" in a good-quality, loud voice gliding low in pitch; hold for 5 seconds | Repeat as many as possible in 5-second trials, each of the following minimal pair combinations with precise articulation: /t-k/, /n-g/, "oo-ee," and "oo-ah" |
| Functional movements, minutes 24 to 30 | Participant reads 10 self-generated phrases he/she says daily in functional living (e.g., "Good morning") using the same effort and loudness as he/she did during the maximum sustained movements exercise | Participant reads 10 self-generated phrases he/she says daily in functional living (e.g., "Good morning") using the same effort for enunciation as he/she did during the maximum sustained movements exercise |
| Hierarchy Exercises, | | |
| Purpose | Train rescaled vocal loudness achieved in the Daily Exercises into context-specific and variable speaking activities | Train rescaled enunciation achieved in the Daily Exercises into context-specific and variable speaking activities |
| Method | Incorporate multiple repetitions of reading and conversation tasks with a focus on vocal loudness | Incorporate multiple repetitions of reading and conversation tasks with a focus on enunciate |
| Tasks | Tasks increase in length of utterance and difficulty across weeks, progressing from words to phrases to sentences to reading to conversation, and can be tailored to each participant's goals (e.g., communicate at work or with caregivers) and interests (e.g., speak on topics of golf, cooking) | Tasks increase in length of utterance and difficulty across weeks, progressing from words to phrases to sentences to reading to conversation, and can be tailored to each participant's goals (e.g., communicate at work or with caregivers) and interests (e.g., speak on topics of golf, cooking) |
| Assign Homework Exercises to be completed outside of the therapy room, minutes 56 to 60 | | |
| Duration and repetitions on treatment days (4 days/ week) | Subset of the Daily Exercises and Hierarchy Exercises; 10 minutes, performed once per day | Subset of the Daily Exercises and Hierarchy Exercises; 10 minutes, performed once per day |
| Duration and repetitions on nontreatment days (3 days/ week) | Subset of the Daily Exercises and Hierarchy Exercises; 15 minutes, performed twice per day | Subset of the Daily Exercises and Hierarchy Exercises; 15 minutes, performed twice per day |
| Conversational Carryover Assignment | Participant is to use the louder voice practiced in exercises in a real-world communication situation | Participant is to use enunciated speech practiced in exercises in a real-world communication situation |
| Difficulty level | Matched to the level of the hierarchy where the participant is in treatment | Matched to the level of the hierarchy where the participant is in treatment |
| Shaping techniques Purpose and approach | Train vocal loudness that is healthy and within normal limits (i.e., no unwanted vocal strain) through use of modeling ("do what I do") or tactile/visual cues | Train speech enunciation that is within normal limits (i.e., no excessive movements) through use of modeling ("do what I do") or tactile/visual cues |
| Sensory calibration | Focus attention on how it feels and sounds to talk with increased vocal loudness (self-monitoring) and to internally cue (self-generate) new loudness effort in speech | Focus attention on how it feels and sounds to talk with increased enunciation (self-monitoring) and to internally cue (self-generate) new enunciation effort in speech |

TABLE 1. Comparison of LSVT LOUD and LSVT ARTIC speech therapy for PD

(Continues)

| Table I. Continued | Table | 1. | Continued |
|--------------------|-------|----|-----------|
|--------------------|-------|----|-----------|

| | LSVT LOUD | LSVT ARTIC | | |
|--|--|---|--|--|
| Focus of treatment | Loudness | Enunciation | | |
| Objective and subjective clinical data collected during each treatment | Measures of duration, frequency, and sound pressure level | Measures of oral pressure and precise articulatory productions | | |
| session | Documentation of percentage of cueing required to implement vocal loudness strategy Observations of perceptual voice quality Participant's self-reported comments about successful use of the improved loudness in daily communication Participant self-reported perceived effort | Documentation of percentage of cueing required to implement enunciation strategy Observations of perceptual speech intelligibility Participant's self-reported comments about successful use of the improved enunciation in daily communication Participant self-reported perceived effort | | |

