

Original Article

Personalized Biofeedback on Inhaler Adherence and Technique by Community Pharmacists: A Cluster Randomized Clinical Trial

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What is already known about this topic? Adherence to inhaled therapy is poor, but interventions to address inhaler adherence and technique are difficult to implement in primary care as educators lack tools to provide objective feedback to patients.

What does this article add to our knowledge? In a community pharmacy setting, adherence was significantly improved when pharmacists gave each patient personalized biofeedback relating to their timing and technique of inhaler use.

How does this study impact current management guidelines? The development of digital-enabled inhalers will empower community pharmacists to address inhaler adherence.

BACKGROUND: Guidelines recommend that patients treated with inhalers receive adherence counseling and device training. Digital technologies that assess both inhaler adherence and technique have been developed. Using these technologies community pharmacists, who have regular contact with patients, are well placed to deliver personalized inhaler education. **OBJECTIVE:** To determine the impact of a pharmacist intervention, informed by digital technology, on inhaler technique and adherence of patients with asthma in the community.

METHODS: A cluster randomized, parallel-group, multisite pharmacy study was conducted over 6 months. All study groups had an electronic device (inhaler compliance assessment device) attached to their maintenance inhaler. A *biofeedback group* received personalized inhaler training informed by data recorded by the device. The *demonstration group* received inhaler training, by physical demonstration with a placebo inhaler. The *control group* received usual care. The primary outcome was inhaler adherence, which was classified as "actual adherence" and expressed as the proportion of expected drug accumulation if

adherence and technique had been perfect. Secondary outcomes were quality-of-life scores as measured by the St George's Respiratory Questionnaire, symptoms, and exacerbations.

RESULTS: A total of 152 participants ($n = 74$ biofeedback, $n = 56$ demonstration, and $n = 22$ control) were recruited. Asthma was the predominant condition among participants ($n = 83$), with chronic obstructive pulmonary disease ($n = 55$) and asthma/chronic obstructive pulmonary disease overlap also reported ($n = 8$). In intention-to-treat analysis, adherence in the biofeedback group during month 2 was 62%, 18% higher (95% CI, 6 to 30) than that in the demonstration group ($P = .004$) and 24% higher (95% CI, 9 to 40) than that in the control group ($P = .003$). During month 6, adherence was 14% higher (95% CI, -1 to 30; $P = .07$) in the biofeedback group than in the demonstration group and 31% higher (95% CI, 13 to 48; $P = .001$) than in the control group. At the end of the study, the biofeedback group had a sustained fall in St George's Respiratory Questionnaire from baseline, -6.1 (95% CI, -9 to -0.4; $P = .04$) and had significantly improved daily respiratory symptoms.

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Conflicts of interest: S. O'Dwyer, is an employee of Boots Pharmaceuticals Ireland. G. Greene and R. W. Costello have a patent on assessing adherence and R. W. Costello has consultancy and grant support from GlaxoSmithKline, Aerogen, TEVA, and Novartis. R. Reilly and R. W. Costello have a patent on the use of acoustics to assess inhaler use and a patent on assessing adherence. The rest of the authors declare that they have no relevant conflicts of interest.

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*Abbreviations used**COPD- Chronic obstructive pulmonary disease**INCA- Inhaler compliance assessment device**ITT- Intention-to-treat*

CONCLUSIONS: Community pharmacist–delivered inhaler training informed by a digital technology improved adherence and health status. © 2019 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;■:■–■)

Key words: Asthma; Inhaler; Adherence; COPD; Clinical outcomes; Randomized clinical trial; Community pharmacy

INTRODUCTION

Inhaled medications are the mainstays of treatment for people with asthma and chronic obstructive pulmonary disease (COPD). However, poor adherence and difficulties in the mastery and maintenance of inhaler technique are common.¹ Poor adherence and inhaler technique are associated with sub-optimal clinical outcomes as well as direct costs, such as medication waste, and increased use of other health care resources,² and indirect costs, such as productive days lost, arising from poor symptom control.³ In recognition of the importance of this problem, guidelines for the management of both COPD and asthma emphasize that all those involved in the care of patients with these conditions provide regular and repeated inhaler training.^{4,5}

Inhaler adherence and technique training takes time, requires trust between the educator and patient, and requires specialist knowledge because of the proliferation of new inhaler devices. One group of health care professionals, community pharmacists, have regular contact with patients and so are ideally placed to deliver inhaler training.^{6,7} Previous intervention studies in community pharmacies have shown improved inhaler technique, adherence rates, and therapeutic outcomes for people with asthma and COPD.^{8–19} However, although the added value of pharmacists in inhaler adherence and inhaler technique is evidenced in clinical research, the translation of these findings into practice is poor, with one of the key factors being the difficulty in assessing daily adherence and confidence in teaching inhaler technique.²⁰

Electronic monitoring is a novel concept in inhaler use assessment, which to date has not been taken up on a regular basis; it provides an objective measure of medication use and hence is considered to be the criterion-standard method to assess adherence.²¹ The inhaler compliance assessment (INCA) device is a unique validated electronic audio recording device that, when attached to an inhaler, records inhaler use, both the frequency and timing of use as well as inhaler technique.²² From an analysis of the date and time data, adherence can be determined, whereas from analysis of the audio features inhaler technique can be determined.^{23–29} Using these data, a health care professional such as a pharmacist is resourced with objective and accurate, real-life data about that individual's adherence and inhaler use. Equipped with this information the pharmacist can then deliver a person-specific biofeedback to that individual that targets the most critical deficit in inhaler use.

