



Overuse of short-acting beta-agonist bronchodilators in COPD during periods of clinical stability



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ABSTRACT

Background: Overuse of short-acting beta-agonists (SABA) is described in asthma, but little is known about overuse of SABA in chronic obstructive pulmonary disease (COPD).

Methods: Prospective 3-month cohort study of patients with moderate-to-severe COPD who were provided a portable electronic inhaler sensor to monitor daily SABA use. Subjects wore a pedometer for 3 seven-day periods and were asked to complete a daily diary of symptoms and inhaler use. Overuse was defined as >8 actuations of their SABA per day while clinically stable.

Results: Among 32 participants, 15 overused their SABA inhaler at least once (mean 8.6 ± 5.0 puffs/day), and 6 overused their inhaler more than 50% of monitored days. Compared to those with no overuse, overusers had greater dyspnea (modified Medical Research Council Dyspnea Scale: 2.7 vs. 1.9, $p = 0.02$), were more likely to use home oxygen (67% vs. 29%, $p = 0.04$), and were more likely to be on maximal inhaled therapy (long-acting beta-agonist, long-acting antimuscarinic agent, and an inhaled steroid: 40% vs. 6%, $p = 0.03$), and most had completed pulmonary rehabilitation (67% vs. 0%, $p < 0.001$). However, 27% of overusers of SABA were not on guideline-concordant COPD therapy.

Conclusions: Overuse of SABA was common and associated with increased disease severity and symptoms, even though overusers were on more COPD-related inhalers and more had completed pulmonary rehabilitation. More research is needed to understand factors associated with inhaler overuse and how to improve correct inhaler use.

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1. Introduction

Adherence to inhaled medications in chronic obstructive pulmonary disease (COPD) is critical to ensure that the medications reach the airways and have their pharmacologic effect. Non-adherence may be defined as underuse, overuse, or improper use of medications [1]. Underuse of maintenance medications that should be taken regularly is common in COPD, with 62% self-reporting low adherence [2]. Similarly, improper use is also

common among patients hospitalized for COPD, with 85% misusing metered-dose inhalers (MDI), and 81% misusing Diskus[®] devices [3]. However, little is known about overuse of inhaled medications in COPD [1].

Most studies of medication adherence in obstructive lung diseases have focused on regularly scheduled maintenance medications such as inhaled corticosteroids or long-acting bronchodilators. Proper use of as needed “prn” short-acting inhaled bronchodilators, however, is also essential in the treatment of COPD. One of the most commonly used short-acting bronchodilators in the United States is the beta-agonist albuterol [4], which is typically prescribed to use 1–2 puffs either as a scheduled medication or as needed up to a maximum of four times per day, a total of 8 puffs per day. Although little data exists on overuse of short-

Abbreviations list: COPD, Chronic obstructive pulmonary disease.

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acting beta-agonists (SABA) use in COPD, data from a randomized clinical trial of asthma treatment found that 27% of patients had at least one episode of extreme beta-agonist overuse, defined as >20 puffs of budesonide-formoterol, or >32 actuations of salbutamol, in any 24 h period [5]. This raises the possibility of similar overuse in COPD.

Overuse of SABA may contribute to known adverse side-effects, including tachycardia, vasodilation, transient hypoxemia, hyperglycemia, hypokalemia, tachyarrhythmias, and tremor [4]. Although cardiovascular effects are generally considered mild, new users of beta-agonists may be at increased risk of myocardial infarction [6].

Assessment of medication adherence in COPD is generally done using self-report, which tends to overestimate adherence, and does not generally measure overuse [1]. Increasing availability of electronic inhaler monitoring devices may allow more accurate measurement of inhaler use, and identify patients with both suboptimal use and overuse [7].

The primary aim of this study was to examine whether overuse of SABA occurs during periods of clinical stability in patients with COPD, and the factors associated with overuse. In addition, we examined whether there was agreement between daily self-reported inhaler use and inhaler use detected by electronic monitoring.

2. Materials and methods

The data for this analysis were obtained from a prospective, observational cohort study of ambulatory patients with COPD at the VA Puget Sound Health Care System in Seattle, WA. This was a pilot study to examine the feasibility of measuring the timing and location of SABA inhaler use, development of worsening symptoms and exacerbations, air pollution, and physical activity patterns. This study was reviewed by the VA Puget Sound Health Care Center Institutional Review Board (ID: 00408); all subjects provided informed consent.

