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EFFECTIVENESS OF A PHARMACIST INTERVENTION FOR ASTHMA CONTROL IMPROVEMENT

PHARMACEUTICAL CARE FOR ASTHMA CONTROL IMPROVEMENT

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ABSTRACT

Education on optimal medication use is an essential strategy to improve asthma control. We investigated whether a pharmacist intervention, focused on appropriate use of asthma medication and tailor-made to the patient's current asthma control, would improve asthma control in adult patients.

We conducted a 6-month randomised controlled parallel-group trial in 66 community pharmacies in Belgium. Patients were randomly assigned to receive usual pharmacist care (n=94) or a predefined pharmacist intervention (n=107). This intervention mainly focused on improving inhalation technique and medication adherence. Primary outcome was the level of asthma control, assessed by the Asthma Control Test® (ACT).

Mean ACT scores did not change from baseline for both study groups. However, a predefined subgroup analysis of patients having insufficiently controlled asthma at baseline showed that the intervention had significantly increased the ACT score after 6 months compared with usual care ($p = 0.038$). The intervention also reduced, for the complete study group, reliever medication use ($p = 0.012$) and the frequency of night-time awakenings due to asthma ($p = 0.044$). Inhalation technique ($p = 0.004$) and adherence to controller medication were significantly better in the intervention group ($p = 0.016$).

Pragmatic community pharmacy-based programs can significantly improve therapeutic outcomes in adult asthma patients. (ClinicalTrials.gov, NCT00263159.)

INTRODUCTION

The aim of asthma management is to gain and maintain control of the disease (defined as 'asthma control'). Although clinical trials have shown that good asthma control can be achieved in a majority of patients [1], this is not the fact in real life situation studies [2]. A large number of patients have not yet benefited from the advances in asthma treatment and are still insufficiently controlled, placing severe limits on daily life and putting them at risk for asthma-related morbidity and mortality. In an attempt to improve asthma control, the Global Initiative for Asthma (GINA) recently updated its asthma management guidelines and now emphasizes asthma management based on clinical control (GINA 2006) [3] rather than on asthma severity (GINA 1995 & 2002) [4, 5]. This is an important paradigm shift for asthma care and implies that the level of asthma control should be continuously monitored (due to the variable nature of the disease) and that treatment should be adjusted according to the patients' current asthma control status (Controlled, Partly Controlled or Uncontrolled).

Nowadays, asthma management programs are mainly delivered in a hospital setting and/or by physicians. However, also community pharmacists could make a useful contribution to asthma management because of their expertise on medication and their frequent contacts with the patient on prescription refill. Pharmacists could assist asthma patients and their physicians to achieve and maintain asthma control by providing the patient with suitable information and training about the asthma

medication, instructing correct inhalation technique, questioning the patient's understanding of the role of their asthma medications, explaining why inhaled corticosteroids are necessary, addressing the patient's concerns about potential side effects of inhaled corticosteroids and facilitating the adherence to controller medication. These factors have already been shown to be an important barrier to the achievement of good asthma control, as prescribing an appropriate asthma control treatment may not be successful when the patient uses the medication inappropriately [6-9]. Only few well-designed studies have yet investigated the effect of pharmacist care for asthma patients [10-15]. These studies have shown improvements in peak flow [12-15], asthma severity [10, 13], symptom scores [11], drug utilization [10, 12-14], and humanistic outcomes (e.g. quality of life, asthma knowledge) [10, 12-14]. However, the pharmacist interventions described in these publications were not tailored to the patient's current level of asthma control (as recommended by GINA 2006). The evaluated interventions also focused at several aspects of asthma management: i) choice of drug therapy: by identifying and solving drug-related problems, for example referral to physician for adding a drug, for a dosage change, for a change of dosage form, etc; ii) appropriate use of the medication: inhalation technique and adherence; iii) self-management: stimulating patients towards more self-management, for example by goal setting. Such "broad" pharmacist interventions are not only time-consuming (e.g. Saini *et al.* recorded that the total mean time spent per patient was 96.4 minutes across 3 visits [13]), but also require extensive education and training of the pharmacists (e.g. learning how to interpret peak flow measurements). Time constraints and lack of education have already been identified as important barriers to the implementation of pharmaceutical care into community pharmacy practice in Europe [16].

Furthermore, none of the previous studies used asthma control as the main clinical outcome measure. They mainly used peak expiratory flow or asthma severity as primary outcome. Several of these studies investigated only certain aspects of asthma control (e.g. daily dose of salbutamol based on dispensed medication history) [10] or MRC dyspnoea scale [12]). However, current GINA guidelines recommend to evaluate all aspects of asthma control, necessary to gain a complete view of the patients' asthma control level, with a clinically validated measure.

For these reasons, we designed a feasible intervention focused only at ensuring that the patient uses his prescribed drug therapy in a correct way (i.e. correct inhalation technique and good medication adherence). To make our intervention in agreement with the new GINA guidelines, we used the Asthma Control Test® as a rapid and easy tool to determine the level of asthma control of patients presenting at community pharmacies and to provide targeted pharmacist advice (Figure 1) [17]. The present randomised controlled trial was set up to study the hypothesis that such pharmacist intervention, focused on the optimal use of asthma medication and tailor-made to the patient's current asthma control, would result in an improved asthma control in adult patients over a 6-month period. Primary outcome was the level of asthma control, as measured by the Asthma Control Test®. Secondary outcomes included the patient's peak expiratory flow, rescue medication use, night-time awakenings due to asthma, inhalation technique, adherence to controller medication, severe exacerbations, quality of life, knowledge on asthma and smoking behaviour.