Both therapies are standardized with respect to intensive dosage. Effort in LSVT LOUD and LSVT ARTIC are based on the participant's self-perceived effort during treatment tasks, on a scale of 1 to 10, with 10 being highest perceived effort.⁸⁷

of test-retest reliability at baseline, 1, and 7-month time periods. Collection times were kept consistent for each participant. Participants were not cued to modify their speech (i.e., use loud or enunciate strategies) as per scripted protocol. Participants (1) read two standard passages (Rainbow and Hunter),^{129,130} (2) described a picture (Picture),¹³¹ (3) spoke about a self-selected topic for 1 minute (Monologue), (4) described an intensely happy event for 90 seconds (Happy Day),¹³² and (5) sustained six "ah" phonations for as long as possible (Ah). Data were collected in an IAC sound-treated booth (IAC Acoustics, North Aurora, IL) using a headmounted AKG 420 condenser microphone positioned 8 cm from the lips. The microphone was calibrated to a Type I Sound Level Meter (SLM; Bruel and Kjaer 2238)¹³³ to extract decibels (dB) of SPL.

The cleaned (e.g., edited of coughs), calibrated microphone signals were submitted to SPL analysis using a fully automated, custom-built software program designed to emulate a Type I SLM resulting in a mean and standard deviation (SD) value for dB SPL at a reference distance of 30 cm.

CETI-M

CETI-M was collected at each time period with a minimum of 50% repeated for reliability purposes.¹³⁴

Participants rated their communicative effectiveness in 10 situations (e.g., "speaking to someone in a noisy environment") on a 10-point Likert scale, where 1 =not effective and 10 = extremely effective (see Supporting Information).

Sample Size

Based on previous studies, $^{87-90}$ the effect size for SPL was expected to be large (approximately 1). For an overall alpha = 0.05 considering three multiple comparisons (Bonferroni), two-tailed tests, 20 participants were required per group to yield 80% power.¹³⁵

Statistical Analysis

Descriptive statistics for SPL are presented as means and SDs, for CETI-M as medians, interquartile ranges, and ranges, and for sex as relative frequencies. Before addressing hypotheses, test-retest reliability (days 1 and 2) for SPL and CETI-M was derived using intraclass correlation coefficients (ICCs) for baseline, 1-month, and 7-month measures.

For Hypothesis 1 (baseline), to compare the combined group of all PD participants to HCs, *t*-tests for independent samples were used for SPL and a Wilcoxon rank-sum test was used for CETI-M.

For Hypothesis 2 (SPL), one-way repeated-measures analyses of variance with Duncan's multiple-range tests were performed. Multiple imputation was not applied, but mixed-effects models were used to support bivariate results with the assumption that the very few missing data values were missing completely at random.

For Hypothesis 3 (CETI-M), if any of the 10 CETI-M items were missing, nonmissing items were prorated to obtain totals. Kruskal-Wallis tests incorporated Bonferroni procedures to evaluate differences among PD groups for changes to 1 and 7 months.

Within-group changes from baseline were tested using mixed-effects models for SPL and Wilcoxon signed-rank tests for CETI-M. ESs and 95% confidence intervals (CIs) were derived using Cohen's d for SPL. Analyses adhered to the intention-to-treat principle. All tests of hypotheses were two-tailed, with an overall α -level of 0.05. No subgroup analyses were conducted, no interim analysis was planned, and there was no data safety monitoring board.

Results

Of 106 individuals screened (81 PD, 25 HC), 64 PD and 20 HCs were enrolled (Fig. 1). Group assignments and descriptive statistics for baseline demographic characteristics and levodopa equivalence¹³⁶ are presented in

Table 2. There were no significant differences among the three PD treatment groups for these characteristics (P > 0.05), and between the combined group of all PD participants and HC group for age and sex (P = 0.28; P = 0.75). No participants experienced serious adverse effects.

Reliability

ICCs for test-retest reliability (days 1 and 2) were >0.80 at baseline, 1 and 7 months for both SPL and CETI-M. To avoid bias attributed to practice effects, day 1 measures were chosen for statistical analysis.