Eligibility criteria included: 1) COPD diagnosis, 2) FEV₁/FVC < 0.70 with a FEV₁% predicted ≤ 80%, 3) use of an SABA inhaler, 4) >10 pack-year smoking history but not currently smoking, 5) age >40, 6) a resident of King or Pierce Counties in Washington State (regions with air pollution monitors), 7) no exacerbations in the four weeks prior to enrollment. Exclusion criteria included: 1) clinical diagnosis of asthma, 2) subjects needing assistance in walking, and 3) a modified Medical Research Council (mMRC) dyspnea score of 4 (“too breathless to leave the house or breathless when dressing”).

At baseline, subjects performed spirometry and completed questionnaires including the UCSD Shortness of Breath Questionnaire (SOBQ) [8] and the Chronic Respiratory Questionnaire (CRQ), a COPD-specific health-related quality of life instrument with four subscales (Mastery, Emotional Function, Fatigue, and Dyspnea) [9]. At baseline participants also completed questionnaires regarding demographic characteristics, and alcohol use measured with the AUDIT-C [10]. Participants were classified into a combined GOLD category which is determined by an assessment of the mMRC, exacerbation history, and FEV₁ [11]. During the 3-month follow-up period, participants completed monthly interviews (either in-person or by telephone) during which they again completed the SOBQ and CRQ measures. On the monthly phone calls, the coordinator ascertained exacerbation symptoms, treatment, and health care utilization using a standardized questionnaire. A COPD exacerbation was defined as a new onset or increase in at least one respiratory symptoms (cough, sputum, wheezing, dyspnea, or chest tightness) lasting ≥2 days.

Subjects were given a waist-mounted Omron HJ-720ITC pedometer, shown to be accurate in COPD [12], to wear for three

seven-day periods corresponding roughly to each month of the study. At their final visit, subjects completed a survey indicating their satisfaction with the inhaler sensor and pedometer used in the study.

2.1. Inhaler sensor

Subjects were provided a portable electronic inhaler sensor (Propeller Health, Madison, WI) to monitor their SABA use during the course of the study [13]. With the exception of the first three subjects enrolled in the study, who used an earlier model [13], all study subjects used an inhaler sensor mounted to the top of the SABA metered dose inhaler (MDI) canister that was automatically paired wirelessly to a smartphone using secure, low-power, Bluetooth technology. Subjects were provided a smartphone by the study which was used to communicate the inhaler use information to the system servers. If the smartphone was not in physical range when an inhaler was used, the sensor stored the details in memory (which can hold approximately 3900 events) and transmitted the information when it was eventually paired with the smartphone.

Research staff tracked inhaler use and sensor battery life for each subject using a secure website. Participants in this study did not have access to the smartphone applications and websites, and could not view the data being collected. All personal health information associated with the Propeller application was encrypted according to The Health Insurance Portability and Accountability Act.

Since this was an observational, non-intervention study, all participants were instructed to continue all of their prescribed COPD medications as directed by their care provider, including their SABA inhaler. Study staff did not make any recommendations to participants on how often to use their SABA inhaler. We asked all participants about their COPD medications that they were prescribed. We abstracted prescriptions from the medical record to determine whether the SABA inhaler was prescribed “as needed” or as a “fixed dose” combined with as needed SABA.

2.2. Daily COPD diary

All subjects were given a calendar to use for the three month follow-up period and asked to record the number of inhaler actuations per day, changes in COPD symptoms, and treatment for exacerbations including medications and health care utilization. The main purpose of this diary was to improve recall during the monthly phone calls with study staff. We used the following question from the diary to examine concordance between patient self-reported and inhaler sensor measured daily inhaler use: “Since yesterday morning, how many inhalations of your rescue medication have you used?”

2.3. Statistical analysis

We analyzed days during which participants were clinically stable and did not report symptoms of a COPD exacerbation. We excluded the first and last days of the study since these were not full days of participation. This version of the inhaler sensor used in this study did not allow us to determine whether a day with no recorded puffs was a day when the participant did not use their SABA inhaler, or if it was a day when the sensor was not charged or turned off. To better understand the missing sensor data, we used data from 9 participants who completed the diary and also had missing sensor data. We found that nearly all participants self-reported using their SABA inhaler on missing sensor days, and therefore we excluded days when no puffs were recorded since imputing those days as 0 would likely be inaccurate.

