Effectiveness of pharmaceutical care for patients with chronic obstructive pulmonary disease (PHARMACOP): a randomized controlled trial

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Previously conducted studies indicated that community pharmacist interventions could improve pharmacotherapy in patients with chronic obstructive pulmonary disease (COPD).
- Until now, few randomized controlled trials addressing this topic have been conducted.

WHAT THIS STUDY ADDS

- This well-designed randomized controlled trial confirms that pragmatic pharmacist care programmes improve pharmacotherapeutic regimens in patients with COPD and could reduce hospitalization rates.
- Community pharmacists should be encouraged to engage in COPD care to sustain effective and safe pharmacotherapeutic treatment in patients with COPD.

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AIMS

Few well-designed randomized controlled trials have been conducted regarding the impact of community pharmacist interventions on pharmacotherapeutic monitoring of patients with chronic obstructive pulmonary disease (COPD). We assessed the effectiveness of a pharmaceutical care programme for patients with COPD.

METHODS

The pharmaceutical care for patients with COPD (PHARMACOP) trial is a single-blind 3 month randomized controlled trial, conducted in 170 community pharmacies in Belgium, enrolling patients prescribed daily COPD medication, aged ≥ 50 years and with a smoking history of ≥ 10 pack-years. A computer-generated randomization sequence allocated patients to an intervention group ($n = 371$), receiving protocol-defined pharmacist care, or a control group ($n = 363$), receiving usual pharmacist care (1:1 ratio, stratified by centre). Interventions focusing on inhalation technique and adherence to maintenance therapy were carried out at start of the trial and at 1 month follow-up. Primary outcomes were inhalation technique and medication adherence. Secondary outcomes were exacerbation rate, dyspnoea, COPD-specific and generic health status and smoking behaviour.

RESULTS

From December 2010 to April 2011, 734 patients were enrolled. Forty-two patients (5.7%) were lost to follow-up. At the end of the trial, inhalation score [mean estimated difference (Δ), 13.5%; 95% confidence interval (CI), 10.8–16.1; $P < 0.0001$] and medication adherence (Δ , 8.51%; 95% CI, 4.63–12.4; $P < 0.0001$) were significantly higher in the intervention group compared with the control group. In the intervention group, a significantly lower hospitalization rate was observed (9 vs. 35; rate ratio, 0.28; 95% CI, 0.12–0.64; $P = 0.003$). No other significant between-group differences were observed.

CONCLUSIONS

Pragmatic pharmacist care programmes improve the pharmacotherapeutic regimen in patients with COPD and could reduce hospitalization rates.

Introduction

Chronic obstructive pulmonary disease (COPD) is a highly prevalent, chronic lung disease, characterized by an airflow limitation that is not fully reversible. Although preventable and treatable, COPD remains a leading cause of morbidity, mortality and elevated healthcare costs worldwide [1]. The natural decline in lung function can be aggravated by temporary worsening of symptoms (exacerbation), which contributes substantially to the overall economic and social disease burden. Chronic obstructive pulmonary disease is projected to be the seventh leading cause of lost Disability-Adjusted Life Years in 2030 and the third leading cause of death in 2020 [1, 2].

To improve management of COPD, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) develops and updates treatment guidelines [1]. As part of the management of stable COPD, GOLD recommends close monitoring of the patient's pharmacotherapy, including the patient's adherence and inhalation technique. Indeed, in many COPD patients, inhalation technique and medication adherence have been shown to be suboptimal [3–5].

Multidisciplinary collaborations addressing these topics in primary care could be successful strategies to improve disease management [1, 6–8]. In Belgium, COPD management programmes are mainly provided in hospital settings, while community pharmacists are only occasionally involved [3, 7, 9]. However, pharmacists are well placed to engage in COPD care programmes due to their frequent patient contacts upon prescription refill and their specific medication-related expertise. Furthermore, recent research showed that mere self-management programmes are insufficient to reduce severe exacerbations [10]. Consequently, monitoring and optimizing COPD maintenance therapy in a community pharmacy to improve COPD management could be a good balance between unsupervised self-management and extensive hospital monitoring [8, 11].