Hypothesis 1

The combined group of all PD participants had significantly lower (less optimal) SPL values at baseline than the HC group (Table 2) for Rainbow (P = 0.04), Hunter (P = 0.01), Conversation (P = 0.04), and Happy Day (P = 0.03); differences were not significant for Picture (P = 0.06) and Ah (P = 0.18). Median baseline CETI-M for the PD combined group differed significantly from HCs (P < 0.0001), with PD participants having less optimal scores.

Hypothesis 2

Descriptive statistics for between and within-group changes in SPL from baseline to 1 and 7 months for each PD group, and corresponding ESs and 95% CIs are presented in Table 3.

Between-group increases from baseline to 1 and 7 months in SPL following LSVT LOUD were significantly larger than those for both LSVT ARTIC and UNTXPD for Rainbow, Hunter, Picture, Monologue, Happy Day, and Ah (P < 0.05; P < 0.05). There were no significant differences between LSVT ARTIC and UNTXPD (P > 0.05). Within-group changes from baseline to 1 and 7 months were significant for all tasks following LSVT LOUD (P < 0.05). Within-group changes in SPL for LSVT ARTIC were significant at 1 month for all tasks (P < 0.05) except for Happy Day (P = 0.65) and not significant for any task at 7 months (P > 0.09). Within-group changes in SPL at 1 and 7 months for UNTXPD were not significant for any task (P > 0.15). SPL Monologue data are plotted in Figure 2A.

Hypothesis 3

Descriptive statistics for between and within-group changes in CETI-M from baseline to 1 and 7 months for each PD group are presented in Table 4.

There were significant between-group differences for CETI-M change from baseline to 1 month indicating greater improvement for LSVT LOUD and LSVT ARTIC relative to UNTXPD (P = 0.02; P = 0.02). Between-group differences for CETI-M change from baseline to 7 months

for LSVT LOUD and LSVT ARTIC versus UNTXPD groups were not significant (P = 0.08).

Within-group changes in CETI-M scores from baseline to 1 month were significant for LSVT LOUD (P = 0.0005) and LSVT ARTIC (P = 0.0001), with no significant changes in the UNTXPD group (P = 0.65). Within-group CETI-M changes from baseline to 7 months were significant for LSVT LOUD (P = 0.0011), but not for LSVT ARTIC (P = 0.27) or UNTXPD (P = 0.73). CETI-M data are plotted in Figure 2B.

At the end of the study, LSVT LOUD and LSVT ARTIC participants were asked, "Out of all the treatment groups you could have been randomized into, do you feel you had the best treatment?"¹²⁵ Positive responses were comparable between groups (100% vs. 95%, respectively).

Discussion

This RCT evaluated the impact of two speech treatments for PD matched in intensive dosage, differing in speech target: *voice* (respiratory-laryngeal/LSVT LOUD) versus *articulation* (orofacial-articulatory/LSVT ARTIC), relative to untreated controls.

Regarding Hypothesis 1, significant differences in SPL and CETI-M were found at baseline between the combined group of all PD participants and the HC group. The finding that SPL was significantly lower in the PD than the HC group is consistent with previous reports of reduced loudness in PD^{8,14,23} and reduced communicative effectiveness and participation.⁸

Regarding Hypothesis 2, there were significant differences among LSVT LOUD, LSVT ARTIC, and UNTXPD in SPL over 7 months. Increases in SPL were significantly greater for the *voice* versus *articulation* target and were maintained through 7 months only for the target of *voice*. This magnitude of increase in SPL is both statistically and clinically significant, having an impact on improving audibility^{8,137} in a population that struggles with "weak voice."^{1,5–7,14,39} The absence of adverse side effects is consistent with previous studies demonstrating that increased SPL can be accompanied by improved vocal fold closure and voice quality without inducing laryngeal hyperfunction post LSVT LOUD.^{9,138}