Table 1
Self-reported SABA use among participants who completed the diary on days with missing sensor data.

| ID | # days missing sensor data | Self-reported SABA use for days with missing sensor data | | | |
|----|----------------------------|--|--------|-----|-----|
| | | Mean | (SD) | Min | Max |
| 1 | 31 | 4.0 | (±0.2) | 4 | 5 |
| 2 | 58 | 0.3 | (±0.7) | 0 | 3 |
| 4 | 5 | 4.0 | (±0.0) | 4 | 4 |
| 5 | 28 | 3.1 | (±0.4) | 2 | 4 |
| 6 | 44 | 2.0 | (±0.0) | 2 | 2 |
| 7 | 15 | 3.9 | (±0.5) | 2 | 4 |
| 8 | 4 | 3.0 | (±0.0) | 3 | 3 |
| 9 | 18 | 2.1 | (±0.3) | 2 | 3 |

We defined overuse of SABA inhaler by participants as >8 actuations recorded by the inhaler sensor on any non-exacerbation day during the 3 month follow-up period. We also defined a category of extreme overuses as those who used >8 puffs for >50% of

observed days during the follow-up period.

The comparison between diary vs monitor puffs per day was assessed using correlation coefficients calculated for repeated measures [14,15]. The relationships were described using two correlation coefficients, one for “between subjects” and one for “within subjects”. The “between subjects” correlation examines whether participants with a higher self-reported inhaler use also tend to have high inhaler use measured with the electronic sensor [15]. The “within subject” correlation examines whether an increase in self-reported inhaler use within the same participant is associated with increased electronically monitored inhaler use and assumes that each subject had the same slope to ensure that the correlation reflected change within, rather than between a subject [14].

3. Results

Between December 2011 and January 2014, 35 subjects enrolled in the study. All participants were prescribed albuterol as their

Table 2
Baseline characteristics, by SABA overuse during clinical stability.

| | SABA use >8 puffs per day | | p-value |
|---|---------------------------|-------------------|---------|
| | n(%) or mean(SD) | | |
| | No overuse N = 17 | Overuse N = 15 | |
| Demographics | | | |
| Age | 69.2(8.9) | 64.1(8.0) | 0.10 |
| Gender, male | 17(100%) | 14(93%) | 0.47 |
| Race, non-Caucasian | 2(12%) | 1(7%) | 0.99 |
| Lives alone | 9(53%) | 3(20%) | 0.05 |
| Married | 5(29%) | 5(33%) | 0.99 |
| Income, < \$20,000 | 7(41%) | 9(60%) | 0.26 |
| Employment, disabled | 2(12%) | 8(53%) | 0.02 |
| Education, high school graduate or less | 2(12%) | 3(20%) | 0.66 |
| Unhealthy alcohol use ^a | 5(29%) | 5(33%) | 0.99 |
| Smoking, pack-years | 66.9(35.0) | 67.2(35.2) | 0.98 |
| BMI | 30.0(4.8) | 27.8(6.5) | 0.27 |
| Enrollment season | | | |
| Winter/Spring | 6(35%) | 6(40%) | 0.99 |
| Summer/Fall | 11(65%) | 9(60%) | |
| Disease severity | | | |
| Exacerbations in the last year | 1.6(2.3) | 1.6(2.0) | 0.95 |
| FEV1 (% predicted) | 50.0(16.3) | 40.1(16.3) | 0.10 |
| Modified Medical Research Council (mMRC) dyspnea score ^b | 1.9(1.0) | 2.7(0.5) | 0.02 |
| GOLD | | | |
| A | 4(24%) | 0(0%) | 0.04 |
| B | 2(12%) | 4(27%) | |
| C | 3(18%) | 0(0%) | |
| D | 8(47%) | 11(73%) | |
| Comorbid illness | | | |
| Heart disease | 7(41%) | 4(27%) | 0.39 |
| Heart failure | 2(12%) | 1(7%) | 0.99 |
| Atrial fibrillation | 4(24%) | 0(0%) | 0.10 |
| Depression | 7(41%) | 7(47%) | 0.75 |
| Anxiety | 6(35%) | 4(27%) | 0.71 |
| Drug abuse | 1(6%) | 4(27%) | 0.16 |
| Symptoms, QOL, Physical Activity | | | |
| Shortness of Breath Questionnaire (SOBQ) ^b | 46.5(60.0) | 60.0(18.2) | 0.08 |
| Chronic Respiratory Questionnaire (CRQ) ^c | | | |
| Dyspnea domain | 4.5(1.3) | 4.1(1.2) | 0.32 |
| Fatigue domain | 4.1(1.4) | 3.7(1.3) | 0.34 |
| Emotional domain | 4.7(1.3) | 4.5(1.0) | 0.65 |
| Mastery domain | 5.1(1.2) | 4.7(1.2) | 0.29 |
| Physical Activity Scale for the Elderly (PASE) ^c | 106.8(52.1) | 99.1(47.6) | 0.67 |
| Pedometer, steps/day | 1690(1075) | 2861(2099) | 0.07 |

P-value based on Fischer's exact, χ^2 , or t-tests.