In the present 3 month randomized controlled trial (RCT), we investigated the effectiveness of a community pharmacist intervention, focusing on optimal use of COPD maintenance therapy. In accordance with the GOLD guidelines about monitoring COPD pharmacotherapy, the patient's adherence and inhalation technique were chosen as primary outcomes. Given their association with suboptimal disease management [4, 5], improvements in both primary outcomes could serve as surrogate markers for enhanced effectiveness of the current pharmacotherapeutic regimen. Secondary outcomes were exacerbation rates, dyspnoea, COPD-specific and generic health status and smoking behaviour.

Methods

Design overview

The PHARMACOP (PHARMAceutical Care for COPD) trial is a 3 month randomized, controlled, parallel-group trial carried out between December 2010 and July 2011 in 170 community pharmacies, well spread throughout Belgium (Clinicaltrials.gov identifier: NCT01260389). The study protocol was approved by the Ethical Committees of the Ghent University Hospital (for Flanders) and Centre Hospitalier Universitaire de Liège (for Wallonia). All patients provided written informed consent. General practitioners (GPs) of all participants were notified about the study by letter.

Setting and participants

Patients filling a prescription for COPD medication (R03, Anatomical Therapeutic Chemical classification) at participating pharmacies were consecutively invited to participate when meeting following inclusion criteria: (i) prescription for daily COPD maintenance medication; (ii) aged 50 years or older; (iii) smoking history of at least 10 pack-years; (iv) regular visitor to the pharmacy; and (v) providing written informed consent. Patients with current asthma and analphabetic patients were excluded. Each pharmacy planned a maximum of six COPD patients to be recruited. The recruitment period ran from December 2010 to April 2011.

Eligible patients were randomized to either the control or the intervention group (1:1 ratio), stratified by centre, with each pharmacy accounting for one recruitment centre. To conceal assignments, pharmacists performed allocation through a central Web-based randomization system, created by an independent investigator. As the intervention was educational, blinding of pharmacists was not possible. Patients, however, were not told to which study group they were assigned. After randomization, pharmacy visits were planned at 1 and 3 months.

Intervention

Before initiation of the trial, all participating pharmacists received a training session addressing pathophysiology of COPD, its nonpharmacological and pharmacological treatment (GOLD guidelines), important referral criteria and study protocol. Control group patients were given usual nonprotocol-based pharmacist care. Patients in the intervention group received a protocol-defined two-session intervention; one session at the start of the study and one session at the 1 month follow-up visit (Table 1), as described in detail in the trial's protocol (Supporting Information Appendix S1). All interventions were given during one-to-one counselling sessions. The content of the sessions was set around predefined themes, but adapted according to patients' needs. Electronic medication

Table 1

Overview of pharmacist intervention

Session 1: at start of trial (t = 0) Structured patient education (verbal and written form) about: COPD pathophysiology COPD medication Dose and time of intake Inhalation technique (including physical demonstration with demonstration inhaler unit) Importance of adherence to maintenance therapy and current problems with adherence Possible side-effects Self-management (e.g. lifestyle advice) Smoking cessation (if patient was current smoker)
Session 2: 1 month follow-up (t = 1 month) Structured patient education (verbal only) about: COPD medication Inhalation technique (including physical demonstration with demonstration inhaler unit) Changes in adherence to maintenance therapy since last visit Self-management (e.g. lifestyle advice) Smoking cessation (if patient was current smoker)

Abbreviation is as follows: COPD, chronic obstructive pulmonary disease.

records, performed inhalation technique and questionnaires completed at start of the study served as the starting point. Questionnaires included questions about behavioural issues concerning adherence, health issues etc. Consequently, the focus of each counselling session could have been different. The duration of interventions was not predetermined; however, we estimated the duration to be between 15 and 25 min. To support interventions, pharmacists were provided with information leaflets on COPD, demonstration inhaler units and a list of practical solutions to specific nonadherent behaviour [12].

Primary outcomes

Inhalation technique The participating pharmacist scored inhalation technique using a checklist [eight-point checklist for metered-dose inhalers (MDIs), 10-point checklist for MDIs with spacer and seven-point checklist for dry powder inhalers (DPIs)] at the start of the study and at the 1 and 3 month follow-ups [3]. One point was assigned for each correctly performed step, and the sum score was expressed as the percentage of correct steps. Patients committing major inhalation technique errors (for MDI, failure to remove cap and/or fail to shake MDI; and for DPI, failure to load device correctly and/or fail to inhale quickly and deeply through device) were assigned a sum score of zero. For ethical reasons, major inhalation technique errors were also corrected in control group patients.