In this study, we investigated whether the delivery of a personalized intervention by community pharmacists, using biofeedback from the INCA technology, could improve adherence and clinical outcomes in practice. To test this hypothesis, we conducted a cluster randomized controlled clinical trial in a nationwide chain of community pharmacies in the Republic of Ireland. Adherence and clinical outcomes were compared between 3 groups: a biofeedback group that received personalized feedback using the INCA technology; a demonstration group that received repeated demonstration of inhaler technique and advice on adherence—the current criterion standard for care; and a pure control group that received usual care only. Randomization was performed on the level of the pharmacy (ie, cluster randomization). Cluster randomization has the advantage of reducing the burden placed on pharmacists, because each pharmacist is required to implement only a single intervention. This also reduces the risk of contamination between study arms, because each participating pharmacist is trained to deliver only 1 of the 3 intervention types.

METHODS

This was a prospective multicenter, cluster randomized open-label clinical trial, conducted between February 2014 and December 2016. The trial was registered as NCT02203266 on ClinicalTrials.gov, and the protocol has been published.³⁰ Because of an administrative error, the trial was not fully registered until July 2014. The study was approved by the Royal College of Surgeons in Ireland Research Ethics Committee (REC712b).

Participants

Adults 18 years and older, prescribed and presenting a new or continuing prescription salmeterol/fluticasone Diskus inhaler (Sere-tide Diskus; GlaxoSmithKline, London, UK), and who had filled at least 3 prescriptions for any medication at the recruiting pharmacy in the previous 6 months were eligible to enroll in the study. Participants were excluded from the study if they had a known sensitivity to salmeterol/fluticasone, if their physician had indicated that they would not be continuing salmeterol/fluticasone Diskus over the 6-month study period, or if they had used any investigational product or device within the 3 months before enrollment.

Study design

This was a nationwide study carried out in a chain of 77 community pharmacies operating in the Republic of Ireland. Potential participants who fulfilled the inclusion criteria and did not violate the exclusion criteria were invited to take part in the study at their pharmacy and were provided with a copy of the participant information leaflet. Voluntary informed consent was then obtained in accordance with the ICH Good Clinical Practice guidelines.

Study interventions

During the course of the study (6 months), participants received a total of 3 INCA-enabled salmeterol/fluticasone Diskus inhalers; the first was at enrollment; participants were asked to use this, as they normally would, that is, without intervention. This allowed for the collection of baseline data on adherence and inhaler technique. At the completion of the 1-month baseline data collection, biofeedback and demonstration education interventions were delivered. The next INCA-enabled salmeterol/fluticasone Diskus inhalers were given to all participants for use in the second month of the study. Over the following 3 months (months 3, 4, and 5), participants continued to

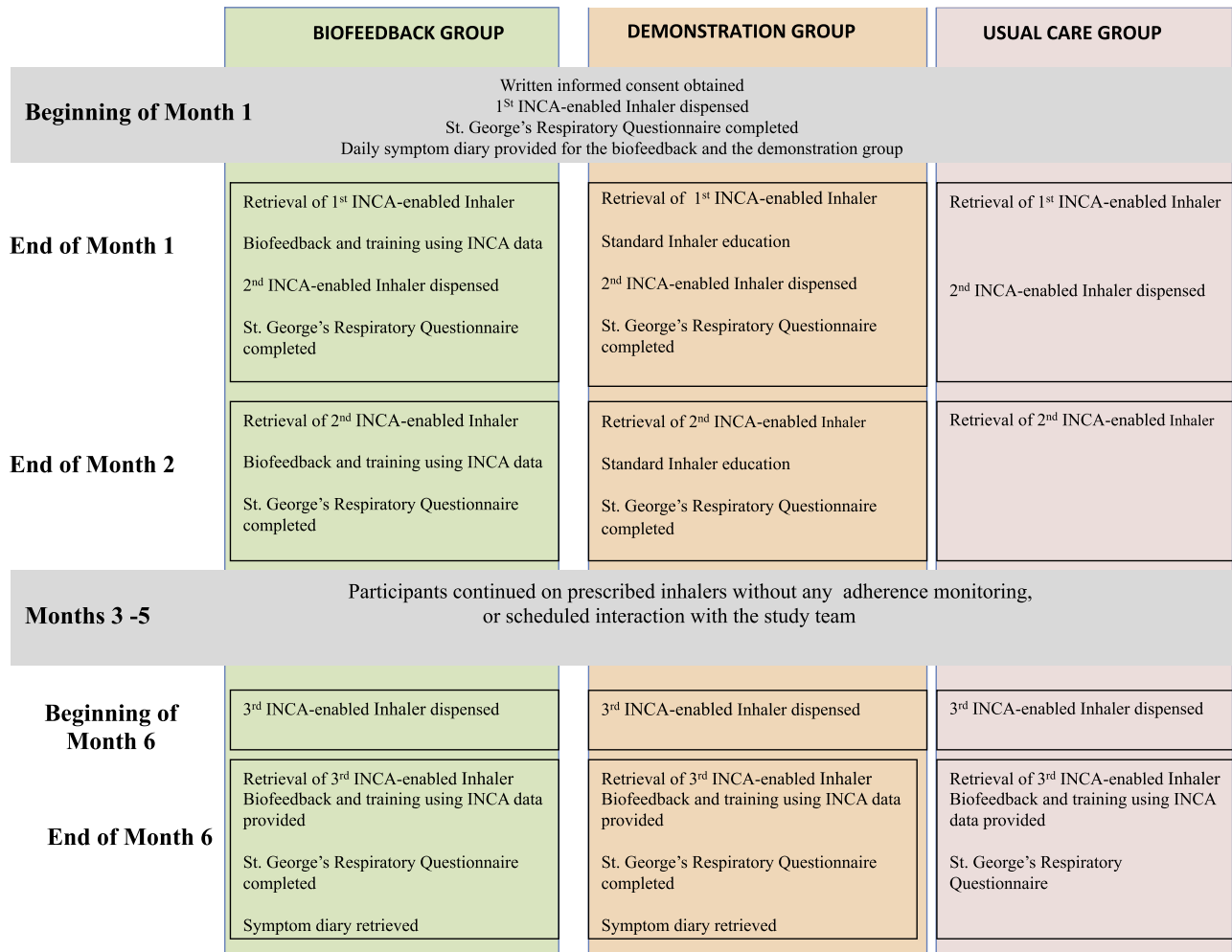


FIGURE 1. Study flow diagram.