METHODS

Patients

Asthma patients were recruited consecutively in 66 randomly selected pharmacies, located in diverse areas of Flanders, the Dutch-speaking Northern part of Belgium. To be eligible, patients were required to carry a prescription for asthma medication (R03, ATC classification). In consecutive order, patients visiting the pharmacy were invited to participate in the study when fulfilling the following inclusion criteria: aged between 18 and 50 years, being treated for asthma for at least 12 months, "using" controller medication and being a regular visitor of the pharmacy. Exclusion criteria included a smoking history of more than 10 pack-years, suffering from another severe disease (e.g. cancer) and having an Asthma Control Test® score at screening lower than 15 (indicating seriously uncontrolled asthma; for ethical reasons, these patients were immediately referred to their general practitioner or respiratory specialist) or equalling 25 (indicating complete asthma control; no room for improvement).

Study design

This 6-month randomised controlled parallel group trial was carried out between January 2006 and October 2006 (patient recruitment period: January - April 2006). The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Approval for this study was granted by the ethics committee of the Ghent University Hospital. All patients gave written informed consent. The general practitioner of each participant was informed about the study by letter.

The study had a 2-week run-in period, followed by 6 months of randomised treatment. There were 5 scheduled visits to the pharmacy: at the start of the run-in period, at randomisation and 1, 3 and 6 months after randomisation.

All patients entering the run-in phase had to keep an asthma diary during 2 weeks (see *Diary Data*). At the end of run-in, patients were eligible for randomisation if they returned to the pharmacy with a diary that was completed for at least 90 %. Eligible patients were randomly assigned to either the control group or the intervention group. The sequence of allocation to control or intervention group was predetermined by the investigators based on a randomisation table generated with SPSS 14.0 software. Serially numbered, closed envelopes were made for each participating pharmacy. The envelope with the lowest number was opened by the pharmacist upon inclusion of a new patient.

Intervention

Patients in the intervention group received a protocol defined intervention at the start of the study and at the 1 and 3 month follow-up visits (Figure 1). Patients in the control group received usual pharmacist care.

Before the start of the study, the participating pharmacists had a training session about asthma (pathophysiology), its non-pharmacological and pharmacological treatment (GINA guidelines) and about the use of the study protocol.

Outcomes

Asthma Control

The primary outcome was the level of asthma control, which was measured with the Asthma Control Test® (ACT) (Dutch version). This is a clinically validated measure for asthma control, consisting of 5 questions each having 5 possible response modalities (classified by decreasing level of asthma control, scored from 5 to 1) [18, 19]. The ACT score (range, 5-25) was determined by summing the response scores to the 5

questions; the higher the score, the better the asthma control. Patients with a maximal score of 25 were considered as “totally controlled”. An ACT score of 20-24 indicated “well-controlled” asthma, an ACT score of 15-19 “insufficiently controlled” asthma, while a score below 15 indicated “uncontrolled” asthma.

The ACT was filled out by patients at the start of run-in, at randomisation and 1, 3 and 6 months after randomisation.

Diary Data

Patients filled in a daily diary during the 2-week run-in phase, after 3 months (during week 11 and 12) and after 6 months (during week 23 and 24) treatment recording (i) nocturnal awakenings due to asthma, (ii) the number of inhalations of rescue medication (during the day or night), and (iii) the best of three measurements of peak expiratory flow (PEF) made with a Mini-Wright Standard Peak Flow Meter (Clement Clarke, Harlow, UK) in the morning and evening before medication. PEF data are expressed as the percentage of maximum predicted value based on patient’s sex, age, and height [20].

During the entire study period, patients also registered asthma-related emergency department visits and hospitalisations.

Severe exacerbations of asthma

A severe exacerbation of asthma was defined as one requiring treatment with oral glucocorticoids (individually recorded in computerized pharmacy records) or an emergency department visit or hospital admission due to asthma.

Adherence to Controller Medication

Adherence during the course of the study was assessed using 2 validated measures: prescription refill rates and self-report [21]. The number of units of controller medication dispensed to each patient during the study period was available through computerized pharmacy records. The daily dose prescribed was read from the prescription or asked to the patient. From these data, adherence to controller medication was calculated and expressed as Adherence Rate (%) = (total days supplied during the study – days of last supply in the study)/(last claim date in the study – first claim date in the study) x 100 [22]. Self-reported adherence was assessed at the end of the study by asking the patients: '*How often do you <u>not</u> take your controller medication as prescribed? (a) Never, (b) 1-2 times/year, (c) 1-2 times/month, (d) 1-2 times/week, (e) Daily.'*

Asthma-specific Quality of Life

Asthma-specific quality of life was assessed at the start of the intervention period and after 6 months follow-up using the Dutch version of the Standardised Asthma Quality of Life Questionnaire (AQLQ(S)) of Juniper *et al*. [23].