Adherence to maintenance therapy Adherence was assessed at baseline and after 3 months, using a recommended measure of administrative data, i.e. Medication Refill Adherence (MRA) [13]. For each patient, the MRA score was calculated by dividing the total days' supply by

the number of days of study participation. The number of days of study participation represents the number of days between inclusion date and the date of the second follow-up visit (after 3 months), which is ~90 days. We refer to the protocol for technical aspects regarding MRA calculations (Supporting Information Appendix S1). Patients with an MRA value ≥ 80 were considered adherent (cut-off selected based on previous use by other investigators [5, 14]).

For patients using more than one inhaled drug, only inhalation technique and MRA score of the principal maintenance therapy was checked or calculated.

Secondary outcomes

Dyspnoea The severity of dyspnoea was determined by the modified Medical Research Council (mMRC) dyspnoea scale [15]. This scale comprises five statements describing the entire range of respiratory disability from none (score 0) to almost complete incapacity (score 4). Patients completed the mMRC dyspnoea scale at baseline and after 3 months.

Chronic obstructive pulmonary disease-specific health status The COPD-specific health status was measured using the COPD Assessment Test (CAT). The CAT is a simple and reliable questionnaire for quantifying the impact of COPD on the patient's health [16, 17]. It comprises the following eight items: cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitations at home, confidence leaving home, sleep and energy. Each item is scored from 0 to 5, giving an overall value ranging from 0 to 40 (corresponding to best and worst health status in patients with COPD, respectively). Patients completed CAT at baseline and after 1 and 3 months.

Generic health status Generic health status was assessed at the start and at the end of the trial, using the EuroQol five-dimension questionnaire (EQ-5D) [18, 19]. The EQ-5D is a standardized, self-administered quality-of-life questionnaire that comprises a descriptive section and a valuation section. The descriptive section inquires the following five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, each to be scored from 1 (no problem) to 3 (extreme problems). These numbers provide a five-digit code that can be converted into a single index (utility score) through a set of weights. The index ranges from -0.18 (worst possible health status) to 1 (full health), using the weights for Belgium. The valuation section is a visual analog scale (VAS), ranging from 0 (worst possible health status) to 100 (full health), where the respondent points out his self-perceived overall quality of life.

Smoking The smoking status of patients was assessed through a questionnaire, including the following questions: 'Do you currently smoke?', 'Did you previously smoke?', 'How long do/did you smoke?' and 'How many

cigarettes do/did you smoke a day?', at the start and the end of the study.

Exacerbations Participants were asked to record occurrence and duration of moderate and severe exacerbations during the study period. We estimated the mean annual exacerbation rate by dividing the total number of exacerbations in both study groups by the total follow-up time of the considered group (i.e. weighted approach) [20]. Exacerbations were defined functionally; exacerbations requiring treatment with oral corticosteroids or antibiotics were regarded as 'moderate'. Exacerbations requiring an emergency department visit or hospitalization were regarded as 'severe' [21].

Statistical analysis

Descriptives were displayed as counts with percentages and means with standard deviations as appropriate. Minimal sample size was calculated based on the ability to simultaneously detect a 10% difference in inhalation technique score ($SD = 0.2$) and a 5% difference in MRA score ($SD = 0.2$) between the intervention group and the control group (i.e. equivalent of a 50% increase in the number of patients with perfect inhalation technique or $\geq 80\%$ adherence) with 90% power at the 5% two-sided significance level. Allowing for a dropout rate of 5%, we aimed to enrol 706 patients.