use their usually dispensed Diskus inhaler without any adherence monitoring or further scheduled interaction with the study team. The final INCA-enabled inhaler was given to all participants during the sixth month of the study. Clinical outcomes were evaluated at the end of month 2, and at the end of month 6 (see Figure 1).

The interventions

All education interventions for the 3 groups (biofeedback, demonstration, and control) were standardized using a manual developed by the study team. Further details are outlined in the published protocol article.³⁰ Briefly, participants in the biofeedback group received 2 types of training. One focused on correcting errors observed by the pharmacist when the participant demonstrated their inhaler use in the pharmacy, and the second used personalized visual feedback about the time and technique of their inhaler use in the previous month, obtained by analysis of the data recorded to the INCA device and generation of visual graphs, which the pharmacist was able to review and discuss with the participant. Participants in the demonstration group were asked to demonstrate their inhaler use in the pharmacy, and errors were corrected using a technique checklist without any reference to, or knowledge of, the data recorded to the INCA device.³¹ The usual care control group members were dispensed the INCA-enabled inhaler as normal. The

control group received neither inhaler education nor adherence advice except if they asked for it, this was in accordance with standard care (ie, the safe supply of medicines and advice on their use).

Pharmacist training

Pharmacists delivered the intervention allocated to the pharmacy in which they practiced and received training specific to that intervention. Training consisted of one 1.5-hour face-to-face workshop with a respiratory physician, nurse specialist, and pharmacist educator/researcher where they were provided with a brief overview of the study and issues related to medication adherence and trained to provide education on inhaler technique. A distance learning study guide specific to each study arm and outlining all study-related procedures including interventions and consultation techniques to support improved adherence, where appropriate, was also completed. Throughout the study pharmacists were supported by the lead pharmacy researcher who was available via phone or email to answer any queries they had.

Data collection

On enrollment participants completed a baseline questionnaire with the pharmacist. Both the biofeedback and demonstration group participants completed the St George Respiratory Questionnaire

TABLE I. The baseline characteristics of the study participants

Characteristic	Biofeedback group (n = 74)	Demonstration group (n = 56)	Control group (n = 22)
Age (y)	54 ± 15	53 ± 15	55 ± 13
Sex: male, n (%)	31 (42)	32 (57)	11 (50)
Diagnosis, n (%)			
Asthma	39 (53)	31 (55)	13 (59)
COPD	30 (40)	21 (37)	4 (18)
ACO	3 (4)	1 (2)	4 (18)
Unknown	2 (3)	3 (6)	1 (5)
Smoking status, n (%)			
Current smoker	7 (9)	3 (6)	3 (14)
Ex-smoker	13 (18)	8 (14)	8 (36)
Never smoked	12 (16)	18 (32)	7 (32)
Unknown	42 (57)	27 (48)	4 (18)
Mean number of exacerbations in the 6 mo before enrollment	0.9 ± 1.2	1.0 ± 1.5	0.9 ± 1.4
Drug payment status,* n (%)			
Medical card	29 (39)	20 (36)	7 (32)
Drugs payment scheme	26 (35)	17 (30)	11 (50)
Private	19 (26)	19 (34)	4 (18)

ACO, Asthma-COPD overlap.

Data are presented as n (%) or mean ± SD.

*Drug payment status: *Medical card*: Patients pay a fixed prescription charge of €2 for each item up to a maximum of €20/mo per family. *Drugs payment scheme*: An individual or family will pay a maximum of €124/mo for prescription medication. *Private*: Patients are responsible for all medication costs.

(SGRQ), independent of pharmacist oversight, at each visit. Participants also recorded, in a diary provided to them on study enrollment, the presence of respiratory symptoms including cough, breathlessness, wheeze, and nocturnal symptoms each day over the 6-month period. The control group completed the SGRQ at the start and end of the study. This group did not complete a symptom diary.

Outcomes

The primary outcome was the between-group difference in actual inhaler adherence during month 2 and during month 6 on the patient. The adherence measures were calculated from analysis of the data recorded to the INCA device. Briefly, data were uploaded to a server and analyzed automatically and accuracy confirmed by 2 independent assessors, as previously described (κ coefficient of agreement was 0.64).³² The following measures of adherence were calculated, using an area under the curve measurement: *attempted adherence*, which refers to the intentional initiation of medication use at the correct time. Because the time intervals between doses vary, doses more than 2 and less than 4 half-lives apart were given a weighted score between 0.75 and 0.25 and if the time interval was 4 or more half-lives, a score of 0 was given and repeated until the next dose was recorded. *Technique adherence* was defined as episodes of inhaler use in which the user made an error that critically affected medication delivery and that could be determined by analysis of audio data. These were exhalation into the mouthpiece before inhalation, failure to prime the inhaler, failure to inhale, or low peak inspiratory flow rate (<35 L/min).²⁶ We have previously demonstrated that these are critical errors because they significantly impact medication delivery.^{24,25,33-35} “Actual adherence” is “attempted adherence” less “technique adherence” adjusted for occasions when removing an erroneous dose increased the time interval between doses. The actual adherence was then expressed as the proportion of

expected cumulative drug exposure that would be achieved if adherence and technique had been perfect. This method of calculating adherence has been demonstrated to be superior to other published methods of calculating adherence for patients with both asthma and COPD.^{22,32}

Secondary outcomes

Attempted and technique adherence,³² the proportion of study participants with adherence greater than or equal to 80% and adherence less than 50%, and quality of life, using the SGRQ, were measured for all 3 groups. The presence of cough, breathlessness, and nighttime symptoms was recorded daily in a diary by the biofeedback and demonstration groups. Exacerbations were assessed by quantifying episodes when either oral corticosteroids and/or antibiotics usually indicated for respiratory infection were dispensed. Reliever use was not reliably reported, and peak expiratory flow was measured using an electronic meter but because of a very high rate of device failures, these data were not included for analysis.