Knowledge about asthma and treatment

Patients' knowledge about asthma and its treatment was evaluated at the start of the intervention period and after 6 months follow-up using an updated version of the Knowledge of Asthma and Asthma Medicine questionnaire (WHO) [24].

Inhalation technique

The inhalation technique was scored using a checklist (8-point checklist for metered dose inhalers (MDI), 10-point checklist for MDI used with a large volume spacer and

8-point checklist for dry powder inhalers (DPI)) at the start of the intervention period and 6 months later. For each correct step, one point was assigned and the sum score of the inhalation technique was displayed as percentage correct steps. Patients committing major errors in inhalation technique (for MDI: fail to remove cap and/or fail to shake MDI; for DPI: fail to load device and/or fail to inhale quickly and deeply through device) were assigned a sum score of zero. For ethical reasons, such major errors were also corrected in patients belonging to the control group.

Statistical analysis

Sample size was calculated based on the ability to detect a 10 % difference in Asthma Control Test® score between the intervention group and the control group with 80 % power at the 5 % significance level. For an estimated 30 % attrition, we enrolled approximately 200 patients.

The success of randomisation was assessed by comparing baseline characteristics of both study groups using independent sample Student t-tests for continuous variables and Chi-Square tests for categorical variables. These tests were also used to compare baseline characteristics of patients who did and did not complete the study.

The primary outcome, i.e. the Asthma Control Test® score, was analysed using an intention-to-treat approach. We used a linear mixed model, with the maximum-likelihood method to handle missing data [25]. To account for any cluster effect (i.e. correlation of patients within pharmacies), a multilevel logistic regression was performed on the primary outcome. Pharmacies were used as level 1 observations, patients as level 2 observations. The intra-pharmacy correlation coefficient showed to be very small (< 0.1), meaning that there was no significant cluster effect. A priori, it seemed likely that mainly the insufficiently controlled patients (ACT score < 20) would

benefit the most from our intervention. Therefore, we decided - before the start of the study - to perform a subgroup analysis of patients with insufficient control on the primary outcome measure, the ACT.

The secondary outcomes were analysed by a per-protocol approach. The continuous parameters measured at baseline, at 3 and at 6 months were analysed using a repeated measures multivariate analysis of variance with baseline values as covariates. Treatment by time interactions were also tested and, if significant, a post hoc-analysis (Bonferroni) was performed to check for between-study group differences at 3 and 6 months follow-up. For the continuous outcomes measured only at baseline and at 6 months, an independent sample Student t-test was conducted on the change from baseline. Outcomes of categorical parameters were evaluated by binomial logistic regression with baseline values and study group as covariates. Exacerbations were analysed with a zero-inflated Poisson regression model. Adherence based on prescription refill was analysed with an independent sample Student t-test.

All statistical analyses were conducted with SPSS Version 14.0 and SAS Version 9.1. A 2-tailed significance level of 0.05 was used.

RESULTS

From January 2006 to April 2006, potentially eligible patients were identified at the participating pharmacies. The flow of participants through the study is shown in Figure 2. Of the 356 eligible patients, 155 were excluded before randomisation. The remaining 201 patients were randomly allocated to control or intervention group. Both study groups were well matched regarding demographic and clinical characteristics (Table 1).

Of the 201 randomised patients, 150 (75 %) completed the study. Completion rates did not differ significantly by study group ($p > 0.05$). Reasons for drop out were personal reasons (15), withdrawal from study of the pharmacist (2), relocation (2), lost to follow up (27) and other reasons (5). Baseline characteristics of patients not completing the study did not differ significantly from patients completing the study ($p > 0.05$).

Asthma Control

Mean ACT scores did not change from baseline for both study groups (Table 2). However, a predefined subgroup analysis of patients having insufficiently controlled asthma at baseline showed that the intervention had significantly increased the ACT score after 6 months compared with usual care (mean ACT change from baseline in intervention group: +2.3; in control group: +0.3 – mean difference (95% CI): 2.0 (0.1 to 3.9); $p = 0.038$) (Figure 3).

The need for rescue medication was reduced in both groups from baseline, with a significantly higher reduction in the intervention arm (-0.56 and -0.57 inhalations per day after 3 and 6 months follow-up, respectively) versus the control arm (-0.03 and -0.43 inhalations per day after 3 and 6 months follow-up, respectively) ($p = 0.012$). Patients in the intervention group experienced less night-time awakenings due to asthma than patients in the control group ($p = 0.044$) (Table 2). For this outcome measure, there was a significant interaction between study group and time ($p = 0.033$). Post hoc analysis showed that the intervention group had significantly less nightly awakenings than the usual care group at 6 months follow-up ($p = 0.004$), while there was no difference at 3 months follow-up ($p = 0.529$). This study found no

within-subject nor between-group differences for the PEF morning and PEF evening values (Table 2).

Severe Asthma Exacerbations

This study found no differences between control and intervention group in the occurrence of severe exacerbations (Table 3).

Adherence to Controller Medication

Adherence to controller medication during the course of the study as judged by the prescription refill rates was higher in the intervention group compared with the control group (mean adherence rate: 90.3 % vs. 74.6 %) ($p = 0.016$). However, there was no significant between-group difference in medication adherence as assessed by self-report ($p = 0.108$).