Consistent with the hypothesis, we compared the intervention group with the control group, performing an intention-to-treat analysis for all primary and secondary outcomes. Missing data were handled as missing completely at random. To test for differences in mean changes between the intervention and the control group, we used mixed-effect models for repeated measurements. For binary outcomes, we used logistic regression models. Both models included terms for baseline measurement, study group, time and time $\times$ group interaction. Least-square means and odds ratios (ORs), respectively, each with 95% confidence limits are reported. For exacerbations, a generalized linear model (i.e. Poisson regression analysis) was used as recommended in the literature [20]. Subgroup analysis was performed to investigate the consistency of the trial conclusions among different subpopulations (age, gender and region). All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA) by an academic statistician. Two-sided P values of <0.05 were considered significant.

Results

The flow of participants through the study is shown in Figure 1. In 170 community pharmacies, 1648 patients were prescreened, of whom 1067 (64.7%) were eligible. About 70% ($n = 734$) of them agreed to participate and were randomized to control ($n = 363$) or intervention ($n =$

371). Both study groups showed similar baseline characteristics (Table 2). Almost 95% of patients ($n = 692$) completed the trial, with a median follow-up time of 3 months (interquartile range, 3–3). Main reasons for dropout ($n = 42$) were hospitalization and death. There was no significant difference between the number of dropouts in both study groups.

Primary outcomes

At baseline, mean percentages of correctly performed inhalation steps were about 68% in both groups (Table 3). At the end of follow-up, the improvement in inhalation technique was significantly greater in the intervention arm compared with the control arm [mean estimated difference (Δ), 13.5%; 95% confidence interval (CI), 10.8–16.1%; $P < 0.0001$]. The intervention corrected almost all major inhalation technique errors; 15.6% of intervention group patients received an inhalation score of 0% at baseline, which was reduced to 1.2% by the end of the trial, whereas in the control group, these percentages were 11.6 and 4.6%, respectively (OR, 0.18; 95% CI, 0.06–0.53; $P = 0.002$). The increase in inhalation technique scores in the control group is predominantly caused by correction of major inhalation technique errors, as requested in the study protocol (for ethical reasons). After 3 months, the odds of obtaining an inhalation score of 100% after receiving the intervention protocol vs. no intervention was 3.03 (95% CI, 2.12–4.34; $P < 0.0001$; Table 3). Supporting Information Table S1 addresses detailed information on patients' inhalation technique errors per inhaler device and per checklist item.

Mean MRA scores were 82.7($SD = 23.9$) in the control group and 84.0($SD = 23.5$) in the intervention group at baseline. At 3 months, we detected a significantly greater improvement from baseline in the intervention group compared with the control group (Δ , 8.51; 95% CI, 4.63–12.4; $P < 0.0001$). Additionally, at 3 months, the odds to obtain an MRA score ≥ 80 in the intervention group compared with the control group was 2.15 (95% CI, 1.46–3.14; $P < 0.0001$; Table 3).

Chronic obstructive pulmonary disease-specific and generic health status

At the end of the study, the number of patients having an mMRC score <2 did not differ between groups ($P = 0.97$). Likewise, no beneficial effects of the intervention were seen in CAT scores ($P = 0.83$), EQ-5D utility scores ($P = 0.19$) or EQ-5D VAS ($P = 0.15$; Table 3). At baseline, approximately 42% of patients reported to be current smokers. After 3 months, nine (6.1%) control group patients and 15 (8.8%) intervention group patients had quit smoking. No significant between-group differences were observed ($P = 0.33$; Table 3).

Exacerbations

During the trial, 450 independent episodes of exacerbations among 302 patients were observed (Table 4). There

Figure 1

Flow of participants through the study

was no difference in the estimated annual rate of moderate exacerbations between the two treatment arms ($P = 0.14$). In contrast, there was a significantly lower number of intervention group patients reporting to have had at least one severe exacerbation during the trial compared with the control group (19 vs. 33; OR, 0.55; 95% CI, 0.31–0.98; $P = 0.038$). Fifty-three independent severe exacerbations were reported in the control arm, compared with 24 in the intervention arm, which generated a significantly lower

estimated annual severe exacerbation rate in the intervention group compared with the control group [0.27 vs. 0.61; rate ratio (RR), 0.45; 95% CI, 0.25–0.80; $P < 0.007$], mainly due to fewer hospitalizations in the intervention arm compared with the control arm (9 vs. 35). The estimated annual hospitalization rate was 72% lower in the intervention group compared with the control group (0.10 vs. 0.40; RR, 0.28; 95% CI, 0.12–0.64; $P = 0.003$). No significant difference in the rate of emergency room visits ($P = 0.20$) or in the