Sample size

Previously, using the INCA technology, we identified that actual adherence among patients recruited from primary care was 47% ± 33%.^{36,37} A preintervention actual adherence of 50% ± 35% at the end of the first month was therefore assumed. The primary end point was the rate of actual adherence postintervention, and comparison between adherence rates in the intervention (biofeedback) and comparator (demonstration) groups was to be conducted at the end of months 1, 2, and 6. The sample size was dictated by comparisons to be made between these 2 groups.

It was hypothesized that the adherence rate in the biofeedback group would improve by 20% more than in the demonstration group. Adherence in the demonstration group also had the potential to improve. Hence, an improvement of 5% was assumed in this group over the study period, giving expected rates of 75% and 55%

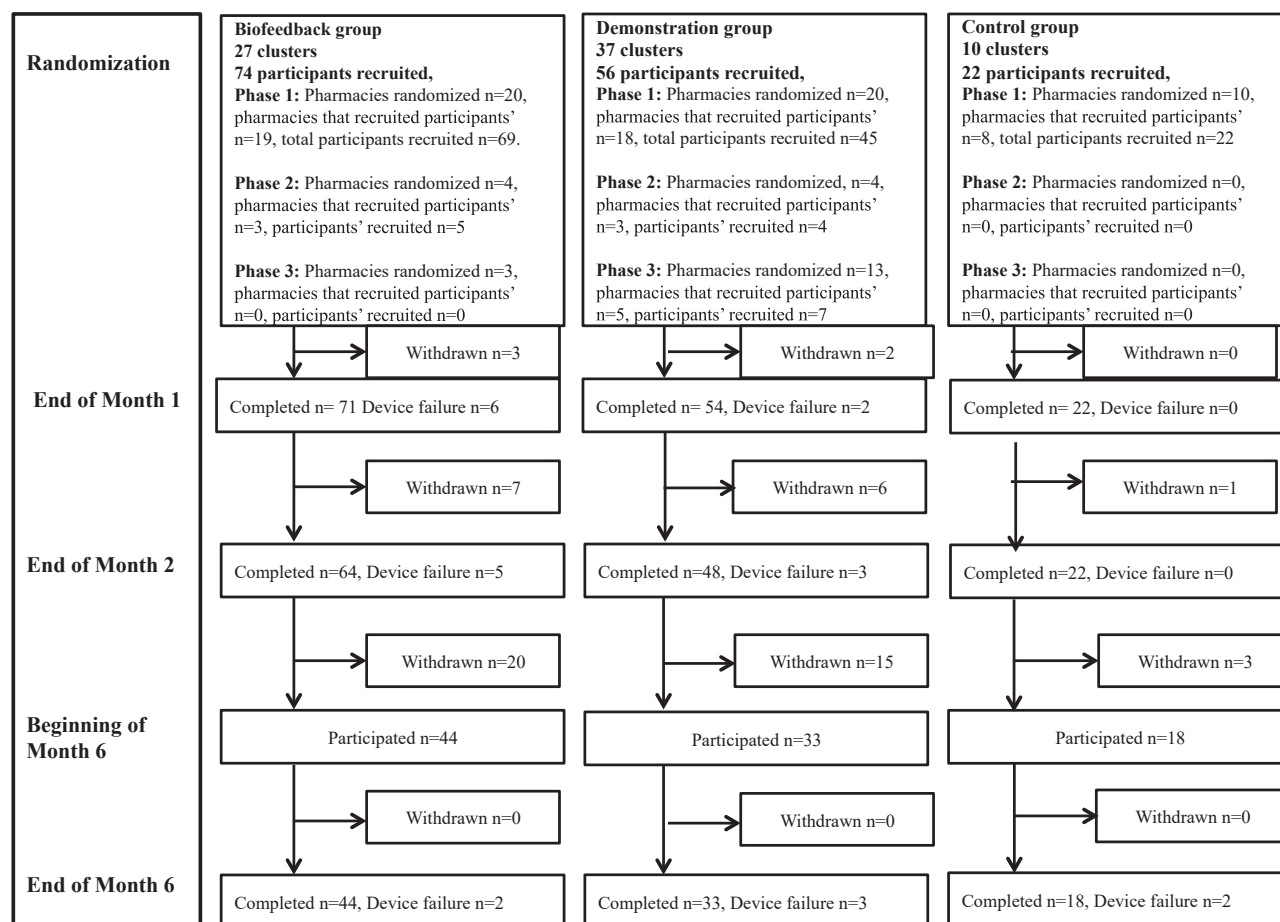


FIGURE 2. Study CONSORT diagram. Number of pharmacy sites and total number of patients in each group are listed.

in the 2 groups. An intraclass correlation coefficient of 0.025 and a loss to follow-up of 10% were assumed. With a power of 0.85 at the .05 significance level to detect a difference in actual adherence rates between the 2 groups of 20%, a sample size of 75 participants across 25 clusters in each of the groups was required.