^a AUDIT-C score ≥ 3 for women and ≥ 4 for men [16–18].

^b Higher score = worse SOB; ranges mMRC 0–4, SOBQ 0–120.

^c Higher score = better health; ranges CRQ domains 1–7, PASE 0–400+.

SABA inhaler. Three subjects were removed from all analysis because they had <7 days of monitor data after excluding exacerbation days. Of the 32 remaining subjects, concurrent diary data was available for 11 subjects. On average, each participant was missing sensor data for 22.8 (± 19.1) of non-exacerbation days. To better understand whether these days were days of zero use or alternatively that the sensor was not charged or turned off, we compared self-reported SABA use for the 9 participants who completed the diary and had missing sensor days in Table 1. We found that nearly all participants reported inhaler use on their diary when the sensor data was missing.

The number of non-exacerbation days recorded with the monitor ranged from 12 to 89 per subject, for a total of 1535 days. Among all 32 participants, the daily mean inhaler use was 5.5 (± 4.5) puffs. For the 17 subjects who never overused their inhaler, the mean use was 2.7 (± 0.9) puffs per day. For the 15 who overused their inhaler at least once, mean SABA use was 8.6 (± 5.0) puffs per day; six subjects had extreme overuse (overusing their inhaler more than 50% of days) with a mean use of 13.8 (± 3.4) puffs per day.

Comparison of the baseline characteristics found that overusers were more likely to be unemployed due to disability (47% vs. 12%, $p = 0.02$), and to experience increased dyspnea (mMRC 2.7 vs. 1.9, $p = 0.02$) (Table 2).

Overusers were more likely to be GOLD categories B and D than A or C ($p = 0.04$) compared to non-overusers. Although not statistically significant, the SOBQ scores were worse in overusers (60.0 vs. 46.5, $p = 0.08$) than non-overusers. The overuse group had a higher average pedometer steps/day (2861 vs. 1690, $p = 0.07$) than the group which never overused their inhaler. Of note, there was no difference in SABA use by season for participants enrolled in winter and spring compared to summer and fall ($p = 0.99$).

With regard to how SABA prescriptions were written by their treating provider, 20% of the 15 overusers had prescriptions instructing them to use their SABA as a “fixed” dose, compared to 29% of the 17 subjects with no overuse ($p = 0.69$) (Table 3). SABA overusers were more likely to be using home oxygen (67% vs 29%,

$p = 0.04$) and be prescribed a long-acting muscarinic agent (LAMA) medication (67% vs. 35%, $p = 0.08$).

Based on GOLD guidelines, there were no differences in the proportion of overusers and non-overusers receiving guideline concurrent inhaler therapy (73% vs. 76%, $p = 0.99$), however, more overusers were on maximal inhaler therapy with combination of a LABA, a LAMA, and an inhaled steroid compared to non-overusers (40% vs. 6%, $p = 0.03$). More overusers had completed pulmonary rehabilitation, compared to those who never overused SABA (67% vs 0%, $p \leq 0.01$).

For the 11 participants who completed a daily diary recording the total number of SABA puffs per day, the number of diary days contributed by each participant ranged from 16 to 84 (Table 4).

Two subjects, #6 and #8, wrote the identical number of puffs in the diary for all days, even though their sensor recorded variability from day to day. The “within subject” correlation, which examines whether an increase in self-reported inhaler use is associated with an increase in monitored SABA use within the same individual, was $r = 0.32$ ($p < 0.001$). In Fig. 1, the self-report and sensor data series were superimposed to show inhaler use by type of monitoring and day for each subject. The sensor method range was 1–26 puffs/day; the self-report range was 0–18 puffs/days (0 puffs were reported for 5 days by subject #2).

We used the “between subjects” correlation to examine whether participants who tended to have high self-reported SABA use also had high SABA use based on the inhaler sensor. Fig. 2 plots the means from Table 3, where the circle sizes represents the number of days which each subject contributed to the analysis. The “between subjects” correlation was 0.94 ($p < 0.001$).