Asthma-specific Quality of Life

This study found no significant difference in AQLQ score between both study groups, neither at baseline nor at the end of follow-up (Table 4)

Inhalation Technique and Knowledge on Asthma

At baseline, the mean percentage of handling steps performed correctly was approximately 75 % in both groups (Table 4). At the end of follow-up, this percentage was significantly higher in the intervention arm ($p = 0.004$). The percentage of patients performing each of the inhalation manoeuvers correctly increased by 40 % in the pharmacist care group and by 20 % in the usual care group. The intervention was also able to correct all major inhalation technique errors, as 9.7 % of the patients

were assigned a sum score of zero before the intervention, a percentage reduced to 0.0 % at the end of the intervention period. For patients receiving usual care, these percentages were 6.6 % (start study) and 4.8 % (end study).

No beneficial effects of the intervention were seen in the asthma knowledge scores (Table 4).

Smoking

At the start of the study, 20 (21.3 %) patients in the control group and 25 (23.4 %) patients in the intervention group reported to be current smokers. Of the smoking patients in the control group, 2 had quit smoking, 12 were still smoking and 6 were lost to follow-up after 6 months. Of the smokers in the intervention group, 4 had quit smoking, 12 were still smoking and 9 were lost to follow-up after 6 months. No significant between-group differences were observed (Table 4).

DISCUSSION

This paper reports on the first randomised controlled trial assessing the impact of a community pharmacist intervention promoting optimal asthma medication use on asthma control. Importantly, in accordance with GINA 2006 guidelines, this pharmacist intervention was specifically tailored to the patient's current asthma control. We found that our program substantially improved inhalation technique and medication adherence, which are both key stones of successful asthma management. The intervention also improved asthma control of insufficiently controlled patients and reduced, for the complete study group, the use of reliever medication and the frequency of nocturnal awakenings. It seems likely that these

clinical improvements result from the more appropriate use of the asthma controller medication.

Although correct use of the inhaler device is essential for the medicine to arrive at its target organ, i.e. the lower airways, its importance is often overlooked. There is evidence that poor inhaler technique is associated with poor asthma control [26-28]. Recently, the Aerosol Drug Management Team (ADMIT) demonstrated that many patients do not use their inhaler devices correctly; ADMIT therefore strongly urged healthcare workers to be more aware of this major problem [29]. Community pharmacists could play an important role in this area, by teaching the patients how to use their inhaler devices properly and regularly checking the technique during the course of treatment (especially when therapeutic goals are not met).

Beside inhalation technique, effective asthma management also depends on the patient's adherence to the prescribed controller medication. Several studies have shown that adherence to chronic asthma therapy is low, mainly with respect to inhaled corticosteroids [8, 30]. Nevertheless, previous studies have demonstrated that regular use of inhaled corticosteroids may reduce asthma-related hospitalisation and death [31, 32]. In the present study, almost all patients were prescribed inhaled corticosteroids as controller treatment. Patients in the intervention arm were about 15 % more adherent than patients receiving usual care (according to the prescription refill data, which are a more objective measure of adherence than self-report), suggesting a beneficial impact of our intervention. Our findings stress the importance of patient education about the necessity of inhaled corticosteroids as a way to improve adherence. For a correct interpretation of the results of this study, it should be emphasized that the medication profiles, i.e. type and daily dose of asthma controller medication, remained unchanged during the study period in both groups

(data not shown). This suggests that the improvements in symptom control seen in the intervention group can be ascribed to the extra pharmacist care and not to changes in pharmacotherapy.

Within the 6 months follow-up period, our program did not affect the patients' knowledge about asthma. A plausible explanation could be the fact that information about asthma was given briefly and limited to the first visit (Figure 1, see Session 1), which is likely insufficient to significantly improve the knowledge of patients. Likewise, the asthma-related quality of life scores (already high at baseline in both groups) remained unchanged. The intervention also did not influence the occurrence of severe asthma exacerbations during the study period.

Our overall results are consistent with those of other community pharmacy-based programs [10-15]. However, some of these previous studies have shown significant improvements in quality of life, peak flow values and asthma knowledge, while this was not found in the present study. A detailed overview of the results for these outcomes of the previous studies is shown in Table 5. Regarding quality of life, the results of these studies are quite heterogeneous. This may be attributed to the use of a variety of quality of life instruments. Only one of these studies [15] used the Asthma Quality of Life Questionnaire [23], which was also used in our study, and this study did also find no significant improvement in the quality of life scores. Moreover, our patients had already high scores at baseline, reducing the room for improvement. For PEF, the studies reporting significant improvements were studies where the PEF measurements were only performed in the intervention group, not in the control group. The reported improvements are thus "within group" comparisons (pre – post), no "between group" comparisons (intervention group versus control group). Except for the study conducted by Weinberger *et al* [15], which reported significantly higher

PEF rates in the intervention group than in the control group, after a follow-up period of 12 months (our study lasted only 6 months). Four of the six previous studies assessed asthma knowledge: all of them showed a significant improvement (2 of them after 6 months follow-up, and 2 after 12 months follow-up). Possible explanation for the fact that we did not observe an improved knowledge is already provided above, namely the limited information about asthma provided in our intervention.