Randomization

Pharmacies were the unit of randomization; hence, participating pharmacists were allocated to 1 of the 3 study groups (biofeedback, demonstration, or control) using a computer-generated list of random numbers, in a 1:1:0.5 ratio, from the sponsor center. Each pharmacy had a target to recruit 3 to 5 participants. Given the nature of the study, neither pharmacists nor participants could be blinded to this intervention.

Statistical analysis

Statistical analyses were conducted using Stata Statistical Software: Release 14 (StataCorp, College Station, Texas) and GraphPad Prism 7 (GraphPad Software, San Diego, Calif). All analyses were adjusted for the correlations between observations within clusters (ie, patients within pharmacies). Initially, appropriate descriptive statistics (frequencies or percentages, means, SDs) were used to describe the patient characteristics. The actual, attempted, and technique error adherence were calculated as described previously.³²

All participants who completed at least 1 month of the study were included in an intention-to-treat (ITT) analysis of the primary

outcome, the actual adherence during month 2 and month 6. A linear regression, accounting for the effects of clustering by pharmacy, was used to compare the rate of actual adherence between groups. Missing data were imputed using multiple imputation by chained linear equations with 20 imputations in Stata 14, and combined using Rubin's rules. The imputation model was fitted using all available demographic and adherence data.³⁸ A secondary per-protocol analysis of people who completed the study was also conducted.

Differences in proportions of participants achieving good actual adherence ($\geq 80\%$) as well as adherence less than 50% were analyzed using a clustered chi-square test. Features of adherence, exacerbation rate, and change in symptoms and SGRQ responses were compared using ANOVA.

RESULTS

The baseline characteristics of participants in all 3 groups are presented in Table 1.

Recruitment rates were lower than expected, and a number of recruitment phases were conducted in an effort to boost study numbers (see Figure 2 for the study flow). Because the study had extended by twice its proposed duration and because of funding constraints, recruitment to the study was stopped when 80% of the initial target population had been enrolled.

TABLE II. Adherence data

Study month	Biofeedback group	Demonstration group	Control group	Between-group difference	Biofeedback-demonstration	Biofeedback-control
				<i>P</i> value	<i>P</i> value	<i>P</i> value
Actual adherence rate						
Month 1	57.9 ± 31.6	44.3 ± 32.8	44.8 ± 32.7	.062	.045	.048
Month 2	62.8 ± 27.8	44.7 ± 33.1	38.2 ± 32.1	.0016	.004	.001
Month 6	60.8 ± 30.4	44.2 ± 30.7	33.2 ± 30.7	.07	.025	.004
Proportion with actual adherence ≥80%						
Month 1	23.4	15.69	22.73	.567	.302	.946
Month 2	37.29	19.57	10.00	.024	.048	.022
Month 6	29.27	14.29	1.00	.030	.148	.015
Proportion with actual adherence <50%						
Month 1	32.8	54.90	50.00	.049	.017	.150
Month 2	28.8	50.00	65.00	.008	.027	.004
Month 6	31.7	60.7	62.50	.023	.017	.033
Attempted adherence rate						
Month 1	73.1 ± 27.8	65.7 ± 28.1	55.3 ± 31.5	.056	.18	.028
Month 2	76.4 ± 23.0	66.5 ± 28.5	54.9 ± 30.5	.006	.059	.002
Month 6	77.7 ± 21.9	66.1 ± 25.2	52.1 ± 32.6	.027	.036	.04
Critical technique error rate						
Month 1	14.8 ± 22.9	19.0 ± 30.7	10.3 ± 16.9	.196	.37	.27
Month 2	14.7 ± 24.6	19.4 ± 30.0	22.8 ± 29.3	.354	.335	.198
Month 6	17.5 ± 26.8	21.9 ± 28.8	36.1 ± 33.0	.098	.500	.032

The actual adherence, the proportion of participants within each group with actual adherence ≥80%, the attempted adherence rate, and the critical technique error rate are shown. Data are presented as mean ± SD. The between-group difference *P* values represent results of ANOVA and χ^2 analyses accounting for the effects of cluster randomization. The table includes all available data for each month. Imputed values are not included.

Primary outcome: Rate of actual adherence at month 2 and month 6

Table II presents the data for the actual adherence for the 3 participant groups on a per-protocol basis. An ITT analysis demonstrated a significant difference in the rate of actual adherence between the biofeedback and demonstration groups at both month 2 and month 6. At month 2, the biofeedback group had a mean actual adherence that was 63%, 18% higher (95% CI, 6-30) than that of the demonstration group ($P = .004$). Despite lower than expected recruitment, based on the observed SD of 30%, the recruited sample size, and the number of clusters per group, the power to detect a 20% between-group mean difference in this primary outcome was calculated at 85%. Furthermore, the impact of feedback appears to be sustained at month 6. Despite no feedback or monitoring for the previous 3 months, adherence was 14.0% higher (95% CI, -1.4 to 29.3; $P = .07$) than in the demonstration group. However, this difference does not meet the threshold for statistical significance, likely because of the high attrition rate between months 2 and 6. There was also a significant difference in the rate of actual adherence between the biofeedback and control groups at both month 2, 25% (95% CI, 9-40; $P = .001$), and at month 6, 28% (95% CI, 13-48; $P = .004$).