4. Conclusions

We found that nearly half of our sample of participants with COPD overused their SABA inhaler at least once during three months of observation, with 19% overusing their SABA more than half of the days. The overusers had evidence of more severe COPD

Table 3

COPD treatments by those who overuse SABA compared to those with no SABA overuse during periods of clinical stability.

| | n(%) or mean(sd) | | | | | |
|---|---|------------------------------------|----------------------|---|---------------------------------------|----------------------|
| | Comparison of no overuse to any overuse | | | Comparison of no overuse to some or extreme overuse | | |
| | No overuse N = 17 | Any overuse ^a N = 15 | p-value ^c | Some overuse N = 9 | Extreme overuse ^a N = 6 | p-value ^d |
| Puffs per day^b | 2.7(0.9) | 8.6(5.0) | <0.01 | 5.1(1.6) | 13.8(3.4) | <0.01 |
| SABA prescription instructions | | | | | | |
| “fixed” use | 5(29%) | 3(20%) | 0.69 | 2(22%) | 1(17%) | 0.99 |
| “as needed” (PRN) use | 12(71%) | 12(80%) | | 7(78%) | 5(83%) | |
| Medication therapy | | | | | | |
| Inhaled Corticosteroid | 8(47%) | 10(67%) | 0.26 | 5(56%) | 5(83%) | 0.40 |
| Long-acting β -agonist | 13(76%) | 9(60%) | 0.45 | 6(67%) | 3(50%) | 0.40 |
| Long-acting anticholinergic | 6(35%) | 10(67%) | 0.08 | 5(56%) | 5(83%) | 0.13 |
| Short-acting anticholinergic | 5(29%) | 3(20%) | 0.69 | 2(22%) | 1(17%) | 0.99 |
| Nebulizer, SABA | 6(35%) | 8(53%) | 0.30 | 6(67%) | 2(33%) | 0.29 |
| Nebulizer, Ipratropium | 1(6%) | 2(13%) | 0.59 | 1(11%) | 1(17%) | 0.75 |
| Theophylline | 2(12%) | 0(0%) | 0.49 | 0(0%) | 0(0%) | 0.69 |
| Chronic prednisone | 5(29%) | 2(13%) | 0.40 | 1(11%) | 1(17%) | 0.64 |
| Maximal therapy ^e | 1(6%) | 6(40%) | 0.03 | 3(33%) | 3(50%) | 0.04 |
| Guideline concurrent therapy ^f | 13(76%) | 11(73%) | 0.99 | 6(67%) | 5(83%) | 0.75 |
| Pulmonary rehabilitation | 0(0%) | 10(67%) | <0.01 | 6(67%) | 4(67%) | <0.01 |
| Home oxygen use | 5(29%) | 10(67%) | 0.04 | 7(78%) | 3(50%) | 0.06 |

P-values based on Fischer’s exact, ANOVA, or t-test.

^a Any overuse: >8 puffs for at least one day; Extreme overuse >8 puffs for >50% of monitored days.

^b Non-exacerbation days.

^c p-value comparing no overuse to any overuse.

^d p-value comparing no, some, or extreme overuse.

^e Using inhaled corticosteroid, long-acting beta-agonist, and long-acting muscarinic agent together.

^f First-line therapy, based on GOLD pocket guide.

Table 4
SABA Use during Clinical Stability: Comparison of Electronic Monitor vs Diary.

| Subject # | Days ^a | SABA puffs per day, by COPD subject | | | | Difference of means |
|------------------|-------------------|-------------------------------------|------|-------|------|---------------------|
| | | Sensor | | Diary | | |
| | | Mean | (SD) | Mean | (SD) | |
| 1 | 29 | 2.7 | 1.3 | 4.0 | 0.2 | -1.3 |
| 2 | 39 | 1.5 | 0.7 | 1.7 | 1.1 | -0.2 |
| 3 | 84 | 10.7 | 4.4 | 12.8 | 1.9 | -2.2 |
| 4 | 16 | 4.6 | 3.2 | 4.7 | 0.9 | -0.1 |
| 5 | 17 | 1.8 | 1.1 | 3.1 | 0.2 | -1.2 |
| 6 | 43 | 4.1 | 0.7 | 2.0 | 0.0 | 2.1 |
| 7 | 77 | 3.3 | 1.2 | 3.9 | 0.7 | -0.6 |
| 8 | 66 | 4.7 | 3.0 | 3.0 | 0.0 | 1.7 |
| 9 | 64 | 2.0 | 1.2 | 2.1 | 0.3 | -0.1 |
| 10 | 46 | 6.2 | 1.5 | 3.8 | 0.7 | 2.4 |
| 11 | 75 | 15.1 | 4.4 | 13.4 | 1.6 | 1.7 |
| All ^b | 556 | 5.1 | 4.7 | 5.0 | 4.1 | 0.1 |

Correlations with repeated measures (Bland & Altman, 1995).

Within subjects: $r = 0.32$ p -value = <0.001.