Our study has two important assets compared with the previously published trials. We were the first to investigate the effectiveness of patient education using asthma control as the primary outcome. Moreover, we tested an intervention that was specifically tailored to the current asthma control status of the patient, concordant with the new GINA asthma management guidelines. The Asthma Control Test® showed to be an excellent tool to measure rapidly [17] and accurately [19] the asthma control of patients presenting at community pharmacies, enabling the pharmacist to provide each patient with specific advice accommodated to his/her clinical needs.

Our investigation also has its limitations. Firstly, we probably underestimated the effect of our intervention, as we did not include newly diagnosed, steroid-naïve asthma patients but only patients being already at least 1 year on chronic asthma medication. In fact, although all our patients were already on treatment for 1 year or more, our program was still beneficial. It is likely that our intervention will have a greater impact on treatment-naïve asthma patients, as they have a higher need for information and training about optimal asthma medication use. For safety reasons, patients with seriously uncontrolled asthma (ACT < 15) were excluded from participation. This generated a study population with limited potential for

improvement, which may also have caused an underestimation of the impact of our intervention. Secondly, our patients may not be fully representative of the overall general population of asthma patients, since they participated voluntary in the study. Moreover, only regular pharmacy customers were recruited in order to ensure sufficient follow-up during the course of the study. This selected patient sample may reflect a stronger interest in self-management, possibly generating a positive selection bias. Thirdly, randomisation was performed on patient level meaning that each pharmacy had to follow up control as well as intervention patients. To prevent contamination between both study groups, participating pharmacists were thoroughly instructed on how to strictly follow the protocol prior to onset of the trial. Fourthly, this study was an open study, where the data collection was performed by the same person as the person who delivered the intervention. Nevertheless, to prevent bias, the final data collection (i.e. after 6 months follow-up) for all outcomes was performed by another pharmacist than the pharmacist who gave the intervention. Lastly, the sustainability of our beneficial outcomes beyond 6 months was not assessed. However, the clear differences between intervention and control group argue for further investigation and larger-scale implementation.

The present study suggests that rigorously designed trials (conforming to the CONSORT statement [33]) evaluating realistic interventions in real clinical practice settings are of paramount importance for asthma control improvement, especially in primary care. Community pharmacists are well placed in the healthcare system to provide patients with education on their asthma medication, as they have the advantages of easy patient access and regular patient contact. Our brief, simple and pragmatic intervention is feasible to implement in all community pharmacies, which argues for the generalisability of our results. Moreover, the random selection of the

pharmacies participating in this study, and the community-based patient selection using fairly straightforward inclusion criteria also plead for the generalisability of the study results [34].

In conclusion, the authors would like to stress that this pharmacist intervention is not meant to replace formal asthma education but rather to complement it. The clear need for patient-focused care on appropriate use of asthma medication has already been highlighted [6-9, 29] and it is an essential strategy to improve asthma control, especially in primary care. Further research should focus on the cost-effectiveness of such interventions.

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TABLES AND FIGURES

SESSION 1 – at start of intervention period:

Personal education from the pharmacist about the following topics:

- Correct use of the inhaler device
- Understanding asthma*:
  - Symptoms
  - Triggers
  - Early warnings
- Understanding asthma medication:
  - Difference between controller and reliever medication
  - Facilitate adherence to controller medication
- Smoking cessation (if relevant)

SESSION 2 & 3 - at 1 & 3 months follow-up, respectively:

Pharmacist advice based on the Asthma Control Test® score of the patient:

- **If Asthma Control Test® score < 15 (= 'uncontrolled' asthma):**
  immediate referral to general practitioner or respiratory specialist
- **If Asthma Control Test® score 15-19 (= 'insufficiently controlled' asthma):**
  review inhalation technique & check controller medication adherence
- **If Asthma Control Test® score ≥ 20 ('well-controlled' asthma):**
  no specific advice needed; inform patient asthma is well-controlled.

Figure 1: Overview of Pharmacist Intervention.

* Using the Dutch version of the GINA Patient Guide 'What You and Your Family Can Do About Asthma' (NIH Publication No. 96-3659C, 1996).