When corrected for baseline differences in adherence, age, and sex between groups, adherence at month 2 in the biofeedback group was 11.5% better than that in the demonstration group (95% CI, 0.2-22.8; $P = .046$) and 17.1% better than that in the control group (95% CI, 2.7-31.5; $P = .02$) in ITT analysis. At month 6, in corrected ITT analysis adherence in the biofeedback group was 7% better than that in the demonstration group (95% CI, -9.3 to 23.3; $P = .381$), although this difference was

TABLE III. ITT between-group analysis correcting for baseline adherence

Month	Difference vs control	SE	<i>P</i> value	95% CI
Month 2				
Biofeedback	17.38	7.08	.018	3.12 to 31.70
Demonstration	6.13	6.04	.311	-7.00 to 21.46
Month 6				
Biofeedback	24.61	7.07	.002	10.07 to 38.89
Demonstration	16.59	8.42	.057	-0.53 to 34.51
Month	Difference vs biofeedback	SE	<i>P</i> value	95% CI
Month 2				
Demonstration	-11.49	5.59	.046	-22.78 to -0.21
Control	17.38	7.08	.018	-31.70 to -3.12
Month 6				
Demonstration	-7.01	7.81	.381	-23.34 to 9.33
Control	-24.61	7.07	.002	-10.07 to -38.89

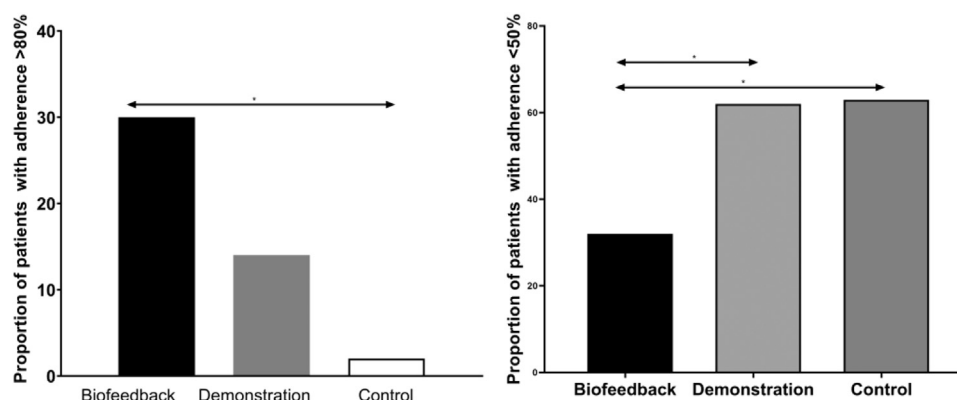
Between-group differences at months 2 and 6 estimated using ITT analysis correcting for baseline differences in adherence, age, and sex. Differences are shown using control (*top*) and biofeedback (*bottom*) groups as reference.

nonsignificant, and 24.6% better than that in the control group (95% CI, 10.2-39; $P = .002$). Between-group differences corrected for baseline adherence are presented in Table III.

In per-protocol analysis, similar differences were observed. The mean actual adherence of participants in the biofeedback group in month 2 was 63%, 18% higher (95% CI, 5.9-30.3; $P = .004$) compared with that in the demonstration group and was 16.6% higher (95% CI, 2.2-31.1; $P = .025$) at month 6.

TABLE IV. ITT analysis of proportion of patients achieving adherence greater than 80% at month 2 and month 6, correcting for baseline differences

Month	Difference vs control	SE	P value	95% CI
Month 2				
Biofeedback	0.244	0.099	.015	0.048 to 0.441
Demonstration	0.117	0.102	.256	−0.086 to 0.319
Month 6				
Biofeedback	0.268	0.099	.008	0.071 to 0.465
Demonstration	0.172	0.113	.133	0.053 to 0.397

**FIGURE 3.** The proportion of patients with adherence more than 80% (*left*) and less than 50% (*right*) during month 6 in the study is shown. There were significantly more patients with adherence more than 80% and significantly less with adherence less than 50% in the biofeedback group, compared with either the demonstration group or the control group. *Statistically significant differences ($P < .05$).**TABLE V.** ITT analysis of proportion of patients achieving adherence greater than 50% at month 2 and month 6, correcting for baseline differences

Month	Difference vs control	SE	P value	95% CI
Month 2				
Biofeedback	0.294	0.119	.015	0.058 to 0.531
Demonstration	0.158	0.141	.266	−0.124 to 0.441
Month 6				
Biofeedback	0.278	0.108	.011	0.065 to 0.492
Demonstration	0.184	0.110	.098	−0.034 to 0.403

The mean actual adherence in the biofeedback group was 24.5% higher (95% CI, 10.1–39.0; $P = .001$) compared with that in the control group at month 2, and 27.6% higher (95% CI, 9.3–45.9; $P = .004$) at month 6.

When corrected for baseline differences, adherence in the biofeedback group was 9.5% better than that in the demonstration group (95% CI, −1.7 to 20.7; $P = .09$) and 16.6% better than that in the control group (95% CI, 2.7–20.5; $P = .02$) at month 2, and 9.7% better than that in the demonstration group (95% CI, −5.6 to 25.2; $P = .21$) and 24.3% (95% CI, 11.2–37.4; $P = .001$) better than that in the control group at month 6.

Secondary outcomes

On comparing the biofeedback group with the demonstration group, significant differences in the proportion of participants

who achieved actual adherence greater than or equal to 80% were seen at month 2, and at month 6 (see [Table II](#), [Table IV](#), and [Figure 3](#)). [Tables IV](#) and [V](#) show ITT analysis of proportion of patients achieving adherence more than 80% and less than 50%, respectively, correcting for differences at baseline. The biofeedback group displays a significantly higher proportion of patients with good adherence at both month 2 and month 6. Comparing the same groups, significant differences in the proportion of participants with adherence less than 50% were seen at both month 2 and month 6. The component of inhaler use, over time by each of the study groups, presented in [Table II](#) indicates that the biofeedback group benefited by improved regularity of

timing. Technique adherence was similar in both the biofeedback and demonstration groups, which were both better than the control group.