These findings extend our previous research^{87–90} by including both an alternative treatment target and untreated control groups. The current findings, that improvements following *voice* treatment exceeded those following *articulation* (ES = 1.53) and no treatment (ES = 2.19), together with those of two earlier RCTs^{89,90} (ES = 0.65–2.03), build solid evidence for the efficacy of intensive treatment targeting *voice* for improving speech in PD.

| R | А | М | Т | G | ΕТ | ΑL |
|-----|-----|---|---|----------|----|----|
| ••• | ••• | | • | <u> </u> | | |

| Demographics and Other Variables (Weights for Minimization) | PD Treated With LSVT | PD Treated With LSVT ABTIC (N = 20) | UNTXPD (N = 22) | All PD Combined (N = 64) | HCs (N = 20) |
|---|-------------------------|---|--------------------|--------------------------------|------------------|
| | (| | () | () | (|
| Males (0.5) | 15 | 15 | 14 | 4.4 | 10 |
| N 0/_ | 10 | 15 75 0 | 14 | 44 68.8 | 13 |
| Females (0.5) | 00.2 | 75.0 | 03.0 | 00.0 | 05.0 |
| N | 7 | 5 | 8 | 20 | 7 |
| % | 31.8 | 25.0 | 36.4 | 31.3 | 35.0 |
| Age (0.5) | | | | | |
| Mean | 68 | 68 | 64 | 67 | 64 |
| SD | 8 | 9 | 9 | 9 | 9 |
| Range | 49,85 | 53,85 | 48,81 | 48,85 | 46,80 |
| Years since diagnosis (0.5) | - | - | - | _ | |
| Mean | 5 | 5 | 5 | 5 | — |
| SD Panga | 0 25 21 | 0.20 | 4 | 0 21 | |
| Nallyt Hoopp and Vabr stage with medication (0.5) | 0.25,51 | 0,20 | 0.5,14 | 0,31 | — |
| Mean | 2 | 2 | 2 | 2 | _ |
| SD | 0.6 | 07 | 0.5 | 0.6 | _ |
| Bange | 1.3 | 1.4 | 1.3 | 1.4 | _ |
| Swallow (1) | .,0 | .,. | .,0 | .,. | |
| Mean | 1 | 1 | 0.9 | 1 | 0.3 |
| SD | 1 | 1 | 0.6 | 1 | 0.6 |
| Range | 0,3 | 0,3 | 0,2 | 0,3 | 0,2 |
| Voice (1) | | | | | |
| Mean | 2 | 2 | 2 | 2 | 0.7 |
| SD | 0.7 | 0.8 | 0.7 | 0.7 | 0.6 |
| Range | 1,3 | 1,3 | 1,3 | 1,3 | 0,2 |
| Articulation (1) | | | | | |
| Mean | 0.7 | 0.8 | 0.8 | 0.8 | 0.1 |
| SU | 0.7 | 0.5 | 0.9 | 0.7 | 0.2 |
| Range | 0,3 | 0,2 | 0,3 | 0,3 | 0,1 |
| DDI-II (U.23) Mean | 10 | 0 | Q | 0 | 2 |
| SD | 10 | 5 | 0 | 5 | 3 |
| Bange | 1 20 | 0 20 | 1 21 | 0.21 | 0 13 |
| MMSE (0.25) | 1,20 | 0,20 | •,=• | 0,21 | 0,10 |
| Mean | 29 | 29 | 29 | 29 | 29 |
| SD | 1 | 1 | 0.8 | 1 | 0.9 |
| Range | 26,30 | 27,30 | 27,30 | 26,30 | 27,30 |
| Levodopa equivalent medication, (mg/d) | | | | | |
| Mean | 689 | 718 | 726 | 711 | _ |
| SD | 486 | 510 | 404 | 460 | — |
| Range | 30,2064 | 0,1773 | 100,1400 | 0,2064 | |
| Baseline SPL Measures by Task, | PD Treated With | PD Treated With | UNTXPD | All PD | HCs |
| (dB at 30 cm) | LSVT LOUD | LSVT ARTIC | (N = 22) | Combined | (N = 20) |
| | (N = 22) | (N = 20) | | (N = 64) | |
| Rainbow | | | | | |
| Mean | 70.5 | 71.9 | 70.8 | 71.0 | 72.6 |
| SD | 3.1 | 2.9 | 3.1 | 3.1 | 2.1 |
| Range | 64.5,76.6 | 66.8,76.9 | 65.1,77.1 | 64.5,77.1 | 68.6,75.5 |
| nuniti Mean | 70.2 | 71 5 | 70 6 | 70 Q | 70 7 |
| SD | 70.0 2 0 | 11.0 2.0 | 70.0 31 | 70.0 3 1 | 12.1 |
| Bange | 64 4 75 Q | 5.2 65 2 70 0 | 65 0 76 1 | 64 4 70 N | ۲.0 68 7 76 ۹ |
| Picture | 0.0,1 | 00.2,10.0 | 00.0,70.1 | 07.7,70.0 | 00.7,70.0 |
| Mean | 69.5 | 70.4 | 69.6 | 69.8 | 71.3 |
| SD | 3.2 | 3.5 | 3.0 | 3.2 | 2.4 |
| Range | 62.5,73.8 | 65.2,79.5 | 64.7,75.3 | 62.5,79.5 | 66.5,76.3 |
| | - , | | - , | , | ,. 510 |