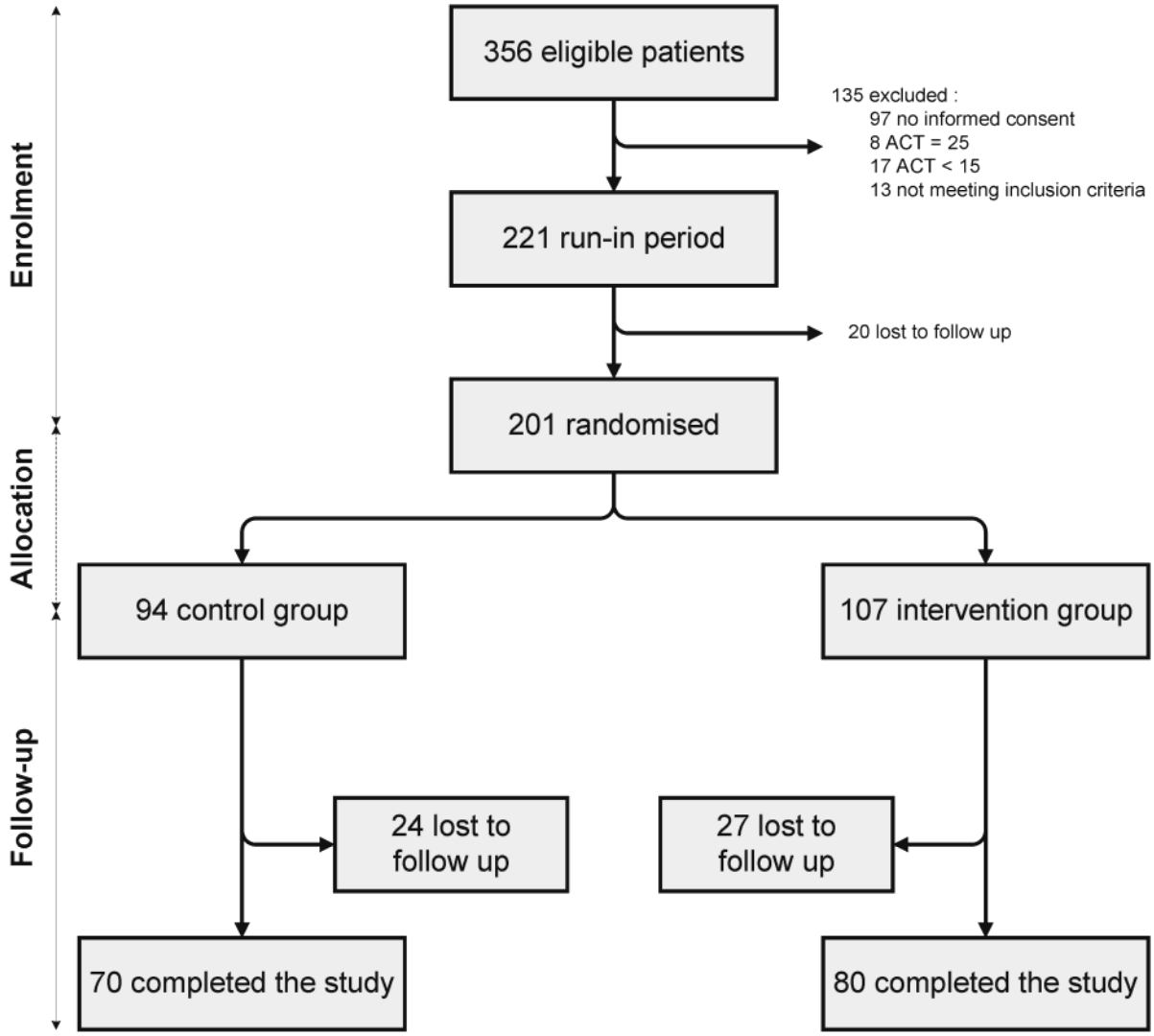

Figure 2: Flow of participants through the study.

	Control group (n = 94)	Intervention group (n = 107)
Male sex, n (%)	46 (49 %)	48 (45 %)
Age, yr	36.3 (17-51)*	35.2 (19-51)*
BMI	24.7 (16.9-38.6)	24.8 (15.7-41.4)
Education		
No high school degree, %	5.3	1.9
High school degree, %	48.9	50.5
Higher education**, %	44.7	47.7
Smoking status, %		
Current smoker	21.3	23.4
Ex-smoker	29.7	20.7
Passive smoker	30.7	29.4
Pack-years of current smokers	5.9 (0.1-10.0)	5.5 (0.5-10.0)
Pack-years of ex-smokers	4.0 (0.1-10.0)	5.6 (0.3-14.0)*
Asthma duration, years	22 (1-48)	20 (1-47)
Allergic asthma†, %	93.5	81.3
Tree, %	47.1	51.7
Grass, %	62.1	59.8
Dog, %	41.4	42.5
Cat, %	65.5	52.9
Dust mite, %	87.4	82.8
Medication, %	14.9	12.6
Asthma action plan, %	34.8	33.6
Peak expiratory flow		
Morning, l/min	390.7 (127.9-755.0)	409.7 (165.7-717.1)
Evening, l/min	409.7 (130.9-786.2)	422.5 (143.1-715.4)
Asthma Control Test® score (ACT)	19.3 (10-25)	19.7 (11-25)
ACT < 15, % of patients	8.5	5.6
ACT 15-19, % of patients	42.6	41.1
ACT 20-25, % of patients	48.9	53.3
Nights with awakenings, %	9.4 (0-100)	7.4 (0-100)
Rescue medication, puffs/day	1.33 (0-15.6)	1.24 (0-10.7)
Controller medication‡		
ICS, %	23.1	25.0
LABA, %	9.2	14.5
ICS + LABA combination, %	70.8	64.5
Theophylline, %	12.3	15.8
Leukotriene modifiers, %	1.5	0.0
Mean daily dose of ICS¶, µg	1211.0 (200-4000)	1184.1 (200-4000)

Data are mean (range) unless otherwise stated. For the parameters recorded on diary cards, the mean values of the 2 weeks of the run-in period were considered for baseline. Values did not differ significantly among both groups, according to independent sample Student t-test for continuous variables and chi-square test for categorical variables.

* Deviation from inclusion criteria (included in all statistical analyses): n=1 for 'age' in control group; n=1 for 'age' in intervention group; n=2 for 'pack-years of ex-smokers' in intervention group.

** Higher education = succeeded any type of higher education (college or university).

† Self-reported allergy (via questionnaire).