Between subjects: $r = 0.94$ p -value = <0.001.

^a Number of overlapping days between Diary and GPS monitor.

^b Weighted mean/SD for 11 subjects over 556 days.

than non-overusers, and were more likely to be using home oxygen therapy and to have increased dyspnea. Despite this, more than 25% of participants were not prescribed GOLD-guideline concordant COPD medications.

It is unclear why so many participants in this study were over-using their as needed short-acting bronchodilator during periods of clinical stability, and little is known in general about inhaler over-use in COPD [1]. A few studies have examined this phenomenon in asthma, and a study in New Zealand reported that 12% self-reported > 8 puffs rescue inhaler use per day at baseline [5]. A study of asthmatics in the US found that 15.8% of moderately or severely symptomatic patients overused beta-agonists [19]. Factors associated with SABA overuse in that study include male gender, those with more asthma symptoms, on more asthma medications, difficulty getting medications for asthma, and prior hospitalizations, whereas those under the care of an allergist had a reduced risk of β -agonist overuse. Our findings that overusers had more dyspnea, increased disability, and more COPD-related medications use are consistent with the findings from asthma.

The majority of overusers in our study were classified as GOLD category D, and according to the guidelines should receive a combination inhaled corticosteroid and LABA and/or a LAMA. Since only 50% of extreme overusers were on combined maximal therapy with all three medications (inhaled steroids, LABA and/or a LAMA), it is possible that maximizing therapy would help improve symptoms and decrease as-needed SABA use.

Although we did not assess inhaler technique in our study, inadequate technique may contribute to overuse if patients do not receive an adequate dose of medications with each inhalation. Up to 80% of COPD patients do not use their inhalers correctly [3], a