TABLE 2. Demographic, baseline clinical characteristics, baseline SPL across tasks and baseline CETI-M for participants by group

(Continues)

| Demographics and Other Variables (Weights for Minimization) | PD Treated With LSVT LOUD (N = 22) | PD Treated With LSVT ARTIC (N = 20) | UNTXPD (N = 22) | All PD Combined (N = 64) | HCs (N = 20) |
|---|--|---|--------------------|--------------------------------|-----------------|
| Conversation | | | | | |
| Mean | 69.7 | 70.4 | 69.9 | 70.0 | 71.5 |
| SD | 3.0 | 3.4 | 3.1 | 3.1 | 2.2 |
| Range | 64.1,73.8 | 65.0,79.9 | 64.7,75.3 | 64.1,79.9 | 66.9,76.2 |
| Нарру | | | | | |
| Mean | 70.3 | 71.2 | 70.8 | 70.7 | 72.5 |
| SD | 2.9 | 3.8 | 2.9 | 3.2 | 2.8 |
| Range | 64.9,75.1 | 64.6,81.2 | 65.3,76.7 | 64.6,81.2 | 65.8,77.6 |
| Ah | | | | | |
| Mean | 75.0 | 73.2 | 76.3 | 74.9 | 76.6 |
| SD | 5.4 | 4.7 | 5.1 | 5.2 | 4.6 |
| Range | 62.8,83.9 | 65.5,81.3 | 67.4,87.1 | 62.8,87.1 | 67.6,82.9 |
| Baseline total CETI-M | | | | | |
| Median | 64 | 58 | 61 | 62 | 84 |
| Range | 26,100 | 28,86 | 14,98 | 14,100 | 62,100 |
| IQR ¹ | 57,77 | 48,75 | 54,73 | 53,76 | 76,90 |

Table 2. Continued

Voice and Articulation were measured on a scale from 0 to 5, where 0 = no disorder and 5 = severe disorder (see Supporting Information). Randomization ratio was 1:1:1 performed using a minimization program based on variables and weights chosen a priori.

Rainbow, Hunter, Picture, Conversation, Happy, and Ah refer to speech tasks described in Materials and Methods.

There were significant differences between HCs and combined PD groups for depression, swallowing, voice, and articulation (P < 0.0001), with PD participants exhibiting less optimal characteristics. Significance levels of differences for SPL are presented for Hypothesis 2 in the Results section.

Total CETI-M score was derived by adding all item scores ranging from 10 (never effective in any situation) to 100 (extremely effective in all situations) and prorated as per Materials and Methods.

¹ IQR is the interquartile range from the 25th to the 75th percentile. Median for changes is the median of within-subject changes from baseline to subsequent time point.