Table 2

Baseline characteristics

Parameter	Control group (n = 363)	Intervention group (n = 371)
Male sex [n (%)]	249 (69)	236 (64)
Age (years) [mean (SD)]	68.9 (9.7)	68.4 (9.6)
BMI [kg m ⁻² ; mean (SD)]	25.9 (4.8)	25.9 (5.4)
Smoking status [n (%)]		
Current smoker	148 (41)	170 (46)
Ex-smoker	213 (59)	200 (54)
Pack-years of current smokers [mean (SD)]	40.8 (24.4)	38.54 (22.9)
Pack-years of ex-smokers [mean (SD)]	45.7 (31.3)	46.49 (29.1)
COPD, duration [years; mean (SD)]	11.2 (9.4)	10.84 (9.7)
COPD management supervised by [n (%)]:		
GP only	134 (37)	149 (40)
Pneumologist only	46 (13)	43 (12)
Both GP and pneumologist	181 (50)	179 (48)
Influenza vaccination [n (%)]	282 (78)	296 (80)
mMRC score* [n (%)]		
mMRC = 0	99 (28)	96 (26)
mMRC = 1	124 (34)	122 (33)
mMRC = 2	61 (17)	60 (16)
mMRC = 3	44 (12)	51 (14)
mMRC = 4	32 (9)	40 (11)
CAT score† [mean (SD)]	16.4 (7.6)	16.7 (7.8)
History of exacerbations in preceding year		
One or more in preceding year [n (%)]	197 (54.3)	200 (54.1)
Moderate exacerbation rate‡ (mean)	0.47	0.50
Severe exacerbation rate‡ (mean)	0.23	0.21
COPD maintenance medication [n (%)]		
SABA	36 (10)	28 (8)
LABA	22 (6)	18 (5)
SAAC	11(3)	6 (2)
LAAC	284 (78)	260 (70)
SAAC + SABA	105 (29)	120 (32)
ICS	26 (7)	37 (10)
ICS + LABA	296 (82)	269 (73)
Triple therapy (LAAC + LABA + ICS)	236 (65)	192 (52)
Theophylline	6 (2)	10 (3)
Oral corticosteroids	12 (3)	7 (2)
Number of COPD medications [mean (SD)]	2.3 (1.0)	2.2 (1.0)

Abbreviations are as follows: BMI, body mass index; COPD, chronic obstructive pulmonary disease; GP, general practitioner; ICS, inhaled corticosteroids; LAAC, long-acting anticholinergics; LABA, long-acting β_2 -agonists; SAAC, short-acting anticholinergics; SABA, short-acting β_2 -agonists. *Scores on the modified Medical Research Council dyspnoea scale (mMRC) can range from 0 to 4, with a score of 4 indicating that a patient is too breathless to leave the house or becomes breathless when (un)dressing. †CAT: COPD Assessment Test; a higher score indicates a worse health status (range, 0–40). ‡Exacerbation rates are expressed as number per patient-year and calculated based on retrospective self-reported patient data.

duration of the hospital stay ($P = 0.84$) was seen, but rate of hospitalization days was reduced by 73% (0.87 vs. 3.51; RR, 0.27; 95% CI, 0.21–0.35; $P < 0.0001$).

Subgroup analysis

Prespecified subgroup analyses on age, gender and region were performed (Figure 2). No significant interactions between study group and any subgroup were found (pre-

determined value for interaction, $P < 0.01$). However, subgroup analyses were slightly underpowered to detect modest differences in subgroup effects if they might exist.

Discussion

In the PHARMACOP trial, we assessed the effectiveness of a protocol-based community pharmacist intervention in 734 patients with COPD. Outcomes were selected based on their association with suboptimal disease management [3–5]. The intervention significantly improved both primary outcomes, i.e. inhalation technique and medication adherence, and significantly decreased the estimated annual severe exacerbation rate. No significant differences in other health outcomes were observed.