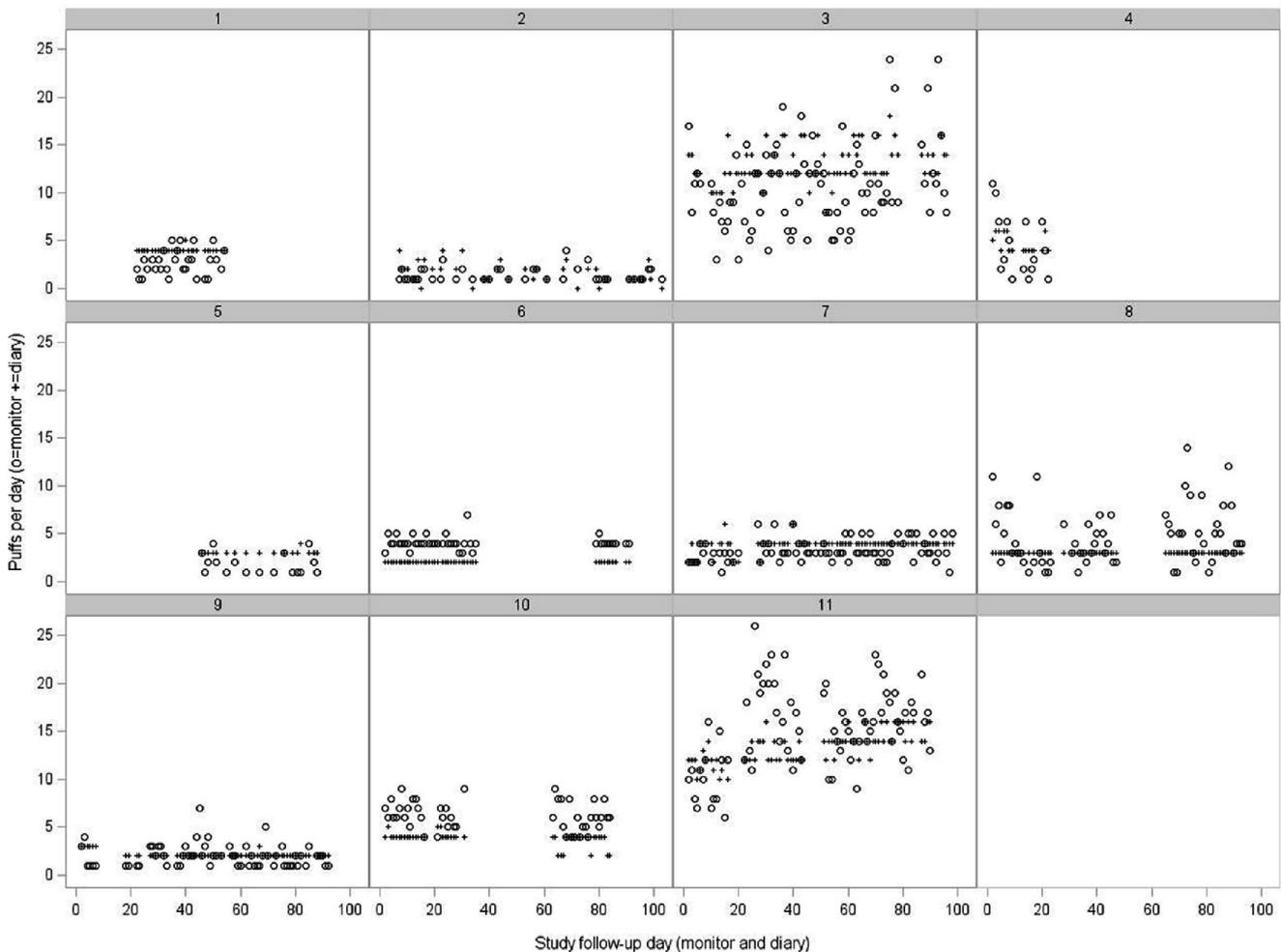


Fig. 1. SABA puffs per day for 11 subjects, Electronic Sensor vs Diary.

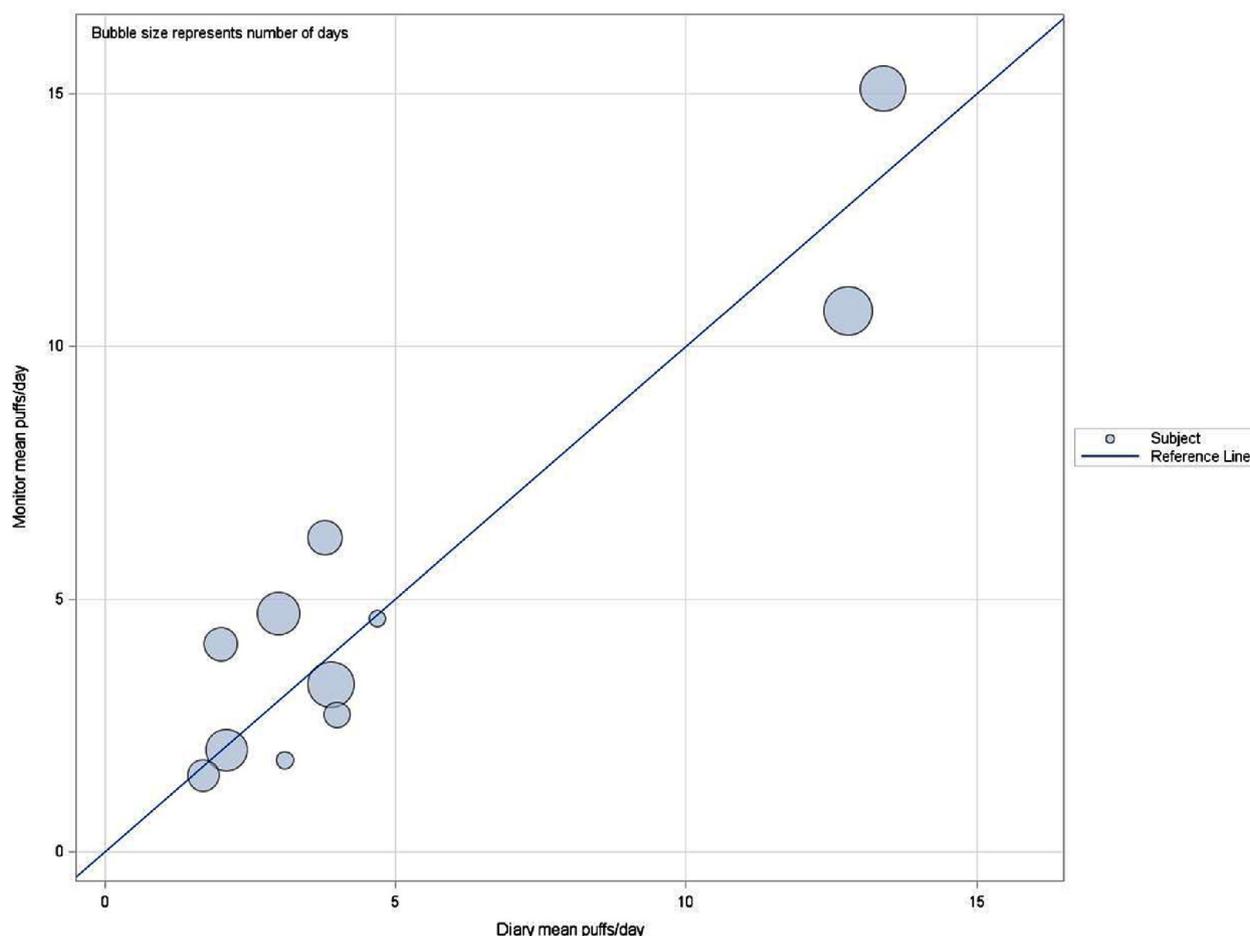


Fig. 2. Mean SABA puffs per day for 11 subjects, Electronic Sensor vs Diary.