‡ ICS: inhaled corticosteroids; LABA: long-acting inhaled β_2-agonists.

¶ Expressed as beclomethasone equivalent.

Table 1: Baseline characteristics of the study patients.

	Control group				Intervention group				Difference[¶] (95% CI); p
	0 months (n = 94)	1 month (n = 94)	3 months (n = 84)	6 months (n = 70)	0 months (n = 107)	1 month (n = 107)	3 months (n = 99)	6 months (n = 80)	
Asthma Control									
ACT[*] score (scale 0-25)	19.3 (3.5)	19.9 (3.5)	20.0 (3.8)	19.7 (4.8)	19.7 (3.1)	20.0 (2.9)	20.3 (3.2)	20.2 (3.5)	0.1 (-0.8 to 0.8) p = 0.492
ACT < 15, % of patients	8.5	6.4	10.7	15.9	5.6	2.8	5.3	8.9	
ACT 15-19, % of patients	42.6	39.4	27.4	24.6	41.1	35.5	32.6	24.1	
ACT 20-25, % of patients	48.9	54.2	61.9	59.4	53.3	61.7	62.1	67.1	
Rescue medication, puffs/day[†]	1.33 (2.36)	-	1.30 (2.55)	0.90 (1.36)	1.24 (2.04)	-	0.68 (1.16)	0.67 (1.33)	-0.34 (-0.60 to -0.08) p = 0.012
Nights with awakenings, %[†]	9.4 (18.9)	-	10.2 (20.6)	10.7 (19.3)	7.4 (15.2)	-	5.2 (13.8)	3.9 (9.1)	-3.5 (-7.0 to -0.1) p = 0.044[‡]
Lung function									
PEF morning, % of predicted[†]	78.0 (18.2)	-	79.4 (21.0)	79.1 (19.0)	80.9 (18.0)	-	81.4 (19.0)	84.0 (19.4)	-0.5 (-3.1 to 2.1) p = 0.703
PEF evening, % of predicted[†]	80.1 (17.8)	-	81.4 (20.9)	81.1 (19.4)	82.6 (17.7)	-	83.3(21.1)	85.1 (19.6)	-1.0 (-3.6 to 1.5) p = 0.430

Data are mean (SD) unless otherwise stated.

[¶] Difference in mean change from baseline between intervention and control group ('intervention effect').

[*] ACT = Asthma Control Test®.

[†] Average over the past 14 days.

[‡] There was a significant study group-time interaction (p = 0.033). Post hoc test (Bonferroni) showed no significant between-group difference at 3 months follow-up (p = 0.529) and a significant between-group difference at 6 months follow-up (p = 0.004).

Table 2: Asthma Control.

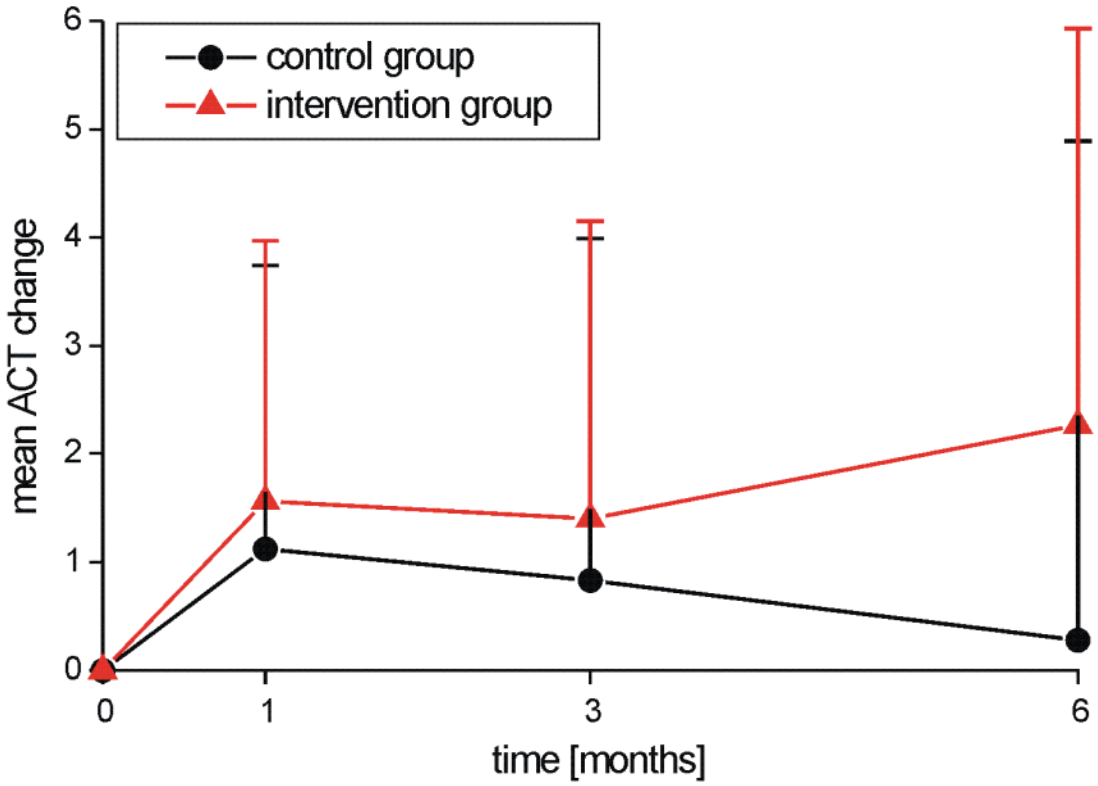

Figure 3: Mean changes (SD) from baseline in ACT score for a predefined subgroup of patients having an ACT score < 20 ('insufficiently controlled asthma') at baseline.