Clinical outcomes

Quality-of-life scores. Both the biofeedback and demonstration groups had statistically significant reductions in the total SGRQ scores from month 1 to month 2, with decreases of −5.3 (95% CI, −9.2 to −1.5; $P = .01$) and −5.7 (95% CI, −9.7 to −1.8; $P = .01$), respectively. However, only the biofeedback group had a sustained reduction to month 6 (−6.1; 95% CI, −9.68 to −0.4; $P = .04$) ([Figure 4](#)).

Self-reported respiratory symptom diary. There was a decrease in daily respiratory symptom of cough, breathlessness, and nocturnal symptoms in the biofeedback group at the end of the study ([Figure 5](#)). In the first month, the patients reported that cough had reduced by 30%, to 9 days per month at the end of the study, comparing month 1 with month 6 (95% CI, −6 to −0.1; $P = .04$); this was not the case in the demonstration group, comparing month 1 with month 6 (95% CI, −7 to 1; $P = .1$). Similarly, breathlessness fell 50% to 5 days of the month in the biofeedback group (95% CI, −7 to −1.2; $P = .001$) and also fell in the demonstration group (95% CI, −5 to −0.3; $P = .02$). Nocturnal symptoms fell 66% to 1 day of the month ($P = .04$; 95% CI, −3 to −0.3) in the biofeedback group, but not in the demonstration group (95% CI, −5 to 1; $P = .1$).

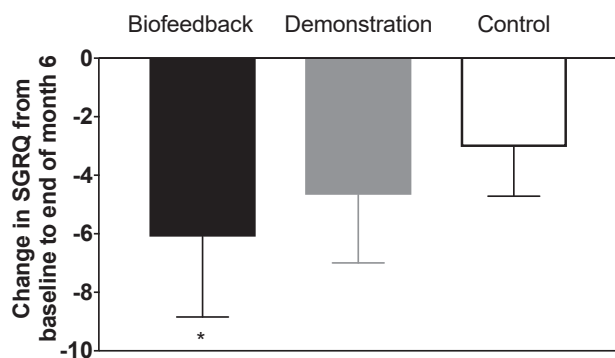


FIGURE 4. Change in SGRQ scores for each of the 3 study groups from month 1 to the end of the study. The error bars are 95% CI of the mean values. *A significant fall from the baseline values.

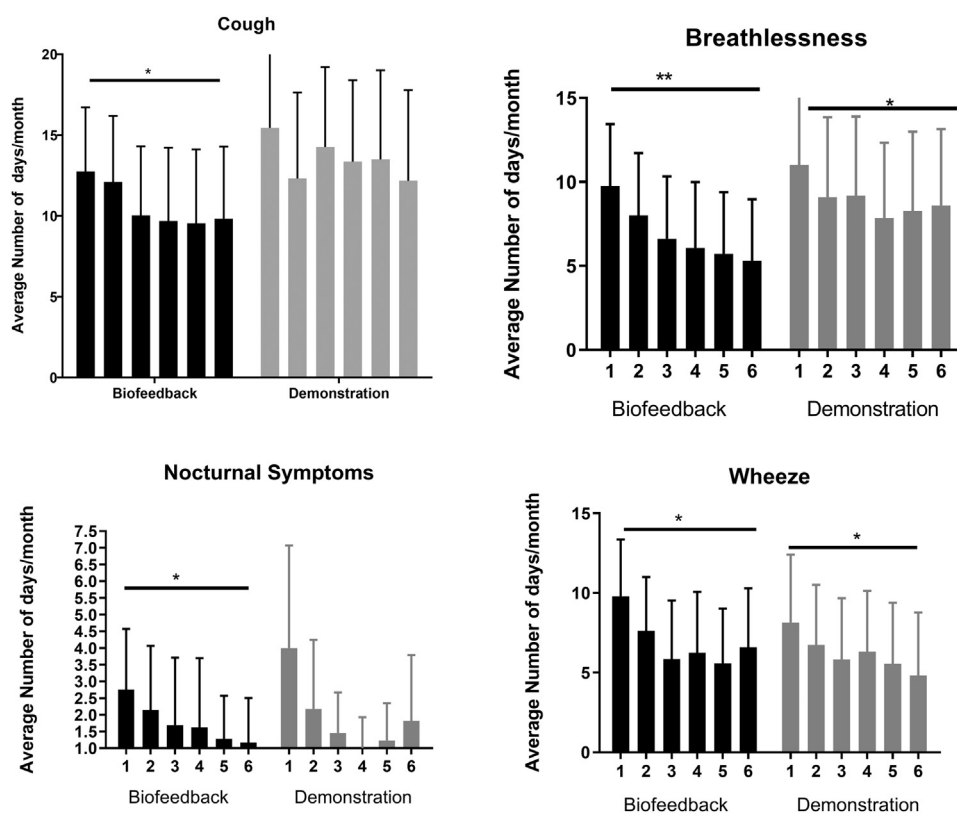


FIGURE 5. The mean monthly daily symptoms of cough, breathlessness, and nocturnal symptoms for the biofeedback and demonstration groups are shown. *Significant ($P < .05$ and ** $P < .01$) improvement compared with baseline values. Error bars are 95% CI of the mean values.

Exacerbation rate. Over the 6-month study period there was a numerically smaller number of moderate exacerbations of airway disease treated with both antibiotics and oral corticosteroids in the biofeedback group, 0.7 (95% CI, 0.4-1.1) compared with 1.1 (95% CI, 0.5-1.7) in the demonstration group and 0.9 (95% CI, 0.1-1.7) in the control group.