One explanation for these findings comes from our PET imaging studies. In addition to observing treatment-related modification of neural systems involved in vocalization, a rightward shift of activation in speech motor control and prefrontal and auditory areas^{139,140} has been observed post-LSVT LOUD and not post-LSVT ARTIC.^{141,142}

Regarding Hypothesis 3, there were significant differences among LSVT LOUD, LSVT ARTIC, and UNTXPD in CETI-M immediately post-treatment with relative improvements for both intensive treatment targets. Improvements in CETI-M were maintained through 7 months only for LSVT LOUD, suggesting that greater SPL improvement from the voice target may impact self-rated communication situations such as speaking in noise.¹²⁸

Limitations and Clinical Implications

Although findings from this third RCT reduce the critical gap in our knowledge of speech treatment in PD, there are limitations.

The RCT was powered based upon previous evidence to detect an effect in the primary outcome SPL. Although the resulting sample size is consistent with behavioral treatment studies,¹⁴³ it precluded using multivariate statistics. However, we did find significant differences in between- and within-group changes over time. Additionally, although we used multiple comparison procedures for the power analysis and to control for inflation of type 1 errors for three pair-wise comparisons, we did not adjust for multiple outcomes for SPL.

Whereas PD participants ranged in disease severity and age, generally they had mild-moderate disease. Nevertheless, it was demonstrated that their speech characteristics and self-evaluation of communicative effectiveness were significantly worse than those of the HC group at baseline, consistent with reports of speech disorders occurring early and throughout the course of PD.^{1,6,7,14,39} Treating speech disorders in mildmoderate PD may help maintain functional communication and quality of life,^{4,5,31,39} which is in accord with rehabilitation literature supporting ongoing exercise in mild-moderate PD.^{85,144}

The ability to generalize these findings to patients with more advanced disease is supported by our finding of no significant associations between time postdiagnosis (ranging 0–31 years) and within-group treatment-related changes in SPL through 7 months (P = 0.30). This suggests that regardless of disease severity, participants showed similar treatment-related improvements within-group. This observation is consistent with our previous RCTs^{87–90} reporting successful outcomes following LSVT LOUD with more advanced patients including those with atypical PD and post-DBS-STN.^{145–148}

Given that these results emerged from an RCT framework, generalization to "real-world" situations may be questioned. However, positive outcomes of similar