Only few studies have investigated community pharmacist interventions to improve pharmacotherapeutic management of COPD [8, 9, 22]. None of these trials distinguished between asthma and COPD patients, although management and health outcomes for both diseases are distinct. This 3 month RCT confirms earlier indications that a pharmacist intervention can significantly improve inhalation technique [9, 22]. Moreover, our trial is the first to demonstrate the positive effects of a community pharmacist intervention on medication adherence in patients with COPD, although comparable with results from trials performed in a hospital environment and led by a clinical pharmacist [23, 24]. It is most likely that improvements are due to the pharmacist-conducted patient education about correct use of the inhalers, their therapeutic effects and possible side-effects. All intervention group patients received oral and written education along with a physical demonstration of inhalation technique, shown to be the most effective mode of instruction [9, 25]. When entering the trial, 7% of patients had never been instructed about inhalation medication and only ~30% had previously received any explanation from the pharmacist, offering a lot of room for improvement [9].

The significant decrease in severe exacerbation rate should be interpreted with caution, considering that it was a secondary outcome and the duration of the study was short. However, previous research indicated that integrated care [7], as well as clinical pharmacy interventions [23, 24], likewise prevented hospitalizations. This effect of multidisciplinary care programmes could be explained by diverse factors. Firstly, the intervention could result in enhanced self-management of the disease. Secondly, intervention patients could have perceived higher accessibility to primary healthcare professionals, prompting earlier detection and, consequently, better exacerbation management (i.e. decreased exacerbation recovery time and hospitalization risk) [26]. Hence, it is plausible that pharmaceutical care protocols diminish the high healthcare costs of severe COPD exacerbations, a presumption to be confirmed by proper pharmaco-economic

Table 3

Primary and secondary outcomes

	Control group		Intervention group		Statistical analysis		
	No. of patients	Mean (SD) or %	No. of patients	Mean (SD) or %	Difference [95% CI]	Odds ratio [95%CI]	P value
Inhalation technique							
Percentage correct steps							
Baseline	363	68.8 (28.8)	371	67.7 (32.5)	–	–	–
1 month	354	76.4 (22.3)	359	86.0 (23.1)	10.0 [7.2–12.9]	–	<0.0001
3 months	346	79.0 (23.3)	346	93.4 (13.8)	13.5 [10.8–16.1]	–	<0.0001
Patients scoring 0%							
Baseline	363	11.6	371	15.6	–	–	–
1 month	354	4.8	359	5.0	–	0.73 [0.39–1.36]	0.323
3 months	346	4.6	346	1.2	–	0.18 [0.06–0.53]	0.002
Patients scoring 100%							
Baseline	363	16.5	371	22.4	–	–	–
1 month	354	20.3	359	51.0	–	2.83 [2.05–3.90]	<0.0001
3 months	346	32.9	346	68.5	–	3.03 [2.12–4.34]	<0.0001
Adherence to maintenance medication							
MRA score*							
Previous year	308**	82.7 (23.9)	307**	84.0 (23.5)	–	–	–
During trial	307**	85.7 (26.6)	292**	93.9 (21.5)	8.51 [4.63–12.4]	–	<0.0001
Patients with MRA ≥80*							
Baseline	308**	63.0	307**	62.9	–	–	–
3 months	307**	62.5	292**	78.1	–	2.15 [1.46–3.14]	<0.0001
Health status							
CAT score† (scale 0–40)							
Baseline	363	16.4 (7.6)	371	16.7 (7.8)	–	–	–
1 month	354	15.0 (7.6)	359	15.1 (8.0)	–0.16 [–0.89–0.57]	–	0.670
3 months	346	15.9 (7.7)	346	15.9 (7.8)	–0.08 [–0.82–0.66]	–	0.832
Patients with mMRC score ≥2‡							
Baseline	363	38.1	371	40.9	–	–	–
1 month	354	37.6	359	39.8	–	0.99 [0.77–1.28]	0.949
3 months	346	36.1	346	37.6	–	1.00 [0.76–1.32]	0.973
EQ-5D utility score§ (scale –0.18 to 1)							
Baseline	363	0.71 (0.25)	371	0.68 (0.25)	–	–	–
3 months	346	0.73 (0.25)	346	0.72 (0.24)	0.02 [–0.01–0.04]	–	0.190
EQ-VAS score¶ (scale 0–100)							
Baseline	363	64.9 (16.0)	371	63.3 (16.4)	–	–	–
3 months	346	64.6 (16.2)	346	65.2 (16.3)	1.31 [–0.48–3.09]	–	0.151
Smoking status							
Current smokers							
Baseline	363	40.5	371	45.8	–	–	–
3 months	346	39.0	346	43.6	–	0.98 [0.86–1.12]	0.760
Quit smoking	147	6.1	170	8.8	–	1.53 [0.65–3.61]	0.331