DISCUSSION

The results of this study demonstrate that participants attending community pharmacies who received a personalized

intervention focusing on specific issues concerning when and how they had used their inhaler achieved a sustained increase in adherence, reduced symptoms, and improved quality-of-life scores. The improvements in adherence and health status were better than those achieved either with the current “criterion-standard” method of repeated physical demonstration of inhaler use or in comparison with usual care. The results of this study indicate the potential scale of impact of delivering personalized inhaler training by community pharmacists were it to be that inhalers were fitted with a digital technology that assessed adherence and inhaler technique. However, this study also had significant limitations, which are discussed later.

Previous inhaler education studies conducted in the pharmacy setting have demonstrated improved inhaler technique, and a recent meta-analysis has demonstrated that when properly funded and integrated into care, pharmacist-led interventions can be

effective in improving adherence.¹⁹ However, past studies have used indirect measures such as checklists to score inhaler technique or medication refill rates to assess persistence of adherence.^{8-17,39} A limitation of these approaches is that even when implemented nationally, with reimbursement for the pharmacists, local pharmacists have felt ill-equipped to deliver this training, both because pharmacists report uncertainty of how to use all the inhalers available in the market and difficulty in coaching adherence.²⁰ Since these original studies were performed, a number of novel digitally enabled inhalers, including the one used in this study, that may overcome these

impediments to pharmacist-delivered inhaler training have been developed.⁴⁰⁻⁴² We designed this study to accurately explore the impact of pharmacist-delivered education at the time of dispensing using digital technology to objectively assess adherence and inhaler technique.

In designing this study we considered that a physical demonstration is currently the method promoted in clinical guidelines, but the reality is that not all patients receive training in how to use their inhaler. Therefore, usual care may not be at the standard of guideline recommendations and thus we included as one comparator group a group that had repeated demonstration of inhaler technique as a "criterion standard" of care. Although it is expected that all patients using inhalers have received education through physical demonstration, this is often not the case, or it is not delivered effectively; therefore, a pure usual care control group was also required in addition to the "criterion standard" of inhaler training by demonstration. The poor adherence and inhaler technique in the usual care group that declined during the study highlight the importance of the results of the present study for clinical practice.

Analysis of the data recorded to the device allowed us to identify which aspect of inhaler use was influenced by the interventions. Specifically, both the demonstration and biofeedback groups had similar rates of errors in inhaler handling, which were lower than in the control groups, confirming that repeated training, whether given by feedback or by visual demonstration alone, reduces inhaler errors. However, compared with the demonstration group, the biofeedback group had a significant improvement in the regularity with which the patients used the inhaler and this led to an increase in the proportion of participants with greater than or equal to 80% actual adherence in the biofeedback group. Notably, this adherence was sustained over the 6-month study period. Compared with the pure control group, the biofeedback group had better regularity of inhaler use and better inhaler technique. Hence, biofeedback on time of use and technique by community pharmacists is an effective way to deliver inhaler training.

Strengths and limitations

The study has a number of strengths. The study used a prospective cluster randomized design and enrolled community-dwelling participants and was delivered throughout the country in 74 of the total of 77 stores of a chain of community pharmacies by staff not routinely familiar with clinical trials. This means that despite being a randomized clinical trial its nature is close to that of a "real-world" study.¹⁶ We provided a scripted intervention that identifies errors in timing and technique of use by a particular patient, which provided the pharmacist with a personalized adherence intervention. However, a significant limitation of this cluster randomized design is that it can allow significant imbalances between groups to occur at baseline. Outcomes recorded at month 1 in our study showed that the biofeedback group had significantly higher adherence at baseline compared with the comparator groups. In addition, recruitment in the biofeedback group was faster than in either comparator group. Although these effects are accounted for in analysis, they may still have a negative impact on the power to detect significant differences. It seems likely that these imbalances may have resulted from differing motivations between pharmacists randomized to each group. In particular, the imbalance in recruitment rates suggests that pharmacists in the biofeedback arm were

more engaged with the study, which may in turn have influenced outcomes.

Another aspect of the study was that there was an interval of 3 months where all study procedures ceased. This allowed us to test whether the improvements in adherence were sustained. The results of the study indicate that the improvements in adherence in the biofeedback group, relative to the other groups, were sustained, a unique finding over most adherence intervention studies.

Limitations of the study include the fact that recruitment was only 80% of our original target. This was due to both suboptimal recruitment within participating pharmacies in the early stages of the study and cessation of funding at 2 years. Because this was a large study in terms of design and scale to be conducted in the community pharmacy setting, the pharmacists involved required training in research protocols and procedures, which was more intensive than originally anticipated by the study team. However, in spite of target recruitment being only 80%, both ITT and per-protocol analysis yielded significant results. An ad-hoc power calculation based on the observed primary outcomes and sample size showed that the statistical power achieved was 85%. This reflects lower than expected intracluster correlation due to the small number of patients per cluster, as well as a slightly lower than expected variance in adherence.

A more conservative ITT analysis was conducted to mitigate against the effect of attrition bias in the study. The dropout rate in the second half of the study while high is not uncommon for studies conducted in the community pharmacy setting.^{43,44} The timeline of the study, 6 months, is a relatively long time in a busy pharmacy. Participants are not used to taking part in clinical trials in the community pharmacy setting and thus the idea of making an appointment to attend study visits, even where this coincided with a visit to collect their medication, was an unfamiliar concept for many participants. A number of participants stated that their reason for withdrawing from the study was related to not having sufficient time to participate.

CONCLUSIONS

The results of this study suggest that person-specific biofeedback on the timing of inhaler use and inhaler technique leads to significant improvements in both adherence and clinical outcomes. The setting of a community pharmacy to deliver this type of personalized inhaler training intervention indicates the potential additional role that pharmacists can provide for the care of patients with respiratory conditions.

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