| | | | | Change Fr | om Baseline | to 1 month | | | |
|-----------|---------------------|-----------------------|---------------------|-----------------------|---------------------|-----------------------|----------------------|---|----------------------|
| | LSVT LOUD (N = 22) | | LSVT ARTIC (N = 20) | | UNTXPD (N = 22) | | LSVT-L V. UNTXD | LSVT-A V. UNTXD | LSVT-L V. LSVT-A |
| | Mean | SD | Mean | SD | Mean | SD | BES | BES BES | |
| | [WES ¹] | [WESCl ²] | [WES ¹] | [WESCI ²] | [WES ¹] | [WESCI ²] | [BESCI] ³ | ESCIJ ³ [BESCI] ³ | |
| Rainbow | 6.3 | 3.1 | 1.3 | 2.2 | 0.5 | 1.7 | 2.32 | 0.41 | 1.84 |
| Hunter | [2.13] | [1.55, 2.59] | [0.62] | [0.14, 1.10] | [0.31] | [-0.14, 0.77] | [1.52, 3.04] | [-0.21, 1.01] | [1.09, 2.53] |
| | 6.4 | 2.9 | 1.4 | 2.2 | 0.4 | 1.7 | 2.52 | 0.51 | 1.93 |
| | [2.31] | [1.71, 2.81] | [0.67] | [0.18, 1.15] | [0.25] | [-0.20, 0.70] | [1.69, 3.26] | [-0.11_1.12] | [1.16, 2.62] |
| Picture | 5.3 [2.06] | 2.7 [1.47, 2.56] | 1.4 [0.53] | 2.8 [0.05, 0.98] | 0.2 | [-0.33, 0.55] | 2.18 [1.40, 2.89] | 0.51 [-0.12, 1.11] | 1.42 |
| Monologue | 5.2 | 3.2 | 1.0 | 2.2 | 0.3 | 1.6 | 1.94 | 0.37 | 1.52 |
| | [1.70] | [1.17, 2.14] | [0.48] | [0.00, 0.95] | [0.20] | [–0.25, 0.65] | [1.19, 2.61] | [–0.25, 0.97] | [0.8, 2.17] |
| Нарру | 3.7 | 2.6 | -0.0 | 2.5 | -0.7 | 1.8 | 1.97 | 0.32 | 1.45 |
| | [1.49] | [0.96, 1.96] | [0.00] | [–0.46, 0.46] | [-0.41] | [–0.87, 0.04] | [1.22, 2.65] | [–0.30, 0.92] | [0.75, 2.10] |
| Ah | 9.3 | 5.2 | 2.0 | 4.2 | -0.2 | 3.2 | 2.20 | 0.59 | 1.54 |
| | [1.88] | [1.34, 2.26] | [0.50] | [0.02, 0.94] | [-0.07] | [–0.50, 0.37] | [1.42, 2.90] | [–0.04, 1.20] | [0.82, 2.19] |
| | | | | Change Fro | om Baseline t | o 7 Months | | | |
| | LSVT L | OUD (N = 21) | LSVT A | RTIC (N = 19) | UNTX | PD (N = 20) | LSVT-L V. UNTXD | LSVT-A V. UNTXD | LSVT-L V. LSVT-A |
| Rainbow | 3.9 | 2.3 | 0.7 | 2.2 | 0.3 | 1.9 | 1.70 | 0.19 | 1.42 |
| | [1.78] | [1.20, 2.32] | [0.34] | [-0.15, 0.81] | [0.17] | [–0.30, 0.64] | [0.96, 2.38] | [0.44, 0.82] | [0.70, 2.08] |
| Hunter | 3.8 [1.90] | 2.1 [1.29, 2.49] | 0.8 | 2.2 [-0.10, 0.86] | 0.3 [0.14] | 2.2 [-0.32, 0.61] | 1.63 [0.89, 2.30] | 0.23 [-0.41, 0.85] | 1.40 [0.68, 2.06] |
| Picture | 3.2 | 2.3 | 0.7 | 2.3 | 0.4 | 2.1 | 1.27 | 0.14 | 1.09 |
| | [1.46] | [0.92, 1.97] | [0.32] | [–0.16, 0.80] | [0.20] | [–0.27, 0.67] | [0.58, 1.91] | [–0.49, 0.76] | [0.40, 1.73] |
| Monologue | 2.9 | 1.8 | 0.6 | 1.8 | 0.5 | 1.8 | 1.33 | 0.06 | 1.28 |
| | [1.69] | [1.09, 2.33] | [0.35] | [–0.13, 0.85] | [0.29] | [–0.27, 0.67] | [0.63, 1.98] | [–0.57, 0.68] | [0.57, 1.93] |
| Нарру | 1.9 | 2.0 | -0.7 | 2.5 | -0.8 | 2.5 | 1.20 | 0.04 | 1.16 |
| | [1.00] | [0.50, 1.50] | [-0.30] | [–0.77, 0.19] | [-0.34] | [-0.18, 0.77] | [0.51, 1.84] | [–0.59, 0.67] | [0.46, 1.80] |
| An | 8.2 | 4.4 | 0.8 | 3.4 | -0.4 | 4.7 | 1.89 | 0.29 | 1.87 |
| | [1.96] | [1.40, 2.36] | [0.25] | [–0.23, 0.71] | [-0.09] | [–0.80, 0.13] | [1.12, 2.59] | [–0.35, 0.92] | [1.09, 2.57] |

TABLE 3. Descriptive statistics for changes in dB SPL at 30 cm from baseline to 1 and 7 months, ESs, and corresponding 95% Cls for all speech tasks by PD group and pair-wise group comparisons

¹ WES is the within group change effect size using Cohen's *d*.