Abbreviations are as follows: CI, confidence interval; no., number. *The Medication Refill Adherence (MRA) score for each patient was calculated by dividing the patient's total days' supply by the number of days of study participation. Patients with a value ≥80 were considered adherent. †CAT: COPD Assessment Test; a higher score indicates a worse health status. ‡Scores on the modified Medical Research Council dyspnoea (mMRC) scale can range from 0 to 4, with a score of 4 indicating that the patient is too breathless to leave the house or becomes breathless when (un)dressing. §The EuroQol five-Dimension questionnaire (EQ-5D) provides a five-digit code that can be converted into a single index (utility score) through a set of weights. Using the value set for Belgium, these scores can range from –0.18 (worst health status) to 1 (full health status). ¶The EuroQol five-Dimension questionnaire visual analog scale (EQ-VAS) can range from 0 (worst health status) to 100 (full health). The respondent points out his self-perceived overall quality of life. **Scores are calculated only for patients with complete pharmacy refill records.

analysis [1, 2]. The exacerbation rate in the control group during the trial seems higher compared with other clinical trials in patients with COPD [27, 28]. Owing to the heterogeneous nature of COPD, geographical differences and the specific population under study, caution is needed when comparing exacerbation rates between trials [29]. Nevertheless, the time period of the trial (i.e. during winter) could be a main factor contributing to the perceived higher exacerbation rate [30, 31].

Our trial did not detect significant changes in health status after 3 months, which is in accordance with other studies, although it concerns heterogeneous pharmaceutical care programmes and healthcare settings [24, 32, 33]. This might be due to the short time span of the trial and the progressive nature of COPD. Furthermore, the health status of our sample was relatively high at start of the trial (mean CAT of 16, and 39% with mMRC ≥2), which decreases the available room for improvement.

Table 4

Exacerbations

	Control group <i>n</i> = 363	Intervention group <i>n</i> = 371	Odds ratio [95% CI]	Statistical analysis Estimated rate ratio [95% CI]	<i>P</i> value
Moderate exacerbations*					
Patients with event [<i>n</i> (%)]	125 (34.4)	125 (33.7)	1.02 [0.75–1.39]	–	0.890
Total events (<i>n</i>)	194	179	–	–	–
Event rate, per patient-year	2.22	2.05	–	0.82 [0.64–1.06]	0.135
Severe exacerbations†					
Patients with event [<i>n</i> (%)]	33 (9.1)	19 (5.1)	0.55 [0.31–0.98]	–	0.038
Total events (<i>n</i>)	53	24	–	–	–
Event rate, per patient-year	0.61	0.27	–	0.45 [0.25–0.80]	0.007
ER visits					
Patients with event [<i>n</i> (%)]	14 (3.9)	13 (3.5)	0.91 [0.42–1.97]	–	0.815
Total ER visits (<i>n</i>)	18	15	–	–	–
Rate of ER visits, per patient-year	0.21	0.17	–	0.59 [0.27–1.31]	0.195
Hospitalizations					
Patients with event [<i>n</i> (%)]	24 (6.6)	8 (2.2)	0.31 [0.14–0.71]	–	0.003
Total hospitalizations (<i>n</i>)	35	9	–	–	–
Rate of hospitalizations, per patient-year	0.40	0.10	–	0.28 [0.12–0.64]	0.003
Total hospitalization days (<i>n</i>)	307	76	–	–	–
Duration of hospitalization (days; mean)	8.77	8.44	–	–	0.835‡
Rate of hospitalization days, per patient-year	3.51	0.87	–	0.27 [0.21–0.35]	<0.0001

*Exacerbations requiring treatment with oral corticosteroids or antibiotics were regarded as 'moderate'. †Exacerbations requiring an emergency department (ED) visit or hospitalization were regarded as 'severe'. ‡*P* value is the result of a Mann–Whitney *U* test.