third of patients have never received instructions on inhaler use [20], and up to 69% of patients state that their provider has never observed them using their inhalers [21]. Providers may also not be familiar with how to use the inhaler devices [22]. Although 67% of the overusers in our sample had completed a pulmonary rehabilitation program, guidelines recommend ongoing, regular assessment of inhaler technique at clinic visits and on discharge from the hospital after an exacerbation [23].

SABA medications have several side-effects including tremor, palpitations, increased blood glucose levels, decreased blood oxygen levels, hypokalemia, and may result in tachyphylaxis [4]. There may be cardiac side effects including myocardial infarction and heart failure, particularly among those with underlying cardiac disease [24]. Given the high prevalence of beta-agonist overuse in our sample, understanding why patients overuse their inhalers and efforts to decrease β -agonist overuse should be considered.

Interestingly, participants who overused their inhalers tended to walk more, despite having more severe disease. Although not statistically significant ($p = 0.07$), overusers walked 69% more steps per day than those who never overused. This raises the possibility that overusers rely on their SABA inhaler to allow them to walk more. In fact, 67% of overusers had participated in pulmonary rehabilitation, compared to 0% of those who never overused, and these patients may have learned to cope with dyspnea during activities by using their SABA inhaler more often with physical activity. Future interventions focused on maximizing maintenance inhalers or teaching breathing techniques may reduce COPD patients' dependence on SABA use. Our results differ from a study of

COPD patients in Finland where questionnaire-based measurement of physical activity and pharmacy refill-based assessment of inhaler use found that physically active patients had less cumulative SABA use [25]. The difference between their study and ours may be due to the fact that we objectively measured physical activity and inhaler use on a daily basis and were able to exclude days during which subjects experienced an exacerbation.

Only one third of these study participants completed the written diary, and it is known that pen and paper diaries may often be imprecise, including untimely and inaccurate entries [26,27]. We found that two subjects entered the same value for self-reported inhaler use for the entire observation period, further suggesting patient self-report entry is unreliable. In addition when analyzing the 11 participants with both electronic and paper diary data, we found only modest correlation ($r = 0.32$) within individual participants. The "between" subject correlation was much higher ($r = 0.94$), consistent with the fact that in general subjects with high SABA use measured with the sensor also had high use by daily diary. Therefore, to obtain reliable data, electronic monitoring is likely a better choice since the electronic sensor more accurately reflects day-to-day variation in inhaler use and is preferred by study subjects [26]. Electronically monitored medication use can also be transmitted to health care providers to help with COPD management.

This study has several potential limitations. Due to the small sample size, the results are exploratory and we were not able to develop multivariable models to examine the factors associated with overuse. These results will therefore need to be confirmed in

studies with larger sample sizes. In addition, the small sample size may have limited the statistical power to detect associations between patient characteristics and SABA overuse. The diary was encouraged to be completed daily by all patients, but was only completed by one third of the participants. It is also possible that participants did not self-report each actuation of SABA if they used more than one puff at a given time. The two early versions of the electronic inhaler sensor we used for this study did not allow us to determine whether a result of zero actuations measured by the electronic monitor was due to the patient not using the inhaler or due to the sensor not being turned on, although this issue is less likely to affect classification of overusers.

In conclusion, we found that nearly half of the COPD patients overused their as-needed SABA inhaler during the 3 month observation period and that overuse was associated with greater disease severity and more dyspnea. Although overusers had greater use of COPD medications, many were not on GOLD-guideline concurrent therapy. Future studies should address reasons for overuse, and whether interventions may reduce overuse while improving respiratory symptoms.

Conflict of interest statement

Dr. Fan reports grants from the Veterans Affairs and the National Institutes of Health during the conduct of the study. Dr. Nguyen reports grants from the National Institutes of Health and Patient Centered Outcomes Research Institute during the conduct of the study. Dr. Sumino, Dr. Magzamen, Rachel Thomas, Emily Locke, and Ina Gylys-Colwell have nothing to declare.

Disclaimer

The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States Government.

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