² WESCI is the 95% confidence interval for the within-group change effect size from Cohen's *d*.

³ BES is the between-group effect size using Cohen's *d* and corresponding 95% confidence intervals [BESCI] for differences; *P* values from mixed-effects model for differences in trends across groups were significant for all tasks at *P* < 0.0001.

magnitude have been reported following LSVT LOUD by independent researchers globally^{149–157} and by thousands of clinicians worldwide¹⁵⁸ trained in LSVT LOUD for implementation in clinical practice.^{5,159}

We did not use a sham treatment to control the effect of differential attention.¹⁶⁰ However, given the limitations of shams as appropriate comparators in behavioral treatment studies¹⁰⁷ and because our RCT was designed to compare two treatments matched in attention, we determined that an untreated control group provided a more useful contrast.

Because this is a behavioral intervention trial, neither clinicians providing treatment nor participants could be blinded. However, great care was taken to evaluate reliability, ensure equipoise, implement standardized training, minimize bias in data collection and analysis, and maintain independence between treating clinicians and those recording data. The finding that participants in both treatment groups perceived they received the most effective treatment supports that treatment delivery was similar across the two approaches and that related attempts to minimize bias were successful.

The choice of the primary outcome of SPL may have been biased inherently towards the *voice* treatment group. However, previous studies of stimulating *articulation*^{23,161} (versus treating) have documented an immediate increase in SPL. The current study is the first to intensively treat *articulatory* effort and measure its impact on SPL and communicative effectiveness. Although there were no between-group improvements in SPL for LSVT ARTIC at 1 or 7 months, there was a small, but significant, within-group change at 1 month



FIG. 2. (A) Means and SDs for dB of SPL at 30 cm for LSVT LOUD, LSVT ARTIC, and UNTXPD at baseline, 1, and 7 months. The monologue task was plotted as most representative of spontaneous speech. (B) Medians and interquartile ranges from the 25th to the 75th percentile for the CETI-M scaled 0 to 100 for LSVT LOUD, LSVT ARTIC, and UNTXPD at baseline, 1, and 7 months.

suggesting an effect on articulatory/vocal linkages,^{95,161} supporting the selection of *articulation* as an appropriate treatment target comparator.

TABLE 4. Descriptive statistics for changes in CETI-M from baseline to 1 and 7 months

| CETI-M | PD Treated With LSVT LOUD | PD Treated With LSVT ARTIC | UNTXPD |
|---|--|---|---|
| Change from baseline to 1 month Median ¹ Range IQR ² Change from baseline to 7 months Median ¹ Range IQR ¹ | (n = 22) 13 -12,36 0,21 (n = 21) 8 -18,31 2,15 | (n = 20) 9 -4,39 3,23 (n = 19) 1 -12,24 -3,7 | $\begin{array}{c} (n=22)\\ 1\\ -16,23\\ -10,9\\ (n=20)\\ 4.5\\ -23,20\\ -10,11 \end{array}$ |

Total CETI-M score was derived by adding all item scores ranging from 10 (never effective in any situation) to 100 (extremely effective in all situations) and prorated as per Materials and Methods.

¹ Median for changes is the median of within-group subject changes from baseline to subsequent time point.

² IQR is the interquartile range from the 25th to the 75th percentile.

Ongoing analyses of speech intelligibility,¹⁶² voice quality,¹⁶³ swallowing,¹⁶⁴ facial expression,¹⁶⁵ and imaging (PET)^{141,142} in these participants will further clarify mechanisms of response to these speech treatment targets in PD.

Conclusions

This RCT contributes to closing the knowledge gap on effective speech treatments for PD.^{108,109} It provides additional support for *voice* (LSVT LOUD) as an efficacious target when delivered intensively in the treatment of speech in PD with outcomes sustained through 7 months for both objective (SPL) and participantreported (CETI-M) measures. These findings suggest that the treatment target of *voice* may be uniquely beneficial in improving speech production in PD. •

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Supporting Data

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