	Control group	Intervention group	Odds ratio[¶] (95% CI); p
Severe exacerbations[*]			
Patients with event, n (%)	8 (11.4 %)	10 (12.8 %)	2.0 (0.75 to 5.7) p = 0.158
Total events	16	15	
Emergency room visits or hospitalisations			
Patients with event, n (%)	5 (10.4 %)	1 (1.6 %)	- [†]
Total events (days with events)	7	1	

[*] Severe exacerbations were defined as oral steroid course, emergency room visit or hospitalisation.
[¶] Study group comparison: odds ratio (95% CI); p value on odds ratio.
[†] The incidence rates of emergency room visits or hospitalisations are too low to compare statistically.

Table 3: Severe Exacerbations.

	Control group		Intervention group		Difference ¶
	0 months (n = 94)	6 months (n = 70)	0 months (n = 107)	6 months (n = 80)	(95% CI); p
AQLQ* (scale 0-7)	5.7 (1.0)	5.8 (0.9)	5.9 (0.7)	6.0 (0.7)	0.2 (-0.1 to 0.4) p = 0.128
Inhalation technique					
% of correct steps	74.7 (23.8)	83.7 (22.5)	74.7 (27.7)	93.2 (10.7)	11.0 (1.0 to 21.1) p = 0.004
patients scoring 100 %, %	16.5	36.5	24.3	64.3	
patients scoring 0 %, %	6.6	4.8	9.7	0.0	
Asthma knowledge score, %	60.8 (15.7)	65.1 (13.4)	68.0 (15.8)	67.9 (16.0)	-3.7 (-8.7 to 1.3) p = 0.133
Current smokers, n (%)	20 (21.3)	12 (17.6**)	25 (23.4)	12 (15.6†)	1.8‡ (0.3 to 10.2) p = 0.501
Adherence to controller medication					
Adherence rate based on prescription refills, %	74.6 (36.5)		90.3 (30.3)		15.7 (3.0 to 28.4) p = 0.016
Self-reported adherence:					
How often do you <u>not</u> take your controller medication as prescribed?					
(a) Never	NA	39.4	NA	47.3	
(b) 1-2 times/year	NA	19.7	NA	20.3	2.0‡,# (0.9 to 4.6) p = 0.108
(c) 1-2 times/month	NA	15.2	NA	17.6	
(d) 1-2 times/week	NA	19.7	NA	13.5	
(e) Daily	NA	6.1	NA	1.4	

Data are mean (SD) unless otherwise stated. NA = not assessed.

¶ Difference in mean change from baseline between intervention and control group ('intervention effect'). Except for adherence, which was assessed during the entire study period (based on prescription refill) and at 6 months only (based on self-report).

* AQLQ = Asthma Quality of Life Questionnaire.

** Percentage was calculated on 68 patients (2 missing values).

† Percentage was calculated on 77 patients (3 missing values).

‡ Odds ratio (95% CI); p value on odds ratio.

For statistical analysis of self-reported adherence, the answers were regrouped in 2 categories: answers a, b and c → "adherent"; answers d and e → "non-adherent".

Table 4: Other Secondary Outcomes.

Study	Duration	Results	Comments
Armour *et al* [10]	6 months	QoL: significantly improved PEF: NA Knowledge: significantly improved	QoL: borderline significant (p = 0.05). No PEF assessed. FEV_1 and FEV_1/FVC were assessed, however no significant improvements were observed.
Barbanel *et al* [11]	3 months	QoL: NA PEF: NA Knowledge: NA	Only asthma symptoms were evaluated in this study (using a self-administered symptom scale)
Mangiapane *et al* [12]	12 months	QoL: significantly improved within the intervention group PEF: significantly improved within the intervention group Knowledge: significantly improved within the intervention group	This study was no randomised controlled trial, but had a pre-post design (without concurrent control group). Consequently, no intervention vs. control group comparison was possible.
Saini *et al* [13]	6 months	QoL: significant improvement PEF: significantly improved within the intervention group Knowledge: significantly improved	PEF was only measured in the intervention group (not in the control group), so no intervention vs. control group comparison possible.
Schulz *et al* [14]	12 months	QoL: significantly improved PEF: PEF morning remained status quo, PEF evening was significantly improved within the intervention group Knowledge: significantly improved after 12 months (not after 6 months)	PEF was only measured in the intervention group (not in the control group), so no intervention vs. control group comparison possible.
Weinberger *et al* [15]	12 months	QoL: no significant improvement PEF: significantly improved after 12 months Knowledge: NA	

NA = not assessed.
QoL: Quality of Life.
PEF: Peak expiratory flow.

Table 5: Detailed overview of the results regarding quality of life, peak expiratory flow and knowledge of the previously published trials of community-pharmacy based programs of asthma care.