Furthermore, in addition to inhalation technique and medication adherence, other factors, such as physical activity, motivation and nutrition, could have influenced health-related outcomes [1]. Although other trials have reported clinically relevant changes in health status after a pharmacist intervention, they ran over a longer time period, recruited patients with worse baseline health status or were performed in a hospital setting [8, 23, 34]. Long-term trials are needed to confirm whether this pharmaceutical care protocol in a primary care setting has a positive effect on health or smoking status.

This RCT is the largest trial to investigate the effectiveness of a protocol-based community pharmacist intervention in patients with COPD and was conducted and reported following CONSORT guidelines [35]. The intervention was protocol based and designed to be easily applicable in community pharmacies by different pharmacists. All actions executed during the trial's scheduled intervention points were documented, both electronically and in written form. However, the trial has some limitations. A first limitation is the relatively short study duration. Regarding exacerbation frequency, this could lead to false-negative results; however, observed differences confirm that the trial length is sufficient. Moreover, a recent meta-analysis detected no differences between short- and long-term trials regarding hospitalizations due to COPD exacerbations [36, 37]. Secondly, the absence of spirometric confirmation of COPD could be considered an important limitation; however, it supports the pragmatic aspect of the trial, because in practice, pharmacists do not have access to such data. The operational definition of

COPD (prescription for COPD medication, aged ≥ 50 years, smoking history ≥ 10 pack-years and excluding patients with current asthma) was chosen in consultation with specialists and provided pharmacists with satisfactory certainty of COPD presence. Thirdly, pharmacists, carrying out the intervention, measured their own performance in teaching and training. This may be a potential source of bias. However, pharmacists had no benefit in untruthfully reporting of an improvement. Counselling was not individually evaluated, nor did pharmacists receive remuneration for improved patients. Finally, selection bias cannot be fully excluded, because participation in trials is usually accepted more frequently by motivated patients.

To increase external generalizability of our study findings, we attempted to recruit a patient sample as representative as possible, using every pharmacy as one recruitment centre. To confirm generalizability, we compared inhalation scores and medication adherence with results of other trials, and similar scores were observed [3, 9, 22]. Moreover, subgroup analysis confirmed consistency of results in different regions and patient subgroups (Figure 2).

In conclusion, we conducted a 3 month RCT in 170 community pharmacies to assess the effectiveness of a protocol-based pharmaceutical care programme in patients with COPD. Both primary outcomes, i.e. inhalation technique and medication adherence, were significantly more improved in the intervention group compared with the control group. Furthermore, a trend towards a reduction in severe exacerbations was observed. This trial should encourage community pharmacists to engage in

Figure 2

Subgroup analysis. Mean estimated differences (filled squares), rate ratios (filled triangles), 95% confidence limits (horizontal lines) and *P* values for the interaction between the study group effect and any subgroup variable. *The Dutch-speaking part of Belgium. †The French-speaking part of Belgium. ‡No significant interaction between the study group and subgroup variables was found, according to the predetermined value for interaction ($P < 0.01$)

COPD care, aiming to sustain an effective and safe pharmacotherapeutic treatment in patients with COPD.

Competing Interests

All authors have completed and submitted the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare the following: Dr Brusselle reported to have received a grant from GlaxoSmithKline; is a member of the board for AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline and Novartis; has received payment for lectures at AstraZeneca, Boehringer-Ingelheim, Chiesi, GlaxoSmithKline, MerckSharp&Dohme, Novartis, Pfizer and UCB. Dr Remon reported to have

received grants from IOF fund, FWO Vlaanderen and IWT; has received royalties from Tibotec/Biovail. Dr Van Bortel reported that he has been a consultant at the Drug Research Unit Maastricht; is employed by the Ghent University; has received royalties concerning educational pharmacological books; has received payment for travel accommodations concerning expenses unrelated to the trial from Daiichi-Sankyo and Servier. No other disclosures were reported. The opinions or assertions herein are the private views of the authors and are independent of the funding sources.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1

Protocol

Table S1

Inhalation technique scores per inhaler device and per